Childhood Obesity
Causes, Consequences, and Intervention Approaches

Edited by Michael I. Goran
Childhood Obesity
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Dedication

This book is dedicated to all of my former students and fellows for their dedicated efforts pushing forward the science of childhood obesity and to my family for always being there with love and support.
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Childhood obesity is now the most prevalent chronic disease of children and adolescents in the United States. Over 17% of our youth have obesity, and the prevalence is greater among African Americans and Hispanics. Recent data indicate that obesity is declining in 2- to 5-year-old children, and has plateaued in older children and adolescents. Nonetheless, the high prevalence, natural history, and complications of obesity allow no room for complacency. In this context, the comprehensive overview provided by Childhood Obesity: Causes, Consequences, and Intervention Approaches is timely, and provides a useful opportunity to assess our progress in the control of the obesity epidemic.

As recently as 40 years ago, childhood obesity was barely recognized. The earliest prevalence data were provided by Stanley Garn, a physical anthropologist at the University of Michigan, writing for an ad hoc committee to review the Ten-State Nutrition Survey conducted between 1968 and 1970. The analyses relied on skinfold thicknesses, and the data were used to provide the first observations on the changes in fatness by age and gender across the life cycle.1 At about the same time, Gil Forbes at the University of Rochester began to describe changes in body composition associated with obesity. As early as 1963, he noted the increase in fat-free mass2 and height associated with childhood obesity.3 Because obesity was not considered a significant problem, few treatment programs existed.

How times have changed. The increase in prevalence since the 1970s has been accompanied by an increase in severity and the recognition that childhood obesity is not a benign cosmetic condition. As with adults, multiple organ systems are affected. Furthermore, the natural history of childhood obesity indicates that it is a significant contributor to the prevalence of obesity in adults and may contribute disproportionately to severe adult obesity. Because few adults with obesity are able to achieve a healthy weight,4 the prevention and successful treatment of childhood obesity must become a priority.

In many respects, we know more about prevention than we do about treatment. Early efforts by the Centers for Disease Control and Prevention documented the increases in the prevalence of childhood obesity, identified the earliest targets for prevention, and provided funding for state health departments to begin to implement strategies that focused on place-based policy and environmental changes. Schools and early care and education facilities became logical targets, insofar as those were locations where children spent substantial time, consumed substantial quantities of food, and had opportunities for physical activity. Successful changes in the food environment within schools have occurred as a consequence of an agreement between the American Heart Association, the Alliance for a Healthier Generation, and the American Beverage Association to reduce the availability of sugar drinks, as well as the changes in meals and competitive foods in schools mandated by the Healthy Hunger-Free Schools Act. Implementation and retention of physical education and other physical activity programs in schools have been less successful. Similar efforts to change the food and physical activity environments within early care and education facilities have just begun.

Clinical efforts for the treatment of obesity appear more fragmented. The United States Preventive Services Task Force has recommended comprehensive moderate-to-intensive behavioral interventions for weight loss, focused on diet and physical activity.5 Moderate intensity consists of 26–75 contact hours, and high intensity consists of more than 75 contact hours. However, the practical translation of this treatment to usual pediatric care presents a challenge. Because few insurance plans will reimburse such a program, its scalability is limited. Because few parents and patients can accommodate this time commitment, its efficacy is limited.

In the last 40 years, as our understanding of obesity has expanded, so has our appreciation of its complexity. The microbiome, epigenetics, toxins, obesogens, mobile health strategies, the role of the built environment, and systems thinking all testify to the rapid diversification of knowledge and
interest in obesity and its solutions. *Childhood Obesity: Causes, Consequences, and Intervention Approaches* includes this information as well as expanding considerably on what we have learned about treatment and prevention. The challenges that lie ahead are how to integrate this information and whether this knowledge enhances our ability to prevent and treat obesity. In some cases, the issue is no longer about what to do but how to do it effectively.

One of the most important barriers that we must confront and resolve is the pervasive bias and stigma related to obesity. Despite its prevalence, obesity remains one of the most stigmatized conditions in the United States. One of the ways that we all can begin to address bias is to use people-first language. An obese person is an identity. A person with obesity is a person with a disease. Such terminology has political implications. An obese person is more likely to be blamed for his or her condition, whereas a person with obesity may be more likely to be viewed as a person in need of medical care and support.

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Michael I. Goran is professor of preventive medicine and pediatrics in the Keck School of Medicine at the University of Southern California in Los Angeles. He is the founding director of the University of Southern California Childhood Obesity Research Center and holds the Dr. Robert C. and Veronica Atkins Endowed Chair in Childhood Obesity and Diabetes. Dr. Goran also serves as codirector of the University of Southern California Diabetes and Obesity Research Institute. Dr. Goran is a native of Glasgow, Scotland, and received his PhD from the University of Manchester, England (1986), prior to postdoctoral training in the United States (1987–1991). He previously served on the Faculty of Medicine at the University of Vermont (1991–94) and the Department of Nutrition Sciences at the University of Alabama at Birmingham (1994–99), prior to joining the University of Southern California in 1999. For the past 30 years, Dr. Goran’s research program has focused on the causes and consequences of childhood obesity. His work is focused on understanding the metabolic factors linking obesity to increased disease risk during growth and development and using this information as a basis for developing new behavioral and community approaches for prevention and risk reduction. He is also especially interested in ethnic disparities in obesity and obesity-related diseases, with a special interest in the effects of dietary sugar on obesity and metabolic diseases among Hispanic populations. His research has been continuously funded by the National Institutes of Health since 1991 and he has published over 300 professional peer-reviewed articles and reviews. He is the coeditor of the Handbook of Pediatric Obesity, published in 2006, coeditor of Dietary Sugars and Health, published in late 2014, and serves as editor-in-chief for Pediatric Obesity. He has been the recipient of a number of scientific awards for his research and teaching, including the Nutrition Society Medal for Research (1996), the Lilly Award for Scientific Achievement from the Obesity Society (2006), the Bar-Or Award for Excellence in Pediatric Obesity Research from the Obesity Society (2009), and the TOPS Research Achievement Award from the Obesity Society (2014). Full details on Dr. Goran’s research can be found on his website at www.GoranLab.com. Outside of work, Michael is an avid tennis player, and enjoys cooking, eating, and traveling with his family.
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Section I

Epidemiology of Childhood Obesity in Different Populations
INTRODUCTION

Obesity is the most prevalent chronic health condition in children, thereby it is a major public health concern. Between the 1960s and 2012, there was an almost fourfold increase in the prevalence of overweight and obesity among both children and adolescents in the United States.\(^1,2\) According to the 2011–2012 National Health and Nutrition Examination Survey (NHANES), approximately 34% of children and 35% of adolescents are overweight or obese.\(^2\) Trends in preschool-age children have been slightly different. Although there has been a substantial increase in the prevalence of obesity, from less than 4% of preschool-age children in NHANES I (1971–1974) to more than 7% in 2011–2012, rates are now decreasing among preschool-age children, but continue to increase among adolescents.\(^3\) Between 2003–2004 and 2011–2012, the prevalence of obesity among two- to five-year-old children decreased from 13.9% to 8.4%;\(^2\) however, this decline is not seen in all subgroups. There are considerable racial and ethnic disparities in the prevalence of obesity among two- to five-year-olds. The rates are highest among Hispanics (15.2% among females, 18% among males) and African Americans (13.9% among females, 9.0% among males) and lowest among non-Hispanic whites (0.6% among females, 6.3% among males).\(^2\)

DEFINITIONS AND AGE DIFFERENCES

Unlike adults, children should gain both weight and height due to growth. Therefore, rather than a single cutoff to demarcate overweight or obesity, age and gender-specific cutoffs are used. In the United States, most clinicians and researchers use the Centers for Disease Control and Prevention.
Childhood Obesity: Causes, Consequences, and Intervention Approaches

(CDC) percentile cutoffs to define weight status. Youth with a body mass index (BMI) ≥85th percentile for age and gender are considered overweight and those with a BMI >95th percentile are considered obese. The standards used to determine percentiles come from the National Health and Examination Surveys. An alternative approach for defining obesity was developed by the International Obesity Taskforce (IOTF). Using data from six countries (Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, and the United States), the taskforce determined the age and gender-specific cutoff point that best predicted having a BMI ≥25 (overweight) or ≤30 (obese) at age 18. Until midadolescence, the CDC and IOTF approaches identified similar cutoffs. However, the CDC cutoffs classify some 17–20-years-olds with a BMI ≥25 as being in the healthy weight range because the 85th percentile of BMI among older adolescents is above 25 kg/m². It is therefore advisable that if using the CDC cutoffs, one should revise the algorithm to make sure that all youth with a BMI between 25 and 29.9 are classified as overweight, irrespective of their BMI percentile. Regardless of which BMI classification is used, it is important to remember that relying on BMI to classify people results in some error. Since BMI does not distinguish between muscle and fat and muscle weighs more than fat, people who are highly active and muscular may have a high BMI despite low body fat. Moreover, puberty is associated with hormonal and body composition changes. Puberty causes females to increase their weight and body fat, whereas males increase their weight and lean mass. Therefore, BMI may misclassify more postpubertal males than females.

In the 1960s, the prevalence of obesity was approximately 5% in both children (6–11 years) and adolescents of both genders. As of 2011–2012, obesity is now more common among adolescents (20.3% among males, 20.7% among females) than children (16.4% among males, 19.1% among females). The patterns among preschool-age children are more complex. In the 1980s and 1990s, the prevalence of obesity increased among preschool-age females, but not males. However, the prevalence in 2011–2012 is higher among males (9.5%) than females (7.8%). It is unclear what explains this gender difference in prevalence over time.

RACE/ETHNIC GROUP DIFFERENCES

There are large differences in the prevalence of obesity across race/ethnic groups in the United States. Currently, Asian female children and adolescents have the lowest rate of obesity and Hispanic males have the highest prevalence of obesity. Although it should be noted that obesity rates are higher among some subpopulations of Asians (i.e., those from Korea and India). Research documenting differences among Hispanics of different origins (i.e., from Mexico vs. Puerto Rico) is lacking. In the 1960s, obesity rates were higher among white (14.4%) than black (9.3%) adolescent males. Among the adolescent females, whites (8.3%) and Hispanics (8.7%) had similar prevalence of obesity, which was lower than the prevalence among black females (14.4%). The issue of race/ethnic differences is described in more depth in Chapter 2.

Race and ethnic differences in obesity may reflect differences in rates of poverty and living in economically depressed neighborhoods. Although the results of studies examining the associations between socioeconomic status (SES) and obesity in youth are mixed, studies focusing on neighborhood or community-level indicators of economic deprivation and hardship have had more consistent findings. For example, among fifth-, seventh-, and ninth-grade schoolchildren living in Los Angeles County, the prevalence of obesity was approximately 27% among those from the highest quartile of community economic hardship, but only 12.5% among those from the lowest quartile. Moreover, using the 2001–2010 NHANES data, Rossen found that after controlling for levels of neighborhood deprivation, African American youth were no longer significantly more likely to be obese. The reduction in association was not completely due to differences in SES since she found that higher SES was only protective for youth living in areas with low levels of neighborhood deprivation. These results suggest that African American youth are more likely than white youth from a similar SES to live in high deprivation communities with minimal resources.
RISK FACTORS

Despite a plethora of studies, relatively few factors have consistently been prospectively linked to the development of overweight or obesity. This reflects several issues. First, except for factors that do not change over time, such as race, one cannot draw any inference from cross-sectional studies. Second, many prospective studies measured dietary intake and physical activity using methods with considerable error. Third, many prospective studies using state-of-the-art diet and activity assessments are relatively small and underpowered. Fourth, obesity is a heterogeneous condition and it is unlikely that more than a few factors are risk factors for all types of obesity. Therefore, analyses predicting overall obesity may end up obscuring risk factors that are not associated with all types of obesity.

DIETARY INTAKE

It is widely accepted that dietary intake must be related to weight gain and the development of obesity. However, other than sugar-sweetened beverages and fast food,9,10 few dietary factors have been consistently linked to obesity and the complications of obesity. A brief overview of the important findings and issues is presented here, and more details of other specific dietary contributions relevant to child obesity are covered in Chapters 6 through 11. Although there are numerous cross-sectional studies on associations between dietary intake and obesity, one cannot draw any inference on the temporal order of the association or whether the diet before the person became overweight was the same as the current diet. Thus, one must rely on prospective observational studies and clinical trials to understand how dietary intake is related to the development of obesity.

Some studies, primarily in adults, have suggested that dietary fat is predictive of weight gain and obesity, but most have not controlled for total calories. It is therefore unclear whether the association is due to fat per se or the fact that there are more calories per gram of fat than protein or carbohydrate. The results for low-glycemic load diets are also mixed.11,12 There have been few clinical trials and the results have not consistently observed that a low-fat or low-glycemic load diet is superior to other dietary strategies for weight control in children or youth.12,13

Although it is widely believed that increasing fruit and vegetable intake should protect against weight gain and the development of obesity, there is little empirical support for a protective effect. Vegetable consumption was unrelated to weight gain among elementary schoolchildren14 and adolescent girls in the National Growth and Health Study,15 or the Growing Up Today Study,16 as well as among adult women in the Women’s Health Study.17 The results have been more mixed for fruit intake, with some studies finding a protective effect15,17 and others finding no association.16 There are several possible reasons for the lack of a consistent protective effect. First, children may need to consume high levels of fruits and vegetables to their diet rather than substituting them for less healthy foods, and thus fruit and vegetable intake might be positively related to total caloric intake. Third, youth may be consuming their fruits and vegetables in high calorie preparations. For example, salads with cheese, lots of salad dressing, and bread products (i.e., croutons, tortilla strips, etc.). Fourth, fruits and vegetables may be part of a heart-healthy diet but unrelated to weight change.

It is possible that few dietary predictors of obesity have been identified because there have been relatively few large prospective studies of children or youth and there has been considerable measurement error in diet assessment methods used in those studies. A further complicating factor is that dietary intake is related to both normal growth and development and obesity during childhood and adolescence, thus making it particularly difficult to identify dietary predictors of excessive weight gain in youth.

DISORDERED EATING

As many as 24.7% of female and 8.3% of male youth report having eating episodes where they felt like they could not stop eating, even if they wanted to stop.18 These episodes are described as loss
of control (LOC) eating. If the amount of food consumed is large in a short amount of time, the episodes are considered eating binges. In both children\textsuperscript{19} and adolescents,\textsuperscript{20} LOC and binge eating are robust predictors of weight gain and the development of obesity. Among adults in weight loss trials, eating binges tend to reduce in frequency as weight is lost. This association has not been studied in children or adolescence.

The definition of binge eating, which requires LOC episodes where a large amount of food, larger than most people would eat in similar circumstances, is consumed in a short amount of time, makes it a difficult topic to study in adolescent males. Since adolescent males tend to eat very large quantities of food, it is hard to define what is abnormally large. Thus, there is likely considerable misclassification in observation studies of binge eating, which could bias the results toward the null.

Many cross-sectional studies have reported higher rates of emotional eating and eating in the absence of hunger among overweight and obese youth, but these associations have not been studied prospectively. However, self-reports of dieting to control weight have been found to predict BMI gain in both children\textsuperscript{21} and adolescents.\textsuperscript{22} Dieting is associated with binge eating and higher BMI z-scores, but the association with BMI change is independent of both these factors. It should be noted that self-reports of dieting do not necessarily mean that the individual is making a meaningful reduction in energy intake, rather it should be thought of as a proxy for concern with weight and taking some action to control weight.

**Physical Activity**

Although increasing physical activity is a public health goal and included in many obesity prevention interventions, there is a surprising lack of empirical support for activity protecting against weight gain. An exception would be the International Study of Childhood Obesity, Lifestyle and the Environment (ISCOLE), which found that high levels of moderate and vigorous physical activity were strongly inversely related to obesity.\textsuperscript{23} However, data from prospective studies found a much smaller effect of activity on prevention of weight gain. Among adults it is generally found that activity is necessary for weight loss maintenance. A very high volume is needed to prevent weight gain in adults.\textsuperscript{24} Most youth decrease their activity level as they age and interventions have had limited success at increasing activity.\textsuperscript{25} Both the Pathways Study\textsuperscript{26} and the Trial of Activity for Adolescent Girls\textsuperscript{25} found that increases in activity predicted lower percentage of body fat at follow-up, but not BMI change or incidence of overweight and obesity. It is possible that the lack of protection against BMI gain and the development of obesity is due to insufficient volume of activity. An alternative explanation is that physical activity may result in decreases in fat mass/increase in lean mass but no change in weight. Since BMI cannot distinguish between lean and fat mass it is a suboptimal outcome measure to employ in studies examining the impact of physical activity. In addition, there is considerable measurement error in many of the activity assessments, other than accelerometers and other methods that directly measure activity, that would make it more difficult to observe a protective association with physical activity. For more details on the role of physical activity interventions to treat or prevent childhood obesity, see Chapter 35.

**Environment**

In the past decade, there has been a growing interest in the impact of the neighborhood and school environment on obesity and obesity risk behaviors. The built environment refers to man-made structures (including fast-food outlets, street design, etc.), green spaces, and parks. Most of the research on the impact of the environment has focused on the toxic food environment, road connectivity, the presence of sidewalks, and green space. More recently, there has been recognition that the social environment can also influence behaviors. The results have not been consistent, but the results do suggest a small impact of the built environment.\textsuperscript{27,28} Many cross-sectional studies have examined
how residential density, distance to or number of parks and green space or food outlets, and street connectivity are related to diet, physical activity, and obesity in youth. One of the largest cross-sectional studies examined associations among 122,118 youth in the United States and found that BMI percentile was positively associated with the number of fast-food outlets and grocery stores and inversely related to the number of parks and fitness centers. However, one needs to be cautious when interpreting cross-sectional studies on the built environment since BMI is inversely related to SES and SES is positively related to more green space. Unfortunately, there have been relatively few prospective studies. However, Epstein et al. studied children who had been in one of four randomized trials for weight loss. They found that few supermarkets and greater parkland were predictive of bigger losses in BMI z-score at 24 months regardless of clinical trials in which they had participated. Another small prospective study found that greenness, but not residential density, was predictive of changes in BMI z-score.

The studies on relationships with food outlets are more mixed. Studies have observed inverse cross-sectional associations between obesity and the number of or proximity to fast-food outlets and convenience stores. Although it was initially thought that more large grocery stores, rather than bodegas and convenience stores, were needed in urban environments with high obesity rates, recent studies have found that the closer a child lives to a large grocery store, the higher his or her BMI will be. Unfortunately, relatively few prospective studies have been conducted. However, one prospective study of 353 adolescent females found that having a convenience store within a 0.25 mile buffer of their residence predicted higher odds of being overweight or obese at the 3-year follow-up and a greater increase in BMI. Most studies have examined the impact of the neighborhood environment, but among adolescents, the environment around their schools may be at least as important as the environment where they live. However, it has been much less studied.

As of 2015, three-quarters of 13- to 17-year-olds reported having or having access to a smartphone. Since smartphones are equipped with global positioning system (GPS) technology, future studies of the built environment will be able to use individual-level GPS information to more accurately classify built environment exposures of adolescents and will allow for testing assumptions about the relative distance from home or school that exert an influence on youth behaviors. For further information on the role of the built environment in childhood obesity, see Chapter 17.

Sedentary Time

Time spent engaged in sedentary behaviors, particularly watching television, is the most robust behavior predictor of weight gain and the development of obesity. Children with televisions in their bedroom have been found to watch more television and gain more weight. Numerious epidemiologic studies have found that the more time a child or adolescent spends watching television, the more weight he or she gains and the more likely he or she is to become obese. Several different mechanisms have been proposed for this association, but it does not seem to be due to television time replacing time spent being active. In both epidemiologic and clinical studies, decreases in television viewing, regardless of whether they are coupled with increases in physical activity, are predictive of less weight gain or weight loss.

The mechanism with the strongest empirical support is that the advertisements on television, which are mostly for foods high in sugar and fat and low in nutritional value, cue people to eat while watching television regardless of whether they are hungry. They are also cued to eat these advertised foods at later times as well. Falbe et al. found that among adolescents, increases in screen time, particularly television time, predicted increases in intake of fast food, sugar-sweetened beverages, and salty snack foods. The findings are even stronger among younger children. Nickelodeon, the Cartoon Network, and Disney (until 2015) channels, which are very popular with children and adolescents, show many advertisements for fast food, sugar-sweetened beverages, and sugary cereals. In fact, Nickelodeon and the Cartoon Network have partnerships with food and beverage companies, such as the Burger King Corporation and PepsiCo. Thus, it is not surprising that more
than 70% of the food advertisements on Nickelodeon are for fast food. The advertising pays off for these companies. Robinson et al. asked 63 preschool-age children to taste five sets of identical foods, one in McDonald’s packaging and the same food in unbranded food packaging. The children were asked which one tasted better or if they tasted the same. Despite being the exact same food, such as carrots, the item in the McDonald’s packing was perceived as tasting better. Thus, the children had been taught that foods from McDonald’s are desirable. For more information on the role of advertising and marketing in childhood obesity, see Chapter 42.

**Sleep**

Children who sleep less have been found to consume more calories and gain more weight than their peers who get more hours of sleep. The associations with sleep are observed at multiple ages in childhood. For example, Gillman et al. found that infants who slept less than the recommended 12 h per day were almost two times more likely to be overweight at age 3. Moreover, the gain is in fat mass, not lean mass. Among adolescents, reasons for suboptimal sleep duration include screen time, being woken by a cell phone, and early start time for high school. The issue of sleep and childhood obesity is covered in more detail in Chapter 28.

**CONCLUSION**

During the past several decades, obesity rates in the United States have increased dramatically among youth, but the rates are now declining slightly among preschool-age children. It remains to be seen whether the decline among preschool-age children and the plateauing among 6- to 11-year-olds is a real change or just part of the natural fluctuation in rates. The still increasing rates among older youth are a cause for concern, as are the racial, ethnic, and neighborhood-characteristic disparities in obesity. Although it is widely accepted that genetics, dietary intake, physical activity, and screen time all contribute to the risk of excessive weight gain and the development of obesity, relatively few risk factors have been consistently identified across studies. There are several reasons for the lack of robust predictors. To study associations with factors that change over time, such as dietary intake, physical activity, sleep patterns, and screen time, one needs prospective data from clinical trials or observational studies. Unfortunately, the majority of the published papers on factors associated with childhood obesity have used a cross-sectional design. Moreover, until recently, many studies used self-report measures of dietary intake and physical activity that had considerable measurement error, thus making it harder to identify associations. Another reason for the lack of identifying robust predictors of obesity is that in children one must disentangle healthy from unhealthy weight gain, which is very difficult, particularly since dietary intake can promote both healthy and unhealthy weight gain.

The next generation of epidemiologic research on pediatric obesity should include the use of new technology that will allow for precise measures of the environment, dietary intake, and physical activity. The inclusion of electronic medical information would also greatly enhance studies. Some of these methods have been developed, but many more will need to be developed and validated for use in epidemiologic samples. Future studies should also be advised to consider obesity as a heterogeneous disease and to identify risk factors for subtypes of obesity.

**REFERENCES**


Racial and Ethnic Disparities in Prevalence of and Risk Factors for Childhood Obesity

Claudia M. Toledo-Corral

INTRODUCTION

Diversification of race and ethnicity in the United States continues to evolve and it is now projected that by 2050 non-Latino Caucasians will no longer be the majority [1]. These estimates show that the fastest migration rates will arise from Latino and Asian countries but Latinos will compose the largest racial and ethnic group [1]. Due to this racial and ethnic population shift, any existing health disparities are of increasing concern in public health and medicine. As a prime example, the rates of obesity in US children, adolescents, and adults are more pronounced in racial and ethnic groups such as Blacks and Latinos [2,3]. The risk of obesity and metabolic disease is also increasing in the Asian population, which has gone unnoticed due to the misclassification of obesity using the current body mass index (BMI) cutoffs [4]. The projected population increase in each of these racial and ethnic groups, coupled with current pediatric obesity rates in the United States, has severe implications for adult health disparity burdens including obesity and overt cardiometabolic disease.

The racial and ethnic inequalities in risk factors associated with childhood obesity can be explained as unique products of multifactorial determinants. Using the multicausational model of chronic disease (Figure 2.1), these layers are (1) inherent risk factors, such as genetics and predispositions affecting biological mechanisms; (2) culturally associated behaviors specific to body image, diet, and exercise routines; and (3) the environmental context, including socioeconomic status (SES) and the environment, which can either foster or inhibit health behaviors. Each of these risk layers can interact and have synergistic effects on childhood obesity risks. For instance, inherent risk factors intersect the behavioral and environmental components of the model, illustrating the interdependency of all three layers (Figure 2.1). Children of certain racial and ethnic groups are not only affected by multiple risk factors, but may also have more inherent risk due to poor maternal health via fetal programing (Figure 2.2). This combination of environment and genetic risk factors reflects the importance of multifaceted public health preventive measures at a family level to combat childhood obesity. As described in this chapter, racial and ethnic groups are increasingly exposed
As public health researchers and officials, we must consider the differences in inherent genetic or biological mechanisms, in conjunction with culturally rooted behavioral choices in environments that support and sustain gene–behavior interactions. However, categorizing race and ethnicity has numerous challenges as terms are constantly evolving and are often used interchangeably or imprecisely [5]. For US census and other government purposes, race is predominantly used for grouping individuals into populations based on observable features including skin color, facial qualities, body composition, and other inheritable traits. Ethnicity is used to group by cultural characteristics including, but not limited to, historical background, language, geographical ancestry, religious
beliefs, and dietary traditions and preferences. For the purposes of this chapter, the race and ethnic categories of Asian (including Pacific Islanders), Black, non-Latino Caucasian, Latino (Caucasian), and Native American will be used, unless otherwise listed as a specific group.

**BACKGROUND: PREVALENCE RATES AND ASSOCIATED CONSEQUENCES**

The trends over the past decade show a stabilization of obesity rates in children (≥95th BMI percentile per Centers for Disease Control [CDC] year 2000 growth curves); however, racial/ethnic disparities in childhood obesity rates are evident [2,3]. Specifically, the 2011–2012 National Health and Nutrition Examination Survey (NHANES) data revealed significant ethnic differences in childhood obesity prevalence: rates were lowest among Asian (8.6%) and non-Latino Caucasian children (14.1%) compared with Black (20.2%) and Latino children (22.4%) [2]. With the exception of Asians, at least 70% of the obesity prevalence was composed of children in the ≥97th BMI percentile, indicating that extreme obesity is overwhelming in these populations. In addition, 12-year US trends (1999–2010) revealed that Black and Latino children had 27% and 99% higher odds of developing obesity compared with Caucasian children [3]. Moreover, Black and Latino obese adolescents were most likely to suffer from persistent obesity (extreme or otherwise) [6]. These extreme disparities in childhood obesity rates were carried into adulthood: 90% of US obese adolescents in 1996 remained obese into the second and third decade of life [6].

Increased childhood obesity rates coincide with similar increases in cardiometabolic sequelae, such as type 2 diabetes, atherosclerosis, and fatty liver disease, in children (see Chapters 25 through 28). Overt disease in children is rare, but subclinical diseases, such as metabolic syndrome (MetS) and nonalcoholic fatty liver disease (NAFLD), show disparate rates by race and ethnicity [7,8]. For instance, MetS is a constellation of three or more risk factors including abdominal obesity, hyperglycemia, hypertension, and dyslipidemias [9]. Between 2001 and 2010, MetS affected approximately 10% of the overall US pediatric population, but Latino children and adolescents had the highest rate of 14% [7]. The most defining feature among Latino children with MetS was a high prevalence (21%) of impaired fasting glucose (defined as ≥100 mg/dL), suggesting early development of type 2 diabetes. The prevalence of type 2 diabetes in US youth remains low (<1%) in all racial and ethnic groups but it is still highest among Native American, Black, and Latino youth between the ages of 15 and 19 years [10]. Rates of subclinical liver disease in children also vary by race and ethnicity. A unique autopsy-based study in youth reported that the prevalence of NAFLD (≥5% of hepatocytes contained macrovesicular fat) was highest among Latinos (11.8%), followed by Asians (10.2%), non-Latino Caucasians (8.6%), and Blacks (1.5%) [8]. Interestingly, MetS, NAFLD, and obesity can coincide more often in some racial and ethnic groups or can be found independently. As an example, rates of obesity, MetS, and NAFLD are highest in Latinos while Asians have lower levels of overall adiposity yet suffer from higher rates of NAFLD. To fully elucidate this racial and ethnic differences in cardiometabolic disease, further study on body composition, genetics, and metabolic adaptation to a Westernized diet is needed.

**BODY COMPOSITION AND FAT DISTRIBUTION**

In children, the applied use of BMI percentiles using age and sex-specific growth curves from the Centers for Disease Control and Prevention (CDC) is the simplest form of obesity assessment; however, this method has significant limitations as discussed in Chapter 1. Currently, the 2000 CDC growth curves cannot fully characterize extreme obesity as the cutoffs used for evaluation did not include a percentile beyond the 97th due to sparse data available prior to the obesity epidemic (pre-1990s). Additionally, these data were based largely on Caucasian children, which led research and public health officials to question their applicability to specific racial and ethnic groups since BMI trajectories do not account for ethnic differences in body composition. In both children and adults, the predictive value of BMI as a true measure of body fat varies between racial groups.
For example, data suggest that higher BMI thresholds for overweight and obesity should be set for Black populations, largely due to higher percentages of fat-free mass compared with other racial/ethnic groups [11]. For the Asian population, there has been ongoing discussions regarding the lowering of the thresholds for obesity diagnosis, yet no consensus has been reached [4]. Despite this, the American Diabetes Association (ADA) recently made a significant revision to its Standards of Medical Care in Diabetes, specifically with regard to screening for type 2 diabetes in Asian adults by lowering the BMI threshold for diabetic screening from 25 to 23 kg/m² [12]. The recommendation was supported by studies in Asians showing higher levels of visceral fat and onset of metabolic disease at lower BMI [4,13]. Collectively, recent data show that existing use of the non-race-specific BMI cutoffs may lead to either misclassification of obesity and/or lack of screening for obesity-related disease in specific racial and ethnic groups. Although no recommendations were made in the pediatric diagnosis of early diabetic disease risk, we can extrapolate that similar indications should be considered for youth.

In addition to the use of BMI, more robust measures of adiposity have been employed in numerous research studies that assess actual body fat percentage as well as body fat distribution using dual x-ray absorptiometry (DEXA) and magnetic resonance imagine (MRI) scans. These studies reveal that racial disparities in cardiometabolic disease are not necessarily a consequence of overall obesity but instead the distribution of fat depots [14–16]. In children and adults, studies have shown that increased abdominal adiposity and high prevalence of NAFLD are more common in Latino and Asian populations [8]. Interestingly, despite the low overall US obesity rate in Asian youth, fatty liver is highly prevalent; a finding that contributed to the lower BMI threshold for diabetes screening in Asian populations [12]. Other race and ethnic differences in fat distribution include intramyocellular lipid (IMCL), or fat found within skeletal muscle. Specifically, IMCL has been shown to be greater in Black and Latino youth than in Caucasians, even after controlling for total body fat [17]. These major differences in body fat distribution by ethnicity have also been associated with disease risk. Abdominal and ectopic fat distribution, such as liver, pancreatic, and muscle fat depots may explain racial differences in obesity-related disease via different underlying pathophysiology associated with each fat depot. These include unique biological mechanisms such as adipose tissue inflammation and nonesterified free fatty acid metabolism [15]. Briefly, abdominal adipose tissue in youth, specifically visceral adiposity, has been associated with markers of insulin resistance. Higher liver fat has been related to lower insulin sensitivity in both Black and Latino youth; however, Black youths’ metabolism appears to be more sensitive to liver fat compared with Latino youth [14,16]. In addition to this finding, another ectopic fat depot, pancreatic fat, has been associated with prediabetes in Black adolescents [16]. To date, there is no definitive study to show that IMCL independently contributes to metabolic risk, but it may be a contributing factor as this form of ectopic fat deposition may have large effects on insulin sensitivity [18]. An examination of each of these fat depots is warranted in future studies to further clarify the ethnic-specific differences in adiposity and fat depots, and their contribution to metabolic disease.

MATERNAL RISK FACTORS DURING PRENATAL AND POSTNATAL/INFANCY PERIODS

Maternal health during the prenatal period can have profound consequences on infant growth and development as overweight and obese mothers are more likely to have obese children [19,20]. This is discussed in more detail in Chapter 12, but is introduced here as it pertains to ethnic differences. The emerging literature supports the notion of early-life programing, which is dependent on the intrauterine environment, maternal genetics, behaviors, and environment [19]. Maternal obesity, excessive gestational weight gain, and gestational diabetes mellitus (GDM) are maternal risk factors that vary by race or ethnicity and associate differently with infant birth weight [20]. When considering all three of these maternal risk factors, Caucasian and Latino mothers have nearly twice the odds of delivering an infant with high birth weight [20]. Asian mothers with only two of these risk factors.
Racial and Ethnic Disparities in Prevalence of and Risk Factors for Childhood Obesity

Factors (obesity and GDM) have the highest odds among all ethnicities of delivering an infant with high birth weight. Interestingly, either a high or a low birth weight has been associated with future obesity [21,22]. Of all the aforementioned risk factors, most of the literature supports GDM as an independent prenatal risk factor for future obesity working via intrauterine mechanisms [21,23,24]. Differences by race and ethnicity are evident in recent trends of increasing GDM morbidity, where Latina women showed a 66% increase from 1999 to 2008 in GDM incidence, while Asian/Pacific Islanders had the highest GDM prevalence (6.48%–10.27%) [25]. Offspring born to GDM mothers have exhibited increased levels of abdominal adiposity [26], higher risk for childhood or adolescent obesity [21,23], and even longer-term consequences of higher BMI in adulthood [24]. To further exemplify these findings in a race-specific context, a longitudinal study of overweight and obese Latino children found that offspring exposed to GDM experienced a sharper increase in total body fat during the pubertal transition compared with those without GDM exposure [27]. Collectively, these findings suggest that the ethnic GDM disparity could have profound consequences on Asian and Latino childhood obesity rates and that the intrauterine environment plays an important role in childhood obesity risk.

In addition to the prenatal period, postnatal development is vulnerable to acquired inherent risks, in combination with the mother’s culturally associated rearing behavior and environment. These include rapid infant weight gain, nonexclusive breast-feeding, earlier introduction to solid and/or sugary foods, and fewer than 12 h of sleep [28,29]. An emerging body of data also shows that alterations in infant microbiota from lack of breast-feeding and antibiotic use are associated with childhood obesity [30,31]. Some of these infant-rearing behaviors have been shown to differ by race and ethnicity and by association with childhood obesity [28,29]. Compared with Caucasian children, Black and Latino children were not only more highly exposed to adverse dietary, breast-feeding patterns, and sleep patterns during infancy [28] but these risk factors were also associated with higher BMI z-score at seven years of age [29]. Postnatal exposures (i.e., during infancy), either acting individually or synergistically, may contribute to early programing of dietary preference to sugar, altered circadian rhythms, and altered microbiota that could lead to childhood obesity.

Exposure to pre- and postnatal risk factors are closely linked to cultural practices, acculturation, socioeconomic factors, and urban environment, all of which will be discussed in further detail. In the context of racial and ethnicity disparities, early-life exposures and transgenerational effects are highlighted due to the increased number and severity of obesity risk factors present in Black and Latino mothers. Presumably, these maternal risk factors will increase the inherent risk of the offspring so that their baseline risk is elevated even before birth (Figure 2.2).

**CULTURALLY ASSOCIATED CHOICES INFLUENCING BODY IMAGE, DIET, AND PHYSICAL ACTIVITY**

Parental and child obesity–related behavior choices can be characterized as either those rooted in ethnic/cultural beliefs of the culture of origin or those of the US (Westernized) lifestyle, or a mixture [32,33]. The level of cultural integration and associated behavioral patterns are difficult to tease apart. Therefore, the current review focuses on any adverse behaviors that stem from either traditionally held ethnic practices or Westernized practices.

Parental views on child weight or underestimation of the health consequences associated with obesity may translate to acceptance of obesity in children. These personal and cultural beliefs further
shape parental choices and influence acculturation and adoption of a Westernized lifestyle, which includes a poor diet, lack of physical activity, and increased sedentary behavior. For example, families who are acculturated to the Westernized culture have increased rates of dietary sugar intake: 82% of Black and 74% of Latino children were already exposed to high sugar-sweetened beverages at age two compared to only 45% of Caucasians [28]. Similarly, by four years of age, 66%, 83%, and 88% of Caucasian, Black, and Latino children had some exposure to fast food [28]. This early-life familiarity with sweets and fast foods leads to increased palatability for sweets and fats, and subsequently, increased consumption. Specifically, high dietary intake of sugars can interact with coexisting risk factors—such as genetic susceptibility to obesity and/or disease risk. For example, it has been shown that high dietary sugar intake interacts with the GG genotype of the PNPLA3 gene in Latino children to increase liver fat [38]. At the same time, interactions between high dietary sugar and cortisol levels have also been associated with higher visceral fat in Latino youth [39]. These studies highlight significant health disparities that are partially attributed to the detrimental effects of diet as seen in Latino children whose genetics and high sugar intake amplify risk for obesity and NAFLD. An examination of these gene–behavior interactions has not been done in other ethnicities; however, it has been shown that on average, compared with Caucasian middle-school children, mostly all other ethnic groups, including Native American, Pacific Islanders, Black, Latino, and multiracial children, consumed more sugar-sweetened beverages [40]. Given the existing obesity risk factors already discussed, investigations of potential additive or synergistic effects of multiple risk factors are warranted.

Physical activity and sedentary behavior patterns also vary by ethnicity. Especially in immigrant groups, adolescents are not as likely to engage in sports or intense physical activity [41]. For example, moderate to vigorous physical activity was reported to be highest in non-Latino Caucasian adolescent girls compared with any other racial and ethnic group, with the lowest being in Latina girls [42]. Sedentary behavior such as television viewing has been shown to be more common in Black and Latino children, many of whom are exposed to televisions in their bedrooms [28], with an average of more than 3 h a day of television screen time [42]. Given these findings, comprehensive studies are necessary to delineate the independent and interactive effects of diet and physical lifestyle, specific cultural practices by ethnicity, and other community-level factors.

SOCIOECONOMIC STATUS AND ASSOCIATED ENVIRONMENTAL BURDENS

When addressing the racial/ethnic disparities in childhood obesity prevalence rates, low SES and associated environmental burdens cannot be overlooked. In general, low SES groups typically have little or no access to higher-quality resources and this results in poor lifestyle choices and increased disease risk [43]. Specifically, low-SES neighborhoods are burdened by neighborhood deprivation, which is characterized by scarce resources and an obesogenic environment (e.g., liquor stores, industry, lack of green space) [44,45]. These neighborhood environments have limited food choice and availability, as well as limited accessible areas for physical activity (see Chapter 17). Moreover, limitations on food access and recreation contextualize and breed obesogenic behaviors. In the United States, many racial and ethnic groups at high risk for obesity are gathered in low-SES areas, possibly accounting for the racial disparity in obesity rates. Specifically in youth, several studies have examined the contributions of race and ethnicity and socioeconomic factors. Longitudinal studies found that the disparity in adolescent obesity between Black and/or Latino versus Caucasian youth was not entirely explained by race, but instead by economic contextual factors, household demographics, and individual SES [41,46]. Interestingly, others have reported that while economic hardship was a defining factor for high childhood obesity rates in Caucasian Latino, and Asian children, in Black children this relationship was attenuated [47]. Differential effects of individual-level SES on childhood obesity, independent of contextual factors, have also been observed. For example, in a study of Caucasian and Black children followed from kindergarten to eighth grade, a higher baseline BMI z-score was associated with a higher SES in Black
male students and a lower SES in Caucasian male students [48]. This study exemplifies how individual versus neighborhood SES may play a smaller role in Black children, possibly due to other stronger risk factors, such as cultural beliefs and behaviors about body image [37]. Based on these studies, low SES on the individual level and/or the neighborhood level has adverse effects on childhood obesity by race and ethnic group and should be considered when holistically examining childhood obesity risk. A more detailed review of economic factors associated with disparities in childhood obesity is provided in Chapter 4.

Low-SES communities also suffer from increased environmental injustices exposing residents to disproportionate burdens of chemical exposures and social–environmental stressors that contribute to ill health, including obesity [49]. Although this is discussed in further detail in Chapters 18 through 20, this topic is briefly covered in this chapter as it pertains to the childhood obesity risk in low-SES minority children residing in urban environments. Toxic chemical exposures in the air, soil, and water have only recently been implicated as possible determinants in childhood obesity. Although the mechanisms behind how pollutants contribute to childhood obesity are not well understood, there is a consensus that exposures during early development may have the biggest impact on obesity during childhood. For example, one study found that compared with maternal exposure in the lowest tertile of ambient air polycyclic aromatic hydrocarbons (PAH), maternal exposure in the highest tertile carried a greater relative risk of 2.26 for offspring obesity at seven years of age [50]. In a separate study of children 6–18 years of age, increased PAH metabolites from urine were independently associated with higher BMI and waist circumference, and simultaneous exposure to environmental tobacco smoke further increased obesity risk [51]. Finally, a longitudinal analysis from the Children’s Health Study (CHS) found that maternal smoking during pregnancy predicted increased BMI in children and interacted with in utero air pollution exposure [52]. At the same time, additional findings from the CHS found that vehicular traffic contributed to higher BMI in children [52,53]. This modest body of evidence suggests that chemical exposures during prenatal and early life may affect neurological, metabolic, and behavioral alterations that may increase metabolic vulnerability and obesity.

In addition to environmental pollution exposure, low-SES minority children residing in the urban landscape are chronically exposed to psychosocial burdens that impact stress levels and contribute to obesity risk. Such community-level stressors include violence, noise, and lack of green space and are thought to contribute to mental stress levels by the decreased sense of safety, decreased social interaction, and decreased physical activity [54]. Conversely, quiet and greener neighborhoods lend themselves to increased social interaction and a sense of community among its members. Physiologically, chronic exposure to the community-level psychosocial stress can alter the hypothalamic–pituitary–adrenal axis [54–56]. Consequently, alterations in cortisol concentrations and diurnal patterns have been associated with community stressors including cumulative exposure to violence [54,55] and loss of green space [56], both of which are common in low-SES communities that are composed of largely Black or Latino populations. Collectively, these studies support the current postulations that the physical and social environment contribute and foster obesogenic behaviors, particularly in low-SES neighborhoods.

**SUMMARY/CONCLUSION**

In the United States, racial and ethnic minority children bear a disproportionate burden of multiple childhood obesity risk factors that encompass heritable traits, pre- and postnatal exposures, culturally associated habits and behaviors, and lower socioeconomic environments with increased chemical and social stressors. Asian children appear to have more of the inherent risk factors while Black and Latino groups suffer from a constellation of risk factors that are likely interdependent and/or work synergistically to increase obesity risk. Consequently, childhood obesity prevention methods should engage ethnic-specific and/or culturally sensitive interventions that involve family-level and community-level transformation toward a healthy lifestyle.
REFERENCES


INTRODUCTION

The childhood obesity epidemic has become a serious public health problem in many countries worldwide [1–4]. During recent years, the prevalence of overweight and obesity has been increasing dramatically in many developing countries, particularly in urban settings and among high socio-economic status (SES) groups [1–4]. Although current understanding of the health consequences of overweight/obesity is predominately based on adult studies, increasing evidence suggests that childhood obesity has a number of immediate, intermediate, and long-term health consequences, as reviewed in other chapters in this book.

This chapter describes the current prevalence and time trends of childhood obesity worldwide. It also discusses the methods for defining childhood overweight/obesity, the factors that have contributed to the current epidemic, and the large differences in the prevalence across countries and population groups worldwide. Understanding the differences in the methods (e.g., body mass index [BMI] cutoff points) used to define childhood overweight/obesity is important to appropriately interpret the reported results regarding overweight/obesity rates and related risk factors. The related recommendations and practices for defining childhood overweight/obesity are complex and
Childhood Obesity: Causes, Consequences, and Intervention Approaches

inconsistent, and much more complex than those for adults. Recently, the World Health Organization (WHO) has called on country leaders worldwide to exert joint efforts to fight against the childhood obesity epidemic [3]. A broad comprehension of the global childhood obesity epidemic will aid understanding of its causes and guide the development of effective intervention programs and policies to address this threat to public health.

CLASSIFICATIONS OF CHILDHOOD OBESITY

Various measures and references have been used to define overweight/obesity in children and adolescents. This has affected prevalence estimates reported over time as well as across populations and studies, which could result in problems in making comparisons of results across studies and countries. The consensus developed since the 1990s is to use BMI (=weight [kg]/height [m]^2) cutoff points to define overweight/obesity both in adults and in children, as research shows that BMI is a good indirect measure of adiposity [4–9]. However, BMI varies substantially by age and gender during childhood and in adolescence. Thus, unlike in adults, age-gender-specific BMI cutoff points should be used in children and adolescents. For adults, BMI of 23, 25, 27, 28, and 30 kg/m^2 are widely used to define overweight/obesity, respectively [8], and the lower cutoff points are used more in Asian populations than in other populations as research shows that with the same level BMI, some Asian population groups have lower percentage body fat and higher obesity-associated health risks.

Since the 1990s, when more attention became focused on childhood obesity, different references based on weight-for-height indexes, such as BMI and weight-for-height, skinfold thickness measures, and waist circumference, have been used to classify body weight status for children [4–9]. Applications of these measures varied considerably across studies and countries [4–9]. For example, in the United States, two sets of sex-age-specific 85th and 95th BMI percentiles have been used. Other countries, such as China, France, the United Kingdom, Singapore, and the Netherlands, have developed their own BMI references using local data. The WHO has published different recommended references since the 1990s. The corresponding BMI cutoff points differ considerably. A global reference would help facilitate international comparisons and monitor the global obesity epidemic. A few references (some are called standards) have been developed and recommended for international use, including those endorsed by the WHO and the International Obesity Task Force (IOTF) [5–8], and these are discussed in the next section.

IOTF BMI Reference

The IOTF endorses a series of sex-age-specific BMI cutoff points for children aged 2–18 years for international use [5]. It was developed based on large data sets from six countries: Brazil, Britain, Hong Kong, the Netherlands, Singapore, and the United States. The cutoff points are linked to adult BMI cutoff points, which are established risk indicators for adverse health outcomes. It is also simple to use and consistent for children and adolescents. However, there are also some concerns about the IOTF reference [10]. The concerns include that only six populations were included in the study and there were differences in maturation status within the populations.

The 2006 WHO Growth Standards for Preschool Children

In 2006, the WHO released new growth standards for children from birth to 60 months (five years old) [11]. In order to establish growth standards for different races/ethnicities, the Multicentre Growth Reference Study (MGRS) recruited affluent, breast-fed, and healthy infants/children whose mothers did not smoke during or after delivery from six cities in Brazil, Ghana, India, Norway, Oman, and the United States. These standards included anthropometric indicators such as height-for-age (length-for-age), weight-for-age, weight-for-height (weight-for-length), and BMI-for-age. A BMI z-score ≥2 was recommended to classify “obesity” and a BMI z-score ≥1 to classify “overweight.”
Global Perspectives of Childhood Obesity

The 2007 WHO Growth Reference for School-Age Children and Adolescents

In 2007, the WHO released another set of growth references for children and adolescents aged 5–19 years [12]. To our knowledge, these have not been widely used. The references were derived based on the same US data set as the 1978 WHO/National Center for Health Statistics (NCHS) growth references, but used different growth curve smoothing techniques. The references included three indicators: BMI-for-age, weight-for-age, and height-for-age. Overweight/obesity cutoff points were based on BMI-for-age z-scores. A z-score of 1 was found to be equivalent to a BMI-for-age 25.4 for boys and 25.0 for girls in 19-year-olds. As these values are equal or close to the WHO BMI cutoff points of 25 used in adults, it was recommended to use a z-score of 1 to classify “overweight” and a z-score ≥2 to classify “obesity.” BMI-for-age z-scores <-2 and <-3 were set as the cutoff points for thinness and severe thinness, respectively.

BMI References Used in the United States

Two sets of different BMI 85th and 95th percentiles have been used in the United States to classify children’s weight status. In 2000, the US NCHS and the Centers for Disease Control and Prevention (CDC) updated growth charts using data from five national health examination surveys from 1963 to 1994. The resultant 2000 CDC Growth Charts provided new BMI percentiles [13] and recommended the use of sex- and age-specific 85th and 95th BMI percentiles to classify childhood overweight/obesity, respectively, in children over two years old. Before the release of the 2000 CDC Growth Charts, the sex-age specific 85th and 95th percentiles developed by Dr. Aviva Must and her colleagues, based on the First National Health and Nutrition Examination Survey (NHANES, 1971–1974) data, were used in the United States and many other countries to classify childhood overweight/obesity [6,14]. The BMI cutoff points of the two sets of percentiles differ.

It is worth noting that to examine the time trends in prevalence estimates of overweight/obesity based on BMI cutoff points is useful, but is limited as it cannot reveal details about shifts in adiposity measures or in distribution over time. For example, we examined changes over time in various adiposity measures among US adolescents [15]. Specifically, the measures that we focused on included BMI, waist circumference, and triceps skinfold thickness. We used the NHANES III (1988–1994) and NHANES 1999–2004 data. We found the overall means of BMI, waist circumference, and triceps skinfold thickness increased significantly over time in adolescents (aged 12–19 years) and noted sex differences. During the study period, the overweight/obese US adolescents had gained more adiposity, especially central adiposity as reflected by waist circumference. Our analysis indicates that an examination that solely focuses on changes over time in overweight/obesity rates is unable to capture such complex patterns. However, to our knowledge, little similar research has been carried out to examine the situation for other populations.

Global Prevalence and Trend of Childhood Overweight and Obesity

Numerous data have demonstrated that childhood obesity has become a global public health crisis with, based on the current prevalence, increasing trends and related health consequences. There are still large variations in the rates of overweight/obesity across countries and across population groups within most countries (e.g., by SES, region, ethnicity, and gender) [1,2,16–19]. This is potentially explained by the many related biological, behavioral, social, economic, and environmental factors.

The prevalence is highest in Western and industrialized countries, but is still low in some developing countries, predominately in Africa and Southeast Asia. The prevalence also varies by age, SES, and gender within countries. The WHO Americas and Eastern Mediterranean regions have higher prevalence of overweight/obesity (30%–40%) than the European (20%–30%), Southeast Asian, Western Pacific, and African regions (10%–20% in the latter three). It is estimated that
about 43 million children (35 million in developing countries) were overweight or obese, and 92 million were at risk of overweight in 2010. The global overweight/obesity prevalence has increased dramatically since 1990, for example, in preschool-age children, from approximately 4% in 1990 to 7% in 2010. If this trend continues, the prevalence may reach 9% or 60 million people in 2020. However, some research also indicates that in some European countries and for some young children populations in the United States, the prevalence of childhood overweight/obesity has leveled off or shown signs of declining [20]. This may be due to the efforts made in those countries to address the epidemic.

**Recent Prevalence and Large Between-Country Differences**

Available data show that the combined prevalence of overweight/obesity (briefly called combined prevalence) is substantial in many regions and countries around the world, but large variations exist. Our previous study that projected the combined prevalence for 2006 yielded a range from 17% in Southeast Asia to 40% in the Americas [1]. In general, combined prevalence is much higher in developed countries than in developing countries. There are also considerable age and gender differences in many populations. Based on our estimations and the findings of others, approximately 26% of school-age children in European countries were overweight or obese in 2006 and 5% were obese. In the Americas, these figures were 28% and 10%, respectively.

There are large between-country variations in the prevalence across and within world regions. Combined prevalence is high in Western and industrialized countries, such as the United States, Canada, some European countries, some countries in South America, some nations in the Middle East, some nations in North Africa, and in the Asia-Pacific region (e.g., in Indonesia and in New Zealand) [21]. According to a recent study examining combined prevalence by WHO region [21], the region of the Americas (approximately 25%–30%) and the Eastern Mediterranean region (approximately 20%–40%) had higher prevalence than the Southeast Asian and Western Pacific regions including nations such as India, Malaysia, Vietnam, China, Australia, South Korea, and Japan. In contrast, the WHO African region had the lowest prevalence rate (about 10%). There were also differences between countries within the same WHO region. In the Eastern Mediterranean region, the combined prevalence in Egypt and Kuwait was about 30% and 45% among girls, respectively, while the prevalence was only 14% among Iranian girls. Self-reported information in a 2001–2002 international school survey of 11-, 13-, and 15-year-olds from 35 countries in Europe and North America (n = 162,305) showed large variations in the adolescent overweight prevalence in these countries, which ranged from 3.5% in Lithuanian girls to 31.7% in boys from Malta [21].

**Time Trends in the Prevalence of Childhood Obesity**

Substantial data have been collected in many developed countries over the past two decades allowing for the examination of time trends of obesity in both adults and young people, but data are limited for developing countries. Nonetheless, some studies have examined the trends over time worldwide [1,17–19]. We studied the global trends in childhood obesity based on data from approximately 70 countries [1]. We found the combined prevalence of overweight/obesity had increased in almost all countries for which data were available. Russia and Poland during the 1990s were exceptions to this trend. From the 1970s to the end of the 1990s, the combined prevalence doubled or tripled in several large countries in North America (i.e., Canada and the United States), the Western Pacific Region (i.e., Australia), and Europe (i.e., Finland, France, Germany, Italy, and Spain).

A recent comprehensive study estimated the global, regional, and national prevalence of overweight/obesity in children and adults during 1980–2013 using data collected from a large number of countries [17]. It reported that the prevalence had increased substantially in children in developed countries: in 2013, 23.8% (22.9%–24.7%) of boys and 22.6% (21.7%–23.6%) of girls were overweight or obese. The figure had also increased in children and adolescents in developing countries.
between 1980 and 2013: for boys from 8.1% (7.7%–8.6%) to 12.9% (12.3%–13.5%); and for girls, from 8.4% (8.1%–8.8%) to 13.4% (13.0%–13.9%). A large variation in the prevalence across countries was observed. The study concluded that obesity had become a major global health challenge, and no national success stories had been reported in the past three decades. Urgent global actions are needed to help countries to effectively intervene. The study’s conclusions are consistent with those from our previous study based on findings from approximately 70 countries, which reported the trend and variation in obesity and overweight rates across countries and also projected that the prevalence of childhood obesity would continue to increase if no effective programs were implemented [1].

Another recent study examined time trends in the combined prevalence in preschool-age children aged 0–5 years from 1990 to 2010 and projected worldwide rates for 2015 and 2020 (Table 3.1) [18]: 43 million children (35 million in developing countries) were estimated to be overweight or obese in 2010, and 92 million were at risk of overweight. This represents an estimated increase in global combined prevalence from 4.2% in 1990 to 6.7% in 2010. If such trends continue, these numbers

<table>
<thead>
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<tr>
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<td>8.8</td>
<td>9.7</td>
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<td>7.6</td>
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<td>7.0</td>
<td>6.5</td>
</tr>
<tr>
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<td>2.9</td>
<td>3.8</td>
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<tr>
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<td>3.4</td>
<td>3.7</td>
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<tr>
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<td>5.6</td>
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</tr>
<tr>
<td>Western</td>
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<td>10.1</td>
<td>14.7</td>
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</tr>
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<td>6.9</td>
<td>6.9</td>
<td>7.0</td>
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<tr>
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<td>4.6</td>
<td>5.1</td>
<td>5.6</td>
<td>6.2</td>
<td>6.9</td>
<td>7.6</td>
<td>8.3</td>
</tr>
<tr>
<td>Central America</td>
<td>4.8</td>
<td>5.3</td>
<td>5.9</td>
<td>6.5</td>
<td>7.2</td>
<td>8.0</td>
<td>8.8</td>
</tr>
<tr>
<td>South America</td>
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<td>7.7</td>
<td>7.4</td>
<td>7.1</td>
<td>6.8</td>
<td>6.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Oceania^</td>
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<td>3.1</td>
<td>3.2</td>
<td>3.3</td>
<td>3.5</td>
<td>3.6</td>
<td>3.8</td>
</tr>
</tbody>
</table>


Note: All surveys included both boys and girls. Cross-sectional data on the prevalence of overweight and obesity were obtained from national nutrition surveys. A total of 450 nationally representative surveys were available from 144 countries. Of the 450 surveys, 413 were conducted in developing countries and 37 in developed countries. About 38% of the surveys (171 surveys) were conducted between 1991 and 1999, 16% (70 surveys) were conducted before 1991, and 46% (209 surveys) after 1999. Linear mixed-effects models were fit to estimate prevalence rates and numbers of affected children by region from 1990 to 2020. Overweight and obese statuses were defined based on >2 SDs (standard deviations) from the weight-for-height median.

^ Including Europe, North America, Australia, New Zealand, and Japan.
^ Excluding Japan.
^ Excluding Australia and New Zealand.
may reach 9.1% (or approximately 60 million children) in 2020. For developing countries alone, the combined prevalence was estimated at 6.1% in 2010 and is expected to rise, perhaps as high as 8.6% by 2020. Rates in 2010 were lower in Asia than in Africa (4.9% vs. 8.5%), but a much larger number of children are affected (17.7 million vs. 13.3 million) in Asia compared with Africa. The study concluded that effective interventions starting as early as infancy were necessary to reverse anticipated trends.

In some developing countries, the prevalence of child overweight/obesity has increased tremendously over the past two decades, with the combined prevalence within some subregions and population groups reaching levels of prevalence on par with some industrialized countries. This is especially the case in countries that are in the midst of rapid social economic transitions such as China, Brazil, and Mexico. China, in particular, is illustrative of dramatic increases in obesity and overweight prevalence that outpace rates observed in industrialized countries. The next section provides two examples of the largest developed and developing countries in the world, the United States and China.

**Trend in the United States**

Since the late 1970s, the prevalence of overweight/obesity (BMI ≥85th percentile) in children has increased for all ages between 2 and 19 years, but the increase in obesity (BMI ≥95th percentile) leveled off in some age groups in recent years [22–24]. Between NHANES II (1976–1980) and 2003–2004, the average annual rate of increase in obesity prevalence was approximately 0.5% in children aged 2–19 years [22]. During this period, the prevalence of overweight only increased from 7.2% to 13.9% in children aged 2–5 years, but almost tripled in children aged 6–11 years (from 6.5% to 18.8%). In adolescents (12–19 years), the prevalence more than tripled, increasing from 5.0% to 17.4%. In contrast, data from NHANES 2007–2008 show a decrease in the prevalence of obesity among children aged 2–5 years, from 13.9% in NHANES 2003–2004 to 10.4%. During the same time period, the prevalence in both children aged 6–11 years and adolescents was only slightly increased. In 2009–2010, the national prevalence of obesity (16.9%) was similar to that in 2007–2008; and it was 12.0%, 18.0%, and 18.4% in children aged 2–5, 6–11, and 12–19 years, respectively [23]. In 2011–2012, 8.1% of infants and toddlers had high weight for recumbent length, and 16.9% of 2- to 19-year-olds were obese. A more recent study reported that there was no significant change from 2003–2004 through 2011–2012 in high weight for recumbent length among infants and toddlers and obesity in 2- to 19-year-olds [24].

**Trend in China**

Good nationally representative data collected in China have allowed for the examination of national time trends in childhood obesity [25,26]. Data from large nationwide school–based surveys showed that by 2005, the combined prevalence in urban areas reached 32.5% in boys and 17.6% in girls aged 7 years or older [26], which was similar to that in some industrialized countries. The Chinese National Survey on Students Constitution and Health Association has conducted these surveys every five years since 1985. Remarkably, the combined prevalence of overweight/obesity in boys and girls has increased approximately 10-fold since 1985, and is currently about 15%.

**FACTORS THAT HAVE CONTRIBUTED TO THE GLOBAL CHILDHOOD OBESITY EPIDEMIC AND THE LARGE VARIATIONS IN THE PREVALENCE AND TRENDS ACROSS COUNTRIES**

Obesity is a result of positive energy balance (=energy intake > energy expenditure), while many factors affect people’s eating and physical activity (PA). The factors are more complex for children than for adults due to the many differences between them [3,4,27]. These global patterns of the obesity epidemic (e.g., consistent increasing trends in a large number of countries, large variations in the prevalence and in the increasing trends across countries, and decline or leveling off in some developed countries) also provide useful insights into the causes of the problem.
Global Perspectives of Childhood Obesity

The increase in childhood obesity worldwide is a result of many changes in society due, in particular, to social and economic development and policies in the areas of agriculture, transport, urban planning, the environment, food processing, distribution and marketing, and education. These factors have contributed to unhealthy eating, lack of PA, and increasing sedentary behaviors in children, which result in excessive weight gain. There has been a global shift in diet toward increased intake of energy-dense foods that are high in fat and sugars but low in other healthy micronutrients and a trend toward decreased PA levels due to the increasingly sedentary nature of recreation activities, changing modes of transportation, and urbanization [3].

Rapid economic development and urbanization have contributed to nutrition transition and thus affected people’s lifestyle (e.g., the shift from under nutrition to over nutrition, energy-dense diets have replaced traditional diets, and sedentary lifestyles) [18]. Many developing countries have experienced rapid economic development and urbanization during the past two to three decades, partially related to the expansion of global trade and the development of technologies.

Over the past decade, there has been a growing interest in studying the impact of environment factors including neighborhood and school environment, on obesity risk and related health behaviors in children. The built environment refers to man-made structures (such as food outlets, grocery stores, street design, green spaces, and parks). Most of the research was conducted in high-income countries; and it has reported some mixed results. It has also been recognized that the social environment can also influence behaviors.

Research shows that time spent engaged in sedentary behaviors, particularly watching television, is positively related to weight gain and the development of obesity [4]. Children with televisions in their bedroom watch more television and gain more weight. Growing evidence from multiple countries, in particular, medium- and high-income countries, suggests that sedentary behaviors are prevalent among children.

Family and parental SES is another important factor affecting children’s risk of developing obesity. The obesity–SES relation is complex and seems to have changed over time, and it varies by gender, age, and country [2]. The reported mixed results are due, in part, to the complex relationship between SES and obesity. The other reason for mixed results is that various different measures have been used to measure SES, such as the use of family income and education levels. In general, research shows that low-SES individuals in industrialized countries and high-SES individuals in developing countries were at greater risk of obesity when compared with referent groups [2]. In developing countries, higher-SES groups (families) have greater access to energy-dense diets and sedentary lifestyles than their lower-SES counterparts. On the contrary, in developed countries, the low-SES groups (families) have greater access to energy-dense diets, including food items such as processed food and fast food, but less access to healthier diets consisting of adequate fresh vegetables and fruits than their high-SES counterparts. A recent large study using data from 78 countries reported that the prevalence of obesity and overweight among young children in the wealthiest quintile was on average 1.31 times higher than the poorest quintile [28]. Maternal education was associated with improved childcare practices related to health and nutrition and, therefore, seems to affect children’s obesity risk [28].

As an example, one recent study [29] used data collected from 5844 children from local study sites (i.e., cities, not nationally representative) in 12 countries (Australia, Brazil, Canada, China, Colombia, Finland, India, Kenya, Portugal, South Africa, the United Kingdom, and the United States). It showed that sedentary behaviors were common among the children studied, although there are large differences across countries (Table 3.2). These children had an average of 8.6 h of daily total sedentary time, and 54.2% of the children failed to meet screen-time guidelines (i.e., had >2 h of screen time/day). In all study sites, boys reported higher screen time, were less likely to meet screen-time guidelines, and had higher BMI z-scores than girls. In 9 of the 12 sites, girls had significantly more total sedentary time than boys. Participants from the China site (Tianjin City, one of the four largest cities in China) engaged in the highest amount of sedentary time (9.4 h/day), but had the second lowest screen-time score (about 1.9 h/day). This indicates that children in cities or/and high-SES groups in developing countries such as China already are similarly, or even more,
# TABLE 3.2

Prevalence (%) of Overweight and Obesity and Sedentary Time of Participants ($n = 5844$) in The International Study of Childhood Obesity, Lifestyle, and the Environment

<table>
<thead>
<tr>
<th>Site Country (City)</th>
<th>World Bank Ranking (Income)</th>
<th>Parental Higher Education* ($n$, [%])</th>
<th>Sample Size (% Boys)</th>
<th>Overweight/Obese* ($n$, [%])</th>
<th>Sedentary Time (h/day, Mean [SD])</th>
<th>Screen-Time Score*d (Mean [SD])</th>
<th>Not Meeting Screen-Time Guidelines* ($n$, [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td></td>
<td>3406 (58.3)</td>
<td>5844 (45.6)</td>
<td>1888 (32.3)*</td>
<td>8.6 (1.2)</td>
<td>2.6 (1.8)</td>
<td>3158 (54.2)</td>
</tr>
<tr>
<td>1. Australia (Adelaide)</td>
<td>High</td>
<td>364 (80.2)</td>
<td>454 (46.0)</td>
<td>169 (37.2)</td>
<td>7.9 (1.0)</td>
<td>2.8 (1.8)</td>
<td>266 (58.6)</td>
</tr>
<tr>
<td>2. Brazil (São Caetano do Sul)</td>
<td>Upper middle</td>
<td>172 (40.3)</td>
<td>427 (48.0)</td>
<td>195 (45.7)</td>
<td>8.3 (1.4)</td>
<td>3.7 (2.3)</td>
<td>309 (72.4)</td>
</tr>
<tr>
<td>3. Canada (Ottawa)</td>
<td>High</td>
<td>458 (91.2)</td>
<td>502 (41.6)</td>
<td>154 (30.7)*</td>
<td>8.5 (1.0)</td>
<td>2.4 (1.9)</td>
<td>227 (45.2)</td>
</tr>
<tr>
<td>4. China (Tianjin)</td>
<td>Upper middle</td>
<td>240 (49.3)</td>
<td>487 (52.0)</td>
<td>204 (41.9)*</td>
<td>9.4 (1.1)</td>
<td>1.9 (1.7)</td>
<td>164 (33.7)</td>
</tr>
<tr>
<td>5. Colombia (Bogotá)</td>
<td>Upper middle</td>
<td>281 (33.6)</td>
<td>836 (49.3)</td>
<td>192 (23.0)*</td>
<td>8.3 (1.1)</td>
<td>2.9 (1.5)</td>
<td>552 (66.0)</td>
</tr>
<tr>
<td>6. Finland (Helsinki, Espoo, Vantaa)</td>
<td>High</td>
<td>331 (73.2)</td>
<td>452 (46.9)</td>
<td>110 (24.3)</td>
<td>8.8 (1.2)</td>
<td>2.7 (1.7)</td>
<td>257 (56.9)</td>
</tr>
<tr>
<td>7. India (Bangalore)</td>
<td>Lower middle</td>
<td>448 (83.0)</td>
<td>540 (45.6)</td>
<td>173 (32.0)</td>
<td>8.6 (1.1)</td>
<td>1.8 (1.3)</td>
<td>169 (31.3)</td>
</tr>
<tr>
<td>8. Kenya (Nairobi)</td>
<td>Low</td>
<td>298 (64.2)</td>
<td>464 (45.9)</td>
<td>90 (19.4)</td>
<td>8.2 (1.1)</td>
<td>2.4 (1.7)</td>
<td>246 (53.0)</td>
</tr>
<tr>
<td>9. Portugal (Porto)</td>
<td>High</td>
<td>116 (21.1)</td>
<td>547 (43.0)</td>
<td>250 (45.7)*</td>
<td>9.2 (1.0)</td>
<td>2.3 (1.5)</td>
<td>265 (48.5)</td>
</tr>
<tr>
<td>10. South Africa (Cape Town)</td>
<td>Upper middle</td>
<td>91 (29.7)</td>
<td>306 (40.0)</td>
<td>80 (26.1)</td>
<td>8.2 (1.1)</td>
<td>3.1 (2.1)</td>
<td>191 (62.4)</td>
</tr>
<tr>
<td>11. The United Kingdom (Bath, Northeast Somerset)</td>
<td>High</td>
<td>294 (72.2)</td>
<td>407 (42.8)</td>
<td>111 (27.3)</td>
<td>8.3 (1.0)</td>
<td>2.9 (1.7)</td>
<td>275 (67.6)</td>
</tr>
<tr>
<td>12. The United States (Baton Rouge)</td>
<td>High</td>
<td>313 (74.2)</td>
<td>422 (41.0)</td>
<td>160 (37.9)</td>
<td>8.7 (1.0)</td>
<td>3.1 (2.3)</td>
<td>247 (58.5)</td>
</tr>
</tbody>
</table>


Note: BMI, body mass index; SD, standard deviation.

* Number (%) of sample who had at least one parent complete more than high school education (i.e., > some college/university).

* Number (%) with WHO BMI z-score classification overweight or obese.

* Sites where boys had significantly higher values than girls ($p < .05$).

* Screen-time score = ([hours of TV on weekdays × 5] + [hours of TV on weekend days × 2] + [hours of video games and computers on weekdays × 5] + [hours of video games and computers on weekend days × 2])/7.

* Number (%) of children not meeting guidelines of ≤2 h of screen time/day.
sédentary than children in many other industrialized countries. This help explains why obesity rates have increased so rapidly in these developing countries; and in urban areas or/and high-SES groups, the obesity prevalence has reached a level similar to that in industrialized countries. The study reported that the prevalence of overweight/obesity ranged from 19% (in the city from Kenya) to almost 46% (in the two cities from Brazil and Portugal).

PREVENTION OF CHILDHOOD OBESITY: GLOBAL IMPLICATIONS

A large number of studies have been conducted regarding childhood obesity prevention and treatment, though the majority are conducted in high-income countries and very little is known about other countries [30–32]. Nevertheless, lessons learned in high-income countries are useful for middle- and low-income countries. The growing obesity problem is societal, and thus it demands a population-based multisectoral, multidisciplinary, and culturally relevant approach, and international collaborations are needed [3]. Unlike most adults, children do not have much power to choose the environment in which they live and the food they eat. Further, they also have a limited ability to understand the long-term consequences of their behaviors. Therefore, special attention and efforts are needed to help them to develop desirable lifelong habits for preventing obesity.

More research is needed in developing countries, as the reported studies are predominately conducted in developed countries. We, and others, have reviewed various interventions conducted in countries worldwide to determine what programs are successful and where more research is needed for childhood obesity prevention [30–34]. A large number of studies have been conducted to study childhood obesity prevention, and mixed results are reported [30,31]. Nevertheless, adequate evidence has been accumulated that supports the possibility that interventions, especially school-based programs, could be effective in preventing childhood obesity. Meanwhile, even if some of the interventions cannot reduce obesity, they may still result in other beneficial changes in other health outcomes, such as lowered blood pressure and improved blood lipid profile, as shown by our recent systematic reviews and meta-analyses [30,31,35,36].

In the most comprehensive systematic review and meta-analysis on childhood obesity prevention studies reported thus far, we evaluated the effectiveness of various childhood obesity prevention programs [30,31]. The findings would help various stakeholders to understand the effectiveness of obesity prevention programs for children and offer insights for future research and intervention development. We assessed 139 studies conducted in multiple settings in high-income countries over the past three decades, focusing on adiposity-related outcomes and strength of evidence (SOE). Our study showed that the SOE varied by intervention strategy and setting. There was at least moderate SOE for school-based intervention and about 50% of schools reported statistically significant desirable effects for adipose-related measures. The SOE for the effectiveness of interventions in settings other than schools and homes was insufficient mainly due to the small number of published research found.

Both healthy eating and PA should be the targets in obesity prevention, though some researchers have argued that it may be more feasible and effective to target the control of energy intake, by using national policies, regulations, programs, etc. Recently, top experts in the childhood obesity research field argued that nutrition policies are needed to tackle child obesity; and such policies need to promote healthy growth, availability of healthy foods in the home and to protect children from inducements to be inactive or to overconsume foods of poor nutritional quality. A public health effort is needed to protect children from the marketing of sedentary activities and energy-dense, nutrient-poor foods and beverages. The governance of food supply and food markets should be improved and commercial activities need be monitored and regulated [33].

CONCLUSIONS

Over the past decade, rich data from both industrialized and developing countries have demonstrated that obesity has become a serious global public health problem. Recently, the WHO has called on countries to take actions to combat the epidemic [3]. The combined prevalence has tripled
in many countries worldwide since the 1980s and the number of people and families affected is expected to continue to rise. Obesity development during childhood has many short- and long-term health and financial consequences for individuals, families, and society. Obesity is already responsible for 2%–8% of health-care costs and 10%–13% of deaths in parts of Europe, and it is projected to be even worse in the United States, reaching 17% of deaths in 2030 [37]. Children are the key target to focus on to control the obesity epidemic.

The obesity burden is huge at present, and will become worse in the future. The many profound changes in society, living environments, and individual behavioral patterns of the past two to three decades have contributed to the epidemic. Economic growth, modernization, urbanization, the globalization of food markets and service have fueled lifestyle shifts, including overconsumption of food and reduced PA in people's daily lives [1–4]. Compared with adults, children are often more sensitive to changes in their living and social environments.

Childhood obesity is a serious public threat in many industrialized and developing countries worldwide and the problem is expected to continue to grow. The epidemic calls for timely and effective population-based approaches to face its challenges. Obesity is largely preventable. However, once developed, it is difficult to cure. Obesity has many health and financial consequences for individuals, their families, and society. Therefore, the prevention of childhood obesity should take high national priority in many countries. The development of effective population-based intervention programs for the prevention and management of obesity in children is crucial to combat the epidemic of obesity and noncommunicable chronic diseases.

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Global Perspectives of Childhood Obesity

Economic Considerations in Childhood Obesity

John Cawley and Ashlesha Datar

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INTRODUCTION

This chapter discusses the economic aspects of childhood obesity. The first three sections discuss the economic causes and correlates of obesity in children and youth. The first section starts with a discussion of the recent literature on the impact of federal food assistance programs that provide subsidized food for low-income families. The next section discusses the evidence on how food prices, in particular the prices of energy-dense, nonnutritious foods and beverages relative to the prices of more nutritious foods and beverages, are related to children’s dietary intake and body weight outcomes. The third section describes the current evidence on how macroeconomic conditions, in particular economic downturns that are characterized by high unemployment rates, are related to children’s dietary intake and body weight outcomes. The fourth section discusses the evidence on one important economic consequence of obesity: higher medical care costs. Finally, the last section discusses what is known from economic evaluations of antiobesity interventions. The method of cost effectiveness has been used to estimate which programs give society the greatest “bang for the buck.” This section lists which interventions have been found to be cost saving, which are cost-effective (i.e., costly but considered good value), and which are not cost-effective (the benefits are small relative to the costs).

FOOD ASSISTANCE AND NUTRITION PROGRAMS

There are four large federal food assistance and nutrition programs (FANP) in the United States that have the potential to substantially influence children’s diets and obesity. A shared goal of these programs is to promote adequate nutritional intake in their specific target populations (all of them low income). We describe each of these programs briefly (for detailed eligibility and benefits, see Aussenberg and Colello [1]) and summarize the current research findings about their impacts on children’s diets and obesity.

Empirical estimation of the effects of FANP is challenging because participation in these programs is nonrandom. Therefore, much of the literature has compared the outcomes of participants with nonparticipants, conditional on observable characteristics (see the discussion in Meyerhoefer and Yang [2]). A much smaller literature, which is the focus of our review, has sought to estimate...
causal effects by addressing selection into the programs using quasi-experimental methods that leverage, for example, variation in program rollout, policy variation, or longitudinal data.

The largest of the four food assistance programs is the Supplemental Nutrition Assistance Program (SNAP), formerly called the Food Stamp Program, which provides low-income households (i.e., those with gross income below 130% of the federal poverty line and who also have low assets) with electronic benefit transfer cards that can be used to purchase groceries. In 2014, the program served 46.5 million individuals, with average monthly benefits of $125 per person [3].

Studies of the effect of SNAP on child BMI find varying effects [2–8]. For example, Gibson [6] examined longitudinal data from the National Longitudinal Survey of Youth 1979 Child Sample and found that SNAP participation led to a reduction in overweight for 5- to 11-year-old boys but an increase in overweight for 5- to 11-year-old girls. Schmeiser [7] analyzed the same data but used the method of instrumental variables to estimate causal effects and found that SNAP participation reduced BMI for most gender-age groups. Yet another study, Kreider et al. [8], addressed selection into and measurement error of SNAP using the National Health and Nutrition Examination Survey (NHANES) data and found that positive or negative effects of SNAP on child BMI could not be ruled out. It is perhaps unsurprising that research has found mixed results regarding the effect of SNAP on child weight, given that there are no nutritional requirements for the types of foods and beverages that can be purchased with SNAP vouchers.

The second largest food assistance and nutrition program is the Special Supplemental Nutrition Program for women, infants, and children (WIC). Only children under age five years and pregnant (or recently postpartum) women in low-income households (i.e., income no higher than 185% of the federal poverty line) are eligible. The program provides nutritious food supplements, nutrition education, and access to health services. WIC benefits can be used to purchase infant formula and a limited range of food items such as milk, cereal, and juice. In 2014, WIC served 8.3 million individuals, of whom 10% were pregnant women, 13% were postpartum or breast-feeding women, 24% were infants, and 53% were children [9].

Much of the literature on WIC’s impact has focused on birth outcomes, especially birth weight, which is an important predictor of later-life health. On the one hand, high birth weight (>4000 g) has been hypothesized to “program” an increased risk of later obesity [10,11]. On the other hand, the “developmental origins of disease” literature proposes that undernutrition during fetal life and infancy is associated with higher risk of coronary heart disease (CHD), type 2 diabetes, stroke, hypertension, and other chronic diseases. The general finding in the WIC literature is that women who participate in WIC are less likely than nonparticipants to have low birth weight babies [4,12–16]. Based on the “fetal programing hypothesis,” this finding implies a reduction in the likelihood of CHD and related chronic diseases in adulthood. Given WIC’s focus on providing nutritious food supplements in early childhood, the program has tremendous potential for reducing child BMI and obesity, but unfortunately there has been no rigorous evaluation of these impacts yet.

The National School Lunch Program (NSLP) and the School Breakfast Program (SBP) provide free and reduced-price meals to low-income children at public and private schools. The NSLP and SBP serve meals to 30.4 million and 13.6 million students, respectively [9]. Meals served as part of these programs are subject to nutritional regulations. In response to concerns about the nutritional quality of school meals, the 2010 Healthy, Hunger-Free Kids Act made major changes to nutrition standards for school meals. Updated program rules have imposed both minimum and maximum calorie rules. The new rules also include stronger requirements for daily and weekly food group servings, including weekly requirements for a variety of vegetables (such as dark green, red/orange, and starchy), restrictions on the fat content of milk, and a phased-in requirement to use only whole grains. The act also gave the US Department of Agriculture (USDA) authority to set nutritional standards for all “competitive foods” sold in schools during the school day.

Research on the NSLP has used data that were collected prior to the 2012–2013 implementation of the Healthy, Hunger-Free Kids Act, so any benefits of that legislation will not yet be evident.
Findings regarding the impact of NSLP participation on children’s diet quality are mixed. Gleason and Suitor [17] used data from the School Nutrition and Dietary Assessment Study and compared observations of dietary intake for a student across multiple days that varied by whether the student did or did not receive a school lunch, and found mixed evidence on nutrition intake. NSLP participation increased the consumption of fat, protein, and six types of vitamins and minerals, but there was no overall impact on total calories eaten at lunch or over a 24 h period. Therefore, not surprisingly, evidence on the relationship between NSLP participation and childhood obesity is also mixed. Schanzenbach [18] and Millimet et al. [19] analyzed longitudinal data on a national sample of children and found that NSLP participants became comparatively heavier as their exposure to school lunches increased, conditional on their BMI at school entry. Mirtcheva and Powell [20] used longitudinal data on children participating in the Panel Study of Income Dynamics (PSID) and found that NSLP had no effect on body weight. In contrast, Gundersen et al. [21] addressed selection and measurement problems in NSLP using NHANES data and found that receipt of free or reduced-price lunch substantially reduced obesity rates. Thus, every possible relationship has been found between school lunch receipt and child weight.

The evidence on the impact of SBP participation is more consistent and encouraging. Bhattacharya et al. [22] found that SBP participation improved dietary quality as measured by the Healthy Eating Index and several measures of diet (vitamin intake, folate, anemia, and high cholesterol) based on the results of blood serum tests. Millimet et al. [19] found that school breakfast participation was associated with a lower risk of childhood obesity. Some states have statutes requiring participation in the SBP for schools that have a critical mass of students (which varies across states, typically between 10% and 40%) eligible for free or reduced-price meals. Frisvold [23] used these thresholds to estimate the impact of SBP for schools near the thresholds. He found that SBP participation improved the nutritional content of breakfast. Finally, evidence from the only randomized experiment conducted on this question found protective effects of SBP participation. Crepinsek et al. [24] analyzed data from a USDA-sponsored, large, randomized-controlled trial of Universal Free Breakfast (UFB) and found that students who attended a school randomly assigned to receive UFB were more likely to consume a nutritionally substantive breakfast, although the program had no impact on 24 h dietary intakes or the probability of skipping breakfast.

The NSLP and SBP programs have enormous potential to influence children’s diets and obesity due to their tremendous reach. It will be important to evaluate whether improvements to the nutritional standards for school meals since 2012–2013 have been successful at reducing childhood obesity.

FOOD PRICES

Understanding how food prices influence food consumption and body weight is important because food taxes and subsidies represent potential policy tools for preventing and reducing obesity. Adults’ food and beverage purchases appear to respond to changes in price, with price elasticities (i.e., the percentage change in purchases of a good associated with a 1% change in its price) ranging from $-0.27$ to $-0.81$ [25]. When elasticities are estimated separately by category of food, food away from home (e.g., restaurant meals), soft drinks, juice, and meat purchases are most responsive to price. However, while consumers buy less of the foods that become relatively more expensive, they may also switch to buying more of the foods that have become relatively less expensive, with little net change in weight (see the review in [26]). Several studies have investigated the relationship between prices of specific food groups—such as meat, fruits/vegetables, and fast food—and childhood obesity. This literature has found that higher prices for fast food and lower prices for fruits and vegetables are associated with lower child BMI [27–30]. More recently, Wendt and Todd [31] estimated the association of food prices with children’s BMI using retail food prices from the USDA’s Quarterly Food-at-Home Price Database (QFAHPD). It found that lower prices for soda, starchy vegetables, and sweet snacks were associated with higher child BMI. It speculated that consumer responses to
price reductions (subsidies) are similar in magnitude to price increases (taxes), though of course in the opposite direction.

Research has also found variation in price responsiveness by household income and weight status. The estimated effects are larger among children in lower-income households, which is consistent with economic theory [32]. Studies also found that price responsiveness is higher among overweight and obese individuals. For example, Sturm et al. [33] found a negative and statistically significant effect of state soda taxes on BMI among children at or above the 85th percentile.

Overall, this literature suggests that, while children's dietary behaviors and body weight outcomes may be responsive to prices of nutritious and less-nutritious foods, the magnitude of those relationships is small [34], and therefore small taxes or subsidies are unlikely to produce meaningful changes in body weight outcomes in children. More research is needed to examine if larger taxes on unhealthy foods and/or subsidies for healthy foods would be effective.

ECONOMIC FLUCTUATIONS

Social scientists have had a long-standing interest in examining how fluctuations in macroeconomic conditions can influence health behaviors and outcomes [35–40]. It is argued that declines in working hours during recessions reduce stress levels and make more time available for positive health behaviors such as exercise and healthy eating [41]. Also, resulting reductions in income may force cutbacks of unhealthy behaviors such as smoking and consumption of alcohol, sugared soft drinks, and restaurant food. Research on adults has found mixed results; some researchers have found that economic downturns are associated with higher body weight [42] and reductions in the consumption of fruits and vegetables [43,44], whereas others have found that economic downturns are associated with a lower probability of obesity [37] and reductions in fat intake [35].

The relationship between economic fluctuations and children's health behaviors and outcomes has received less attention. Economic downturns can affect children through household-specific shocks (e.g., income shocks and stress resulting from parents' job loss, home foreclosure) that might lead to changes in households’ consumption and expenditure patterns related to diet and activity behaviors. Two recent studies suggest that the Great Recession may have been associated with adverse diet and BMI outcomes among children. Ng et al. [45] analyzed the Nielsen Homescan data and found that the caloric purchases of households with children increased slightly in areas with higher unemployment rates; Oddo et al. [46] analyzed children's statewide fitness data from California and found that the recession was associated with an increase in BMI z-score and the risk of overweight and obesity. In contrast, a growing literature suggests that decreases in maternal work, induced by economic downturns, are associated with better dietary behaviors and lower obesity in children [47–50]. Research examining the effects among adolescents and teenagers [51] has found interesting gender differences: increases in the state unemployment rate are associated with higher BMI in female teenagers but lower BMI in male teenagers, possibly because teenage males are more physically active than females during downturns.

MEDICAL CARE COSTS OF CHILDHOOD OBESITY

Estimates of the medical care costs of childhood obesity are useful for several reasons. First, they give a sense of the burden on the health-care system (and, more generally, the economy) imposed by childhood obesity. Second, such estimates are necessary to calculate the cost effectiveness of programs designed to prevent or treat childhood obesity. Third, they provide information about the extent of external costs, which are the costs that are paid by people other than the decision maker.

The vast majority of the medical care costs of children in the United States are paid by private health insurance companies or public health insurance programs such as Medicaid and the State Children's Health Insurance Program (SCHIP). Neither the premiums paid in private group health insurance nor the taxes that fund Medicaid and SCHIP are indexed to weight, and as a result those who are not
obese subsidize the medical care costs of those who are obese. Such external costs impose deadweight loss (inefficiency) on society, and they represent an economic rationale for government intervention.

Ideally, we would like to know the causal effect of obesity on medical care costs for youth. However, causal effects are difficult to measure in this context. It would, of course, be unethical to conduct a randomized controlled trial (RCT) that made youth obese in order to measure the resulting increase in their medical care costs. We could conduct an RCT for a weight loss intervention and measure the extent to which medical care costs fall with the resulting weight loss, but the method of weight loss could have a direct effect on medical care costs, independent of weight loss. For example, bariatric surgery or prescription weight loss drugs could result in complications or side effects that raise medical care costs, or a more nutritious diet or physically active lifestyle could have health benefits (aside from weight loss) that lower costs.

Given these complexities, there is little evidence on the causal effect of childhood obesity on medical care costs. Instead, numerous studies have measured the correlation of childhood obesity and medical care costs; that is, the extent to which the medical care costs of overweight or obese youth exceed those of healthy-weight youth. These correlations could be quite different from the causal effect if obese youths have comorbidities or behaviors that also affect health-care costs.

Trasande and Chatterjee [52] estimated the extent to which childhood obesity is associated with higher expenditures on outpatient visits, prescription drugs, and emergency room visits. They examined data for youths aged 6–19 years in the Medical Expenditure Panel Study (MEPS) for 2002–2005, with all medical expenditures converted to year 2005 dollars. Youth were classified as overweight or obese based on weight and height that were proxy reported by parents (for those aged 6–17 years) or self-reported (for youths aged 18–19). The MEPS consisted of up to six interviews over two years. The authors estimated that children who were obese in both years of the MEPS had $194 higher outpatient visit expenditures, $114 higher prescription drug expenditures, and $12 higher emergency room expenditures, per year than children who were normal weight or underweight in at least one of the 2 years. Children who were overweight in both years of the MEPS, or overweight in one year and obese in the other, had $79 higher outpatient visit expenditures, $64 higher prescription drug expenditures, and $25 higher emergency room expenditures, per year compared with children who were normal weight or underweight in at least one of the two years. The authors estimated that overweight and obesity combined cost the United States $14.1 billion annually in additional outpatient visits, prescription drugs, and emergency room visits.

Trasande et al. [53] estimated the hospital costs associated with childhood obesity. They examined data for children aged 2–19 years in the 1999–2005 National Inpatient Sample, which samples 20% of community hospitals each year. Hospital charges were converted to costs using hospital-specific cost-to-charge ratios from the Centers for Medicare and Medicaid Services, and were expressed in year 2005 dollars. BMI and weight were not observed; the authors identified obese youths using ICD-9 codes that indicated obesity was a primary or secondary diagnosis (which presumably results in a high degree of false negatives). Among hospitalizations with obesity as a secondary diagnosis, the most common primary diagnoses were affective disorders (e.g., depression, bipolar disorder, and anxiety disorder), pregnancy-associated conditions, asthma, and diabetes mellitus. Obesity as a secondary diagnosis was associated with, on average, a 0.85 day longer length of hospital stay and $727 higher hospitalization costs. For pregnancy-related conditions, the increase in hospitalization costs was $2319; for affective disorders, $1031; and for asthma, $1479. The authors estimated that the total costs of hospitalizations of youths with any diagnosis of obesity totaled $237.6 million in 2005. Note that this does not represent the additional costs associated with obesity—these are the total costs of hospitalizations for any youth assigned an ICD-9 code for obesity. Some of these youths might still have been hospitalized (albeit at lower cost) if they were healthy weight. This is also almost certainly an underestimate given that many hospital stays for obese youths will not receive an ICD-9 code for obesity.

Finkelstein et al. [54] reviewed the literature on the medical care costs of obesity and estimated that the incremental lifetime medical cost of an obese child relative to a normal-weight child who
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maintains normal weight throughout adulthood is $19,000 in year 2006 dollars. If one takes into account the likelihood of eventual weight gain among normal weight youth, the incremental lifetime costs are lowered to $12,660.

One interesting question is whether the duration of childhood obesity matters. That is, do children who have been obese for a longer period have higher medical care costs than those who have been obese for a shorter period? This question is difficult to answer using US data; the MEPS has only up to 2 years of data on each individual. However, Au [55], using data from the Longitudinal Study of Australian Children for 2004, 2006, and 2008, found that the duration of childhood overweight (classified using BMI based on measurements of weight and height) does raise medical care costs, but only starting at age 8–9 years.

There is general consensus that the medical care costs of obesity are smaller for children than adults [56]. For example, Ma and Frick [57] estimated models of medical care expenditures using the MEPS data for 2006 and found that obese adults spent $1548 more and obese children $264 more per capita than healthy-weight adults or children. In terms of annual medical expenditures for the United States, Trasande et al. [53] estimated that childhood obesity is associated with $14.1 billion higher costs (in 2005 dollars) per year, while Cawley et al. [58] estimated that adult obesity raises medical care costs by $315.8 billion (in 2010 dollars) per year. Thus, one of the greatest costs of childhood obesity is that it increases the risk of adult obesity, which is quite expensive.

The increase in the medical care costs of obesity with age also implies that the cost effectiveness of interventions to prevent or reduce childhood obesity will be much greater the more durable the weight loss or prevention of weight gain [56]. Programs with benefits that dissipate rapidly will generate far lower savings than programs that cause weight loss that persists into adulthood.

COST EFFECTIVENESS OF INTERVENTIONS TO PREVENT AND REDUCE CHILDHOOD OBESITY

The method of cost effectiveness analysis allows decision makers to compare the benefits per unit cost (or “bang for the buck”) of various interventions. One challenge is that the benefits from each program must be expressed in the same units; the most common such unit is the quality-adjusted life year saved or QALY. An intervention is generally considered cost-effective if it costs less than $50,000 per QALY saved (although this threshold is debatable and somewhat controversial). Other studies measure all benefits in terms of disability-adjusted life years (DALY) averted.

There exist estimates of the cost effectiveness of several US interventions to prevent and reduce childhood obesity. One of the most cost-effective such programs is the Coordinated Approach to Child Health (CATCH), a comprehensive intervention in elementary schools that promotes healthy eating and physical activity; it costs $900 per QALY saved [59].

Planet Health, a comprehensive intervention in middle schools that also promotes healthy eating and physical activity, is cost effective for girls (for whom it costs $4305 per QALY saved) but is not effective for boys [60].

Not all interventions measure program benefits in terms of QALYs and DALYs. One recent study evaluated the cost effectiveness of FitKid, an after-school program for third graders that promoted physical activity and healthy snacks, as well as academic enrichment and tutoring [61]. The outcome of focus was percentage body fat, rather than QALYs or DALYs. Based on a randomized controlled experiment, Wang et al. estimated that students who attended 40% or more of the intervention reduced percentage body fat by 0.76%, at a cost of $317 per student. Although the use of body fat as an outcome has its advantages—relative to measuring BMI, it does not penalize students who gain muscle through physical activity—it has the disadvantage of complicating comparisons with other cost effectiveness studies.

Facilitating comparisons of different programs is the goal of Assessing the Cost Effectiveness of Obesity (ACE Obesity), an ambitious project in Australia that seeks to estimate the cost effectiveness of all major antiobesity interventions in that country using a consistent methodology.
The extent to which each intervention reduced future morbidity and mortality was expressed as DALYs. A review of the project [62] classified such projects as either cost saving, cost-effective (i.e., costs less than $50,000 AUD per DALY), or not cost-effective (i.e., costs more than $50,000 AUD per QALY).

The list of cost-saving interventions to prevent or treat childhood obesity include (see Ananthapavan et al. [62], table 1)

- A family-based general practitioner program targeted to obese children
- A multifaceted targeted school-based program for overweight and obese children
- A school-based education program to reduce television watching
- A multifaceted school-based program to promote good nutrition and physical activity
- A school-based education program to reduce consumption of sugar-sweetened beverages
- Reducing advertising of unhealthy food and beverages to children
- Front-of-pack traffic light nutrition labeling
- A tax on unhealthy foods and beverages

The list of cost-effective interventions includes (see Ananthapavan et al. [62], table 1)

- Orlistat medication for obese adolescents
- A family-based general practitioner program targeted at overweight and moderately obese children

The list of interventions that were deemed not cost effective includes (see Ananthapavan et al. [62], table 1)

- Walking school bus
- TravelSMART (a program that works with primary schools to promote safe and active ways to travel to school)
- Active after-schools communities program

A recent study [63] estimated the net savings associated with a variety of policies to address childhood obesity in the United States. Using published estimates of program effects and costs, and a microsimulation model, it estimated that three policies would save more in medical expenditures than they cost: (1) an excise tax on sugar-sweetened beverages; (2) elimination of the tax deduction for advertising unhealthy food to children; and (3) nutrition standards for food and beverages sold in schools outside of meals. In contrast, bariatric surgery for adults was found to be a much more expensive way to reduce BMI, leading the authors to conclude that investment in prevention, rather than treatment, should be prioritized.

This relates to the old adage “prevention is cheaper than cure.” This is not a universal rule, but is something that can be determined on a case-by-case basis using cost effectiveness analysis. The Ananthapavan et al. [62] review finds considerable heterogeneity; for both primary prevention programs and treatment programs, some specific interventions are cost saving, others are costly but cost-effective, and some are not cost-effective. In other words, prevention is sometimes, but not always, cheaper than cure; one must check the evidence from cost effectiveness analysis.

CONCLUSION

Economic research on child and youth obesity has yielded important insights. Research on the economic causes of obesity has found that school lunches may promote childhood obesity, while school breakfasts may prevent it, that people are responsive to the prices of food but that existing food taxes may be too small to have any detectable impact on weight, and that the impact of
the macroeconomy on obesity is ambiguous. Research on the economic consequences of obesity indicates that childhood obesity raises health-care costs in the United States by at least $14.1 billion annually, but perhaps its greatest cost is that it increases the probability of adult obesity, which is extraordinarily expensive ($315.8 billion per year in the United States). Finally, the method of cost effectiveness provides vitally important information about which interventions work, and which provide the greatest “bang for the buck,” which is important because there will always be a limited budget devoted to the prevention and reduction of childhood obesity. While not every method of prevention has been shown to be cheaper than treatments, in general the most cost-effective interventions are prevention programs for children. Using the results of cost effectiveness analysis to guide policymaking will ensure that those limited budgets achieve the greatest possible prevention and reduction of childhood obesity.

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Assessment of Body Composition and Fat Distribution in Infants, Children, and Adolescents

Elizabeth M. Widen and Dympna Gallagher

INTRODUCTION

With the increasing global prevalence of overweight and obesity, pediatric body composition continues to be of high interest to clinicians, researchers, and the general public. Measurement of body composition and fat distribution, and changes in these factors among infants, children, and adolescents, can provide more information about nutritional status than simple anthropometric measurements alone and may provide important insights about later size and health that can be used to guide nutritional interventions and clinical practice. Assessing body composition and body composition changes in this population is, however, challenged by several factors, including the limited number of methods that can be used continuously from infancy through adolescence, physical challenges (excessive movement, crying, equipment designed only for a specific range of body sizes), and lack of validation studies.

From birth through adolescence, body composition changes considerably with more marked changes during infancy and puberty. These changes include gains in overall mass (weight) and stature (recumbent length and height) with concomitant changes in fat mass (FM) and fat-free mass (FFM), which include muscle, body water, organs, and other components. After birth, dynamic changes in body composition occur. Weight loss occurs during the first 24 h period, but weight is relatively stable in the periods 25–48 and 48–72 h [1]. Some have reported weight loss of 4%–10% in the first 2 weeks [2]. These changes are attributable to loss of body water rather than FM [3]. Total body water (TBW), or the hydration of FFM, declines rapidly from a peak of about ~0.80 at birth, to values around ~0.78–0.79 from 1 to 12 months [5], eventually stabilizing at adult values
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(-0.73) in adolescence [6]. FFM (as a proportion of body weight) increases during infancy [5,7], while the proportion of FM decreases. Percentage body fat varies by ethnicity, sex, and age, with some studies reporting higher body fat than others at specific ages (e.g., at 3 months, %fat in Butte's study was greater than the %fat in Fomon's study) and at pubertal stage [5,7–9].

Although total body composition, namely FM and FFM, is often measured, body fat distribution is more closely linked to later health; specifically, evidence suggests that visceral fat is more positively associated with cardiometabolic health and disease risk compared with subcutaneous fat [10]. While there is substantial variability in visceral and subcutaneous fat deposition by age, sex, and ethnicity, some general trends are apparent [9]. In infancy, subcutaneous adipose tissue is the predominant depot, as there is minimal intra-abdominal adipose tissue [11]. Visceral adipose tissue increases with age, but accumulation slows down over time and is affected by many factors including gender and pubertal staging; however, to date, no reports have examined visceral fat changes from infancy through adolescence in a single cohort, thus understanding of these factors that drive changes is somewhat limited [9,12]. Taken together, more work is needed to establish population-specific reference data with the most advanced body composition assessment methods.

There are several available methods for estimating total and regional body composition. Here, we provide a brief review of the most commonly used methods to assess body composition in infants, children, and adolescents and describe other methods that are forthcoming (Table 5.1).

ANTHROPOMETRY

Anthropometric measurements include body weight, circumferences of specific regions (typically head, arm, waist, or hip), skeletal breadths, physical length (recumbent length in infants <2 years and stature or height ≥2 years), and skinfold thickness. Weight and length are most often used to determine body mass index (kg/m^2) or relative size based on a reference population (e.g., body mass index z-scores by the Centers for Disease Control and Prevention or the World Health Organization growth charts, which provide information on weight relative to height and are often used as a proxy for adiposity). Circumferences and skeletal breadths are used to determine body proportions. Typically, measured circumferences include mid-upper arm, waist, hip, and thigh circumference, and head circumference (frontooccipital, measured in infants and young children). Waist circumference is often used as an indicator of visceral adipose tissue. In children (7–16 years), waist circumference was positively correlated with visceral adipose tissue assessed by magnetic resonance imaging (MRI) (R^2 = .64, p < .0001) [13]. However, in infants aged 3 and 12 months, waist circumference was not correlated with visceral adipose tissue assessed by MRI (R^2 = .16) [14], suggesting that waist circumference is not an appropriate indicator of visceral adiposity in younger children. The measurement site selected for waist circumference has important implications for use in research and clinical practice [15–17]. Commonly used sites for waist circumference include (1) the measured midpoint between the palpated iliac crest and the lowest rib along the midaxillary line; (2) the umbilicus; (3) the narrowest waist; (4) the lowest rib; (5) the iliac crest; or (6) immediately above the iliac crest. In prepubertal children, the lowest rib measurements (boys: r = .76, p < .001; girls: r = .73, p < .001) were more strongly correlated with visceral adipose tissue than midpoint and iliac crest waist circumference measures in both boys and girls [15]. However, in pubertal children, measures at the rib, crest, and midpoint were similarly correlated with visceral adipose tissue [15]. For reproducibility in longitudinal studies, measurement using bony landmarks is strongly recommended, such as the midpoint between the iliac crest and lowest rib.

Skinfold thickness is typically measured with Harpenden, Lange, or Holtain calipers. Common skinfold measurement sites include triceps, biceps, subscapular, suprailiac, and midthigh; at each of these sites, bony landmarks are used to standardize measurements. The caliper is applied to a double layer of fat and skin and measurement is obtained after the reading has stabilized; in young infants the reading should be obtained at approximately 30 s, while in older infants and in children/adolescents, the reading should stabilize in a much shorter period (i.e., 3 s). After each
**TABLE 5.1**

Summary of Methods to Measure Body Composition from Infancy through Adolescence

<table>
<thead>
<tr>
<th>Method(s)</th>
<th>Age and Size</th>
<th>Body Components</th>
<th>Pros/Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air Displacement Plethysmography</td>
<td>0–6 months</td>
<td>Body volume from which estimates of FM and FFM are derived</td>
<td>Pro:• Noninvasive and quick measurement.</td>
</tr>
<tr>
<td>(ADP) PEA POD</td>
<td>(&lt;8 kg)</td>
<td></td>
<td>Con:• Infants &gt;8 kg cannot be measured.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Density constants may not be appropriate for study population.</td>
</tr>
<tr>
<td>BOD POD with attachment</td>
<td>2–6 years</td>
<td></td>
<td>Pro:• Noninvasive and quick measurement.</td>
</tr>
<tr>
<td></td>
<td>(&lt;25 kg)</td>
<td></td>
<td>Con:• Movement and crying limits usability of measures.</td>
</tr>
<tr>
<td>BOD POD</td>
<td>&gt; 6 years</td>
<td></td>
<td>Pro:• Noninvasive and quick measurement.</td>
</tr>
<tr>
<td></td>
<td>(&lt;250 kg)</td>
<td></td>
<td>Con:• Density constants may not be appropriate for population.</td>
</tr>
<tr>
<td>Dual-energy x-ray absorptiometry</td>
<td>&gt;0</td>
<td>Fat mass</td>
<td>Pro:• Provides total and regional (arms, legs, trunk, android, gynoid) estimates of body composition (fat mass, fat-free mass, and bone).</td>
</tr>
<tr>
<td>(DXA)</td>
<td></td>
<td>Lean mass</td>
<td>Con:• Challenging to limit movement in some younger children.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone mineral content</td>
<td>• Radiation exposure.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Measurement error (especially smaller sizes).</td>
</tr>
<tr>
<td>Anthropometry</td>
<td>&gt;0</td>
<td>Relative size (BMI, ponderal index, waist-to-hip ratio); Subcutaneous adipose tissue (skinfold)</td>
<td>Pro:• Can be used from birth through adulthood.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Estimate body composition with prediction equations</td>
<td>• Provides information on body size, proportions, and regional adiposity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Equations can be applied to estimate body fat in select populations and age groups.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Con:• Equations may not be available for population of interest.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Specialized training needed.</td>
</tr>
</tbody>
</table>

*(Continued)*
### Summary of Methods to Measure Body Composition from Infancy through Adolescence

<table>
<thead>
<tr>
<th>Method(s)</th>
<th>Age and Size</th>
<th>Body Components</th>
<th>Pros/Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnetic resonance imaging (MRI)</td>
<td>&gt;0</td>
<td>Adipose tissue, muscle volume</td>
<td>• Can be used from birth through adulthood.</td>
</tr>
</tbody>
</table>
| Quantitative magnetic resonance (QMR) | 0–12 kg (infant) <80 kg (adolescent) <250 kg (adult) | FM FFM Free water mass Total water mass | • Quantify tissue in vivo.  
  Con:  
  • Challenging to limit movement in some younger children. |
| Hydrometry                 | TBW by dilution | >0                       | TBW from which estimates of FM and FFM are derived | Pro:  
  • High accuracy and precision.  
  Con:  
  • Challenges associated with (1) insuring that full dose has been ingested in infants and (2) collection of some physiologic samples such as urine. |

**Note:** FM, fat mass; FFM, fat-free mass; TBW, total body water.
measurement, the tissue should be allowed to normalize before obtaining replicates. Typically, one replicate is obtained and a third measurement is conducted if differences exceed 1–3 mm, which depends on skinfold site and child age.

While skinfold thickness measures can be used to assess regional adiposity (e.g., trunk) or general distribution (e.g., trunk-to-limbs ratio), values are often used in prediction equations along with other anthropometric measures (i.e., height, weight, circumferences) and age to estimate body fat or lean mass [6]. These equations, however, are prone to error at the individual level and are most useful for specific age groups (consistent with the populations where validation was performed). Furthermore, the racial/ethnic composition of the source population for the prediction equation may not be generalizable to the study population of interest. For example, the Slaughter equation was developed in prepubescent (Tanner stages 1 and 2; male %fat: 19.0% ± 8.1% [mean ± standard deviation (SD), all such values]; female %fat: 23.2% ± 6.6%), pubescent (Tanner stage 3; male %fat: 17.3% ± 7.3%; female %fat: 23.7% ± 6.8%), and postpubescent (Tanner stage 4 and 5; male %fat: 14.0% ± 6.2%; female %fat: 23.6% ± 6.0%) black and white males and females. The equation utilizes the sum of the triceps and the calf or subscapular skinfold thickness to estimate body fatness [18]. Body fat estimates with the Slaughter equation were compared with dual-energy x-ray absorptiometry (DXA) based on estimates in two populations: (1) white, black, Hispanic, or Asian children aged 5–18 years from New York City (n = 1169), and (2) black and white children aged 5–17 years from Bogalusa, Louisiana (n = 6725) [19]. Although body fat estimates with the Slaughter equation were highly correlated with DXA estimates overall (r = .90), there were differences depending on the level of body fatness with greater accuracy among nonobese children [19]. Among children with lower skinfold values (<15 mm for boys and <20 mm for girls), the difference between Slaughter and DXA %fat was minimal (<1%); but among heavier children, body fat was overestimated by 12% among boys and by 6% among girls with thicker skinfold thickness values (sum of subscapular and triceps skinfold ≥50 mm for boys and ≥60 mm for girls) [19].

Due to low cost and portability, anthropometric measures can be obtained in most research settings assuming standardization of measurement devices, including scale calibration up to the highest participant weight with certified calibration weights, and standardization within and between observers, but there are limitations. First, training in a similar population in terms of age and body size is necessary to achieve optimal within and between observer variability, particularly for skinfold measurements. Second, infants and young children need to be calm and cooperative during measures to minimize error, which may be challenging in hungry, thirsty, or otherwise distressed subjects.

**DENSITOMETRY**

Densitometry methods for estimating body composition include hydrostatic weighing (underwater weighing), which estimates body density, and air displacement plethysmography (ADP), which estimates body volume from which body density is derived (e.g., density = mass/volume) and body composition is estimated. For FFM estimation, the assumed density of FFM changes from infancy through adolescence until chemical maturation (i.e., adult values) and is also subject to between-individual variability [5,7,20]. In addition, there is variation in the density of FFM by age and race/ethnicity; in general, the density of FFM is greater in blacks than whites [21]. As participant cooperation is necessary to follow directions and hold breath for hydrostatic weighing, this method is not recommended for infants, toddlers, and younger children. Thus, this section will focus on ADP, which estimates body volume by applying the principles of Boyle’s and Poisson’s gas laws. The PEA POD and the BOD POD (Cosmed USA) are currently available ADP systems for measuring infants and children. For both systems, the subject is placed inside the enclosed test chamber and the amount of air displaced by the subject is measured. For infants 1–8 kg (approximately 6 months of age), the PEA POD estimates body fat by applying sex- and age-specific density constants and residual thoracic lung volume estimates [4,7]. The PEA POD was validated against
deuterium dilution estimates of body fat in infants, where the mean difference in percentage body fat between methods was very small ($-0.07 \pm 3.39\%$, $p = .9$) and the values were highly correlated ($R^2 = .76$) [22]. The limits of agreement in Bland–Altman analysis were narrower than other methods previously used in infants, but were still wide ($-6.84\%$ to $6.71\%$ body fat) [22]. This suggests that there may be biological contributions (FFM hydration) or other individual differences (i.e., feeding, crying, sweating, water turnover) contributing to the error [22].

The BOD POD is used for estimating body composition in children ($\geq 2$ years) and adults up to 250 kg. Measurements include body weight, body volume, body density, FM, FFM, and thoracic gas volume (if not estimated). A pediatric adaptor seat for young children aged 2–6 years (and 12–27 kg) is available for use for the BOD POD GS system (November 2007 and thereafter); the seat is similar to a high chair with a small tray and is accompanied with a pediatric calibration cylinder (20.02 L). The BOD POD pediatric adaptor system was validated against the four-compartment (4C) model (Lohman) in 31 children aged 2–6 years, where bone mineral content was estimated by DXA (described in DXA section), total body water (TBW) was assessed with deuterium dilution (described in the TBW section), and body volume was estimated by ADP and body mass [23]. Compared with the 4C model, the coefficient of variation was 3.5% for percentage body fat. Based on the Bland–Altman plot, there appeared to be no bias between the %fat estimates between the BOD POD with pediatric option and the 4C %fat estimates [23]. However, one %fat estimate was substantially lower than 2SD from the mean and two others were adjacent to 2SD from the mean [23], and unfortunately, information on subjects with aberrant %fat values was not provided. This indicates that the BOD POD with the pediatric option may considerably underestimate %fat in some circumstance and, therefore, limit the validity of %fat estimates in this population. Obtaining satisfactory participant cooperation represented by limited movement and minimal crying was problematic in this report (i.e., several subjects’ data were unacceptable due to crying [23]), thus, this challenge may be important to consider for planning body composition assessment in younger children. This report corroborates other reports in infants aged 6–48 months [24] and children aged 3–5 years [25] comparing the BOD POD with pediatric option with DXA or D$_2$O-derived body fat estimates that indicated that the ADP with pediatric option was invalid in younger children. In children aged 5–18 years, BOD POD estimates of body fat have been compared with the 4C model as the criterion method [26,27]. In 30 children aged 11–17 (mean 14 years), ADP estimates of body fat were highly correlated with 4C ($r \geq .95$), and the ADP estimates that applied Lohman equations [28] were more similar to 4C than Siri-derived estimates [26]. In another report of 25 children aged 9–14, the regression between ADP FM and 4C FM did not differ from the line of identity ($R^2: .97$; intercept, kg: $0.88 \pm 0.64$; slope: $1.036 \pm 0.38$) and no bias was observed in residual plots ($p = .1$) [27]; however, two outliers were beyond the limits of agreement and the limits of agreement were wide, which suggests that ADP may not be accurate in some instances in this population [27].

ADP is a safe and noninvasive method for body composition assessment in infants, children, and adolescents, which does not require sedation; however, there are some challenges in using this method in this population. First, ADP is not appropriate for use in children >8 kg (~6 months) and ADP has not been validated in children from 6 months to 2 years. Furthermore, obtaining participant cooperation of children aged 2–6 years may be challenging and, as such, data may not be usable. The age and sex-specific density constants for FFM and thoracic gas volume estimates may not be appropriate for the study population of interest. In particular, the FFM constants may not reflect the dynamic changes in body water occurring during infancy.

**DUAL-ENERGY X-RAY ABSORPTIOMETRY**

DXA uses two x-rays, one that detects bone and the other that estimates fat and lean soft tissue based on an algorithm. Several systems are available for use in pediatric populations that have instrument-specific software and pediatric-specific algorithms. The system and software used for
measurements impact body composition estimates [29], thus, for longitudinal studies, use of the same system and software over time is advised.

In infants, one study has compared DXA with ADP in infancy; 84 infants, who were full term at birth, were measured at 6 months of age [30]. In this report, DXA and ADP were highly correlated, but compared with ADP, DXA estimates of percentage body fat were higher by an average of 4.4% and FFM estimates were lower by an average of 166 g [30]. Several studies have compared body fat estimates from DXA with the 4C model, as the criterion method, in children [6,31]. Among a sample of children (n = 411) aged 6–18 years of black (n = 89, 21.7%), Hispanic (n = 74, 18.0%), white (n = 153, 37.2%), Asian American (n = 47, 11.4%), and “other” (n = 48, 11.7%) ancestry, DXA (Lunar DPX/DPX-L) was found to overestimate percentage body fat, compared with 4C [31]. While the estimates were correlated with each other (R^2 = .85), DXA overestimated percentage body fat with a mean difference of 1.012% (p < .001) between methods [31]. Agreement, however, varied by subjects’ body fat; among subjects with higher percentage body fat, DXA underestimated body fat compared with 4C [31]. In obese children and adolescents aged 5–21 years (mean 10.7 years), DXA was found to overestimate FM by 0.9 kg and underestimate lean mass by 1 kg, compared with 4C estimates, and the limits of agreement were wide (i.e., ~4 kg) [32]. Based on a study of 176 multiethnic children and adolescents aged 5–17, prediction models can be applied to DXA total body fat to estimate total adipose tissue and subdepots, including subcutaneous, intermuscular, and visceral adipose tissue [33]. Simple methods to derive estimates of visceral fat with DXA software have not been validated in pediatric populations against criterion methods. One study compared DXA estimates of skeletal muscle, derived from an adult prediction model, with reference estimates by MRI in children aged 5–17 (BMI < 35 kg/m^2) [34]. The adult model was found to be valid for Tanner 5 children, but for ≤Tanner 4 children, the adult model overestimated skeletal muscle and, thus, a pediatric prediction formula for estimating skeletal muscle in children at or below Tanner 4 was developed [34].

The advantages of this system include short measurement time (varies by height of participant), good precision, ability to estimate regions (arms, legs, and trunk) and for the whole body or any specific region, the separation of body into fat, bone, and bone-free lean. There are limitations; the DXA system exposes subjects to radiation (whole body scan, 1–5 µSv), where 5 µSv is equivalent to 25% of the radiation dose of a chest x-ray (20 µSv) [3]. Radiation exposure requires females of child-bearing potential to have a pregnancy test before the DXA test. The DXA system is expensive (>70,000), younger children need to be sleeping or tightly wrapped in a sheet to limit movement, and finally, the dynamic changes in FFM hydration and bone changes during growth may introduce error.

**IMAGING**

**MAGNETIC RESONANCE IMAGING**

MRI can be used to estimate total-body and regional adipose tissue volume (i.e., visceral, subcutaneous, bone mineral adipose tissue), skeletal muscle, and the volume of other lean tissues [6,35]. Other depots and tissues that can be quantified include organ mass, such as high metabolic rate organs, including spleen, liver, and kidney, and brain mass [6,36,37]. Multiple cross-sectional images are assessed from which tissue volumes are reconstructed, which are converted to tissue mass by applying known assumed densities [38]. Tissue volume is measured, rather than mass as in other methods, which needs to be considered when making comparisons between MRI and other assessment methods. Assumptions regarding the composition and density of tissues are made to derive estimates of mass, and these vary with age from infancy until adult levels are attained [6]. The advantages of MRI include the ability to test all ages provided they can remain motionless for 15–20 min in a confined magnet, no radiation exposure, detailed and high-quality images, and the ability to discern specific tissue subdepots and regional body composition. There
are limitations. First, MRI access is limited to radiology facilities as these highly specialized instruments that are costly to purchase and maintain must be operated by certified radiology technicians and study-specific protocols must be developed and implemented. The costs associated with MRI scanning time (e.g., $550 for a 30 min block; variable by institution) and postprocessing for image analysis are high; postprocessing analyses are dependent on scan protocol and specific measurement. MRI requires the subject to be completely motionless, thus, infants and younger children need to be asleep for measurements. Sedation for nonclinical research studies is not recommended. Yet, the scanning time in younger subjects is relatively fast due to their smaller size (i.e., <10 min for infants) [6]. Although MRI has acceptable reproducibility ~2%–~4% for adipose tissue volume estimates in infants [11,35,39] and 17.4% for internal adipose tissue [11], further validation of body composition estimates in children from infancy through adolescence is needed [3].

**Quantitative Magnetic Resonance**

Quantitative magnetic resonance (QMR) is a nonimaging method that estimates whole body FM but not the distribution of lean tissue mass, TBW, and free water (water not bound to tissues) based on the magnetic properties of tissues and water. There are several QMR analyzers that are size and age specific. EchoMRI-Infants can be used to assess body composition in infants up to 12 kg and validation of this analyzer is currently in progress. Thus far, the system shows high precision and reproducibility for estimating FM, lean mass, and body water [3]. Another QMR analyzer (EchoMRI-AH) was compared with deuterium dilution and the 4C model for infants and children up to 50 kg. This analyzer overestimated body fat by ~10% when compared with 4C and underestimated body fat by ~4%, when compared with deuterium dilution in children ≥6 years. Subsequently, the equations were redeveloped to account for this bias [40]. The EchoMRI-Adolescent was developed for children/adolescents up to 80 kg, but information on its validity is lacking. The system has many strengths including that it does not use ionizing radiation, several systems sizes are available for different ages and body sizes, and finally, the measurement time is short ~4 min and the subject does not need to remain still during the measurement. The primary disadvantage is that these systems are very expensive to purchase (EchoMRI, LLC, Houston, TX: http://www.echomri.com) and currently are only available in select research facilities.

**Hydrometry (Total Body Water)**

As mentioned in the introduction of this chapter, TBW, or the hydration of FFM, changes markedly from infancy through adolescence. FFM hydration peaks at birth (~0.8) and declines thereafter, eventually plateauing at adult values of ~0.73 in adolescence [5–7,41]. TBW is estimated with hydrometry, where naturally occurring isotopes, $^2$H or $^{18}$O, are measured in physiologic samples (blood, saliva, or urine) at baseline and then measurements are obtained after dosage with a stable isotope and an equilibrium period [41]. Labeled water, as $^{2}$H$_2$O (deuterium) or H$_2^{18}$O (Oxygen 18), is administered, typically via a syringe or a small cup. After equilibrium, follow-up physiologic samples are obtained, from which TBW is estimated [7]. Body fat estimates can be derived from TBW measurement; however, due to high between-individual variability and dynamic changes in the hydration of FFM, especially in infancy, this method may not be appropriate for estimating body fat in some circumstances (i.e., newborn period) [42].

Hydrometry is accurate and precise for measuring TBW (coefficient of variation (CV) 1%–2% [41]); however, estimates of body fat may be prone to error due to the rapid and variable changes in hydration of FFM in this population. Other limitations include (1) spillage due to regurgitation during oral dose administration in younger children and infants; (2) challenges in obtaining saliva or urine samples when phlebotomy is not practical or appropriate; (3) time involved for equilibrium (range 3–4+ h) depending on dose administration route and estimation method; and finally
(4) difficulties because hydrometry is based on the assumption of no feeding during the equilibration period, which may not be feasible in infants or younger children.

**BIOELECTRICAL IMPEDANCE**

Bioelectrical impedance (BIA) is based on the principles of the electrical conductivity of various tissues, where the impedance or resistance to the delivered electrical current is measured. From the resistance and other factors (age, sex, etc.), prediction equations are applied to estimate TBW from which estimates of FM and FFM are derived. The applicability of BIA is limited for use in infants and younger children due to the wide variability in the hydration of FFM, which underlie BIA estimates, thus impacting the accuracy of body composition estimates. Recently, an equation that leverages BIA estimates (resistance) and anthropometry for use in 2-year-olds was found to strongly predict DXA FFM estimates in 2-year-old New Zealanders [43]; however, more work is needed to extend the age and applicability to other populations. In older children, body composition estimates derived from BIA should use prediction equations that account for age, sex, and pubertal stage; unfortunately, appropriate prediction equations are often not available. Furthermore, it is important to determine if the BIA device has been validated against gold-standard methods in a population similar to the study population in age, race, and pubertal stage, or alternatively, if other specific prediction equations are available that may be more appropriate and can be used with the raw BIA values [6,44,45].

**FOUR-COMPARTMENT METHODS**

The 4C model is considered the gold-standard method for assessing body composition (FM) in general and is often appropriate for assessment in children. The 4C model typically uses estimates of total body water by dilution, total body bone mineral content by DXA, body volume by ADP or hydrostatic weighing, and body weight to estimate FM. The Lohman equation is often used for ages 1–16 years, where Bd is body density in grams per cubic centimeter, W is TBW in liters, BMC is total bone mineral content (BMC by DXA × 1.22) [28], and FM (kg) = (2.749/Bd − 0.714 W + 1.146 bmc−2.0503).

**SUMMARY**

There are many widely available methods that can be applied to assess body composition and its distribution in infants, children, and adolescents, but few of these methods can be applied across the full life course. As pediatric body composition becomes more widely used and methods are further refined and developed, understanding of the assumptions and limitations of available methods is of utmost importance. As we gain a greater understanding of the dynamic changes in body composition in this period, standards for body composition by age, sex, and race/ethnicity need to be established in order to ensure that body composition measurements can be clearly interpreted by clinicians and patient populations.

**REFERENCES**

Section II

Nutritional Factors Contributing to Childhood Obesity
INTRODUCTION

Among the myriad factors contributing to overweight and obesity among children, the timing and distribution of energy intake across daily eating occasions (henceforth referred to as “daily eating patterns”) have been recognized as variables influencing weight status during childhood and adolescence (Table 6.1) [1]. Although daily eating patterns at the individual level are influenced by biological factors, including hunger and satiety cues and circadian rhythm, they are also influenced by environmental factors, such as social norms, culture, media exposure, family routines, and institutional settings and schedules [1–4]. Children in today’s society typically distribute their time across a wide variety of settings and activities [5], which vary in structure and opportunity for energy intake and expenditure. Taking a closer look at temporal shifts in eating patterns and the coincidence of these trends with rising obesity rates could shed light on modifiable behavioral changes that may alter energy balance.

Because of the salience of daily eating patterns to children’s everyday lives and variability observed across cultures in timing and composition of eating occasions, related hypotheses have been generated and tested over the past half century. In this chapter, we will review evidence on the respective relationships between breakfast, snacking, and eating frequency on weight status among children. We will present prevalence and trends estimates of children’s daily eating and results of studies investigating potential links between daily eating patterns and weight status. Prevalence
Childhood Obesity: Causes, Consequences, and Intervention Approaches

Before providing an overview of the extant peer-reviewed literature addressing these topics, it is important to recognize that humans consume food episodically over the course of a day. While it is theoretically possible to feed an individual at a continuous rate in a laboratory or health-care setting intravenously, consuming food constantly throughout the day is practically impossible. Free-living individuals usually consume food in discrete bouts, often described as eating episodes or eating occasions [6]. In modern societies, eating episodes/occasions are generally dichotomized into two categories: meals and snacks. Meals, which are generally larger and consist of a greater diversity of foods and food groups, typically include breakfast, lunch, and dinner [7–9]. Though the timing, relative importance, and composition of meals varies among and within countries, families, and individuals [10], meals are generally consumed at a roughly fixed time of day and are often eaten in the company of others. Snacks, on the other hand, are commonly defined as any food(s) consumed outside the boundaries of typical mealtimes. While the Dietary Guidelines for Americans includes meal and snack patterns, frequency, and quality under the umbrella of a wide variety of “eating behaviors,” [1] precise and standardized definitions of each are lacking for research purposes, and the lines between the two are considerably subjective and ambiguous. Though idiosyncratic patterns have generated increased attention in recent years [11], the majority of the US population consumes three meals and at least one snack per day [1]. Though little change in daily eating patterns has been observed in recent years (2005–2010) [1], trends over the past 40 years indicate shifts in meal frequency, type, and timing among adults [6].

Research on daily eating patterns in children has predominantly focused on breakfast and snacking, as two distinct behaviors that may independently influence weight status. Total daily eating episodes/occasions, which incorporate both snacking and breakfast but encompass eating frequency more generally, have also been considered in association with adiposity outcomes. Each of these topics will be discussed independently and conjointly in the sections that follow.

### TABLE 6.1
Percentage Skipping Breakfast and Percentage of Total Energy Consumed at Breakfast by Age Group and Gender

<table>
<thead>
<tr>
<th>Age-Gender Group (years)</th>
<th>% Skipping (NHANES 2009–2010)</th>
<th>% Total Energy (NHANES 2011–2012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–5</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>6–11</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>12–19</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–5</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>6–11</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>12–19</td>
<td>25</td>
<td>15</td>
</tr>
</tbody>
</table>

BREAKFAST

PREVALENCE AND TRENDS

Though the content, timing, and size of the breakfast meal vary considerably within and between cultures [12], according to the English definition, the only requisite is its ordinal position as the first meal of the day [13]. Despite the universality of the breakfast meal and its colloquial—and increasingly scientific—recognition as the “most important meal of the day,” consumption trends in the United States suggest incongruity between adage, evidence, and behavior. In fact, the most recent prevalence estimates based on nationally representative What We Eat in America (WWEIA) and National Health and Nutrition Evaluation Survey (NHANES) 2009–2010 data suggest that breakfast skipping increases as children age, from 6% of males and 5% of females ages 2–5 years to 26% and 25%, respectively, ages 12–19 years, and that these prevalence estimates have remained stable since 2005 [1]. Though estimates have not been compared for 2011–2012 data, previous evidence consistently suggests that breakfast skipping may be more prevalent in children from lower socioeconomic backgrounds [14]. Another recent analysis, using data from a nationally representative sample of US students in 6th–10th grades, recruited using a multistage stratified design by census region, found that adolescents consumed breakfast approximately 5 days per week and were more likely to eat breakfast on weekends than weekdays [15]. In this study, significant interactions were found by gender, age, and race/ethnicity, with girls reporting eating breakfast less frequently than boys, older children less frequently than younger, and African American and Hispanic children less frequently than white and other race/ethnicities. Based on the same data, breakfast consumption on weekdays increased from 2001–2002 to 2005–2006, whereas breakfast eating on weekends did not change significantly over time. Among boys, breakfast eating on weekdays increased from 2001 to 2009, and, among girls, breakfast eating on weekdays increased across all three time points [15].

The majority of evidence suggests that breakfast consumption among children and adolescents is positively associated with daily nutrient intake and diet quality [1,14,16]. According to the most recent NHANES data, the breakfast meal contributes a higher nutrient-to-energy ratio for shortfall nutrients (fiber, calcium, vitamin D, potassium, and iron) and lower nutrient-to-energy ratio for nutrients to limit (sodium, saturated fat, added sugar) than any other eating occasion among Americans 2 years and older (Figure 6.1). This is especially true for calcium, vitamin D, and iron. For males and females ages 2–19 years, breakfast contributed approximately 17% of total energy intake (337 kcals) on average [1]. Though research also suggests that

![Percentage of daily nutrient intake relative to energy intake by eating occasion for children 2–19 years. (Adapted from DGAC 2015 Figure D1.40 using original data sourced from What We Eat in America, NHANES 2009–2010.)](image-url)
breakfast consumption is positively associated with energy intake [14], more evidence is needed to confirm these findings.

Trend data from 1965 to 1991 suggest that children increased consumption of low-fat milk, ready-to-eat cereals, and juices, and decreased consumption of high-fat milk, whole-grain breads, and eggs across the latter half of the twentieth century [17]. Cross-sectional 2001–2002 NHANES data showed that ready-to-eat cereal (RTEC), milk, 100% fruit juice, and breads, bagels, roll, and muffins were among the most commonly reported foods consumed at breakfast (at least 20% of participants reported), with no differences reported by age group [18]. Breakfast composition did appear to differ between meals consumed at home and away from the home, with RTEC and milk more commonly consumed at home. Although not from a nationally representative sample, data on breakfast type and location collected from a large, ethnically diverse sample of 4th–6th grade children provides some insight into more recent patterns [19] (Table 6.2); across all locations, cereal, milk, water, 100% fruit juice, bread, and muffins/donuts were most commonly consumed. An earlier analysis of NHANES data collected from 1999 to 2006 showed that 35.9% of children and 25.4% of adolescents consumed RTEC for breakfast, and that diet quality was positively associated with RTEC consumption [20]. In this study, RTEC consumers had lower intakes of total fat and cholesterol and higher intakes of total carbohydrate, dietary fiber, and several micronutrients compared with breakfast skippers and other breakfast consumers. RTEC consumers also had the highest mean adequacy ratio (MAR) for micronutrients, which was the lowest for breakfast skippers.

<table>
<thead>
<tr>
<th>Category</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ate at any location</td>
<td>87.6</td>
</tr>
<tr>
<td>Cereal</td>
<td>32.5</td>
</tr>
<tr>
<td>Milk, yogurt, or cheese</td>
<td>31.7</td>
</tr>
<tr>
<td>Water</td>
<td>29.0</td>
</tr>
<tr>
<td>100% fruit juice (Juicy Juice)</td>
<td>27.5</td>
</tr>
<tr>
<td>Bread (bagel, toast, or roll)</td>
<td>21.0</td>
</tr>
<tr>
<td>Muffin, donut, pastry, cake, or pie</td>
<td>18.9</td>
</tr>
<tr>
<td>Waffles, French toast, pancakes</td>
<td>17.9</td>
</tr>
<tr>
<td>Breakfast sandwich</td>
<td>17.6</td>
</tr>
<tr>
<td>Chips (Doritos, potato chips, Cheetos, etc.)</td>
<td>17.5</td>
</tr>
<tr>
<td>Eggs</td>
<td>15.3</td>
</tr>
<tr>
<td>Fruits (apple, pear, peaches, etc.)</td>
<td>14.6</td>
</tr>
<tr>
<td>Meat (bacon, ham, sausage), chicken, or fish</td>
<td>13.7</td>
</tr>
<tr>
<td>Soda, lemonade, Capri Sun, Sunny D, Hug, etc.</td>
<td>12.6</td>
</tr>
<tr>
<td>Candy</td>
<td>11.7</td>
</tr>
<tr>
<td>Coffee, tea, iced tea (Arizona, Brisk, etc.)</td>
<td>10.7</td>
</tr>
<tr>
<td>Vegetables (lettuce, green beans, broccoli, etc.)</td>
<td>5.7</td>
</tr>
<tr>
<td>Other</td>
<td>4.3</td>
</tr>
<tr>
<td>Cracker</td>
<td>1.2</td>
</tr>
<tr>
<td>Pretzel</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Source: Adapted from Lawman et al., *BMC Public Health*, 14, 604, 2014.

Note: Ate at any location indicates the proportion of the sample that endorsed eating breakfast in that location. All three schools provided all students with access to free breakfast before school hours. Category descriptions are presented as they were shown to participants.
RELATIONSHIP BETWEEN BREAKFAST CONSUMPTION AND CHILDHOOD OVERWEIGHT AND OBESITY

Regular breakfast consumption among children has been recognized as a daily eating pattern that is possibly protective against overweight and obesity [21]. Large-scale observational studies using nationally representative samples have consistently supported inverse associations between breakfast consumption and adiposity outcomes [20,22–26], as have a systematic review and meta-analysis of European [27] and Asian/Pacific [28] studies, which included studies with cross-sectional designs. A National Evidence Library (NEL) systematic review conducted by the US Department of Agriculture (USDA) in 2010 including 15 non-cross-sectional international studies (one randomized controlled trial [RCT], one non-RCT, and 13 prospective cohort studies) published between 2000 and 2010 [21] found moderate strength of evidence for increased risk of overweight and obesity among children who do not eat breakfast, with a stronger association observed among adolescents. This review supported a 2005 review of 16 studies published between 1970 and 2004, which also reported a generally positive association between breakfast skipping and childhood adiposity despite higher daily energy intake relative to skippers [14]. Between the years 2010 and 2015, 12 additional non-cross-sectional studies were published, including 10 longitudinal, 1 case control, and 1 experimental study ([29], Table 6.3). Eight of the ten longitudinal studies along with the case control and experimental study reported inverse associations between breakfast consumption and adiposity. The sole experimental study investigated breakfast in combination with a nutrition education program; it found that, after one school year, children in the intervention group experienced reductions in body mass index (BMI) while those in the control group (education alone) experienced increases in BMI. Overall, effect sizes and likelihood/risk estimates for these studies ranged considerably, and the variety of adiposity indices used renders cross-study comparison challenging. Regardless, the magnitudes of several estimates were notable, particularly in the two studies with the longest follow-up time [30,31], which may better reflect the long-term impact of breakfast consumption throughout development. One reported a 3.74 kg/m$^2$ mean difference in waist circumference and 1.31 cm mean difference in BMI [31], while the other reported a 2.18 times greater risk of central adiposity among breakfast skippers compared with consumers [30]. The results achieved in the experimental study are especially promising. In the experimental group, the prevalence of overweight dropped 10.2% among boys (31.5–21.3) and 7.7% among girls (21.7–14), while the prevalence of obesity dropped 2.4% (7.9–5.5) among boys and 0.8% among girls (4.7–3.9) [32]. Although the remaining studies reported relatively smaller effect sizes, even these could have meaningful implications at the population level. Together, the results of these studies, in combination with previous reviews and cross-sectional studies reporting similar findings, support some role for breakfast consumption in the prevention of overweight and obesity among children. However, methodological limitations, discussed in the conclusion, render casual conclusions elusive.

SNACKING

PREVALENCE AND TRENDS

In the United States, the majority of studies considering nationally representative samples report notable increases in snack consumption among children over the past four decades [33–37]. According to the most recent National Health and Nutrition Examination Survey (NHANES) data (2009–2010), the vast majority (96% ages 2–19 years) of children consume at least one snack per day, approximately half of whom consumed two or three per day [1]. On average, children who consume snacks do so 2.2 times per day [38]. Repeat cross-sectional analysis of NHANES (1977–1978 to 2003–2006) investigating trends in snacking behavior over time indicates that the prevalence of snacking among all children increased from 74% to 98% overall, with the average number of snacks consumed per day nearly doubling within each age group. The most substantial increases were observed from 1989 to 1994 and 1994 to 2006 [37]. Children ages 2–6 years consumed the
<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Location Study Name</th>
<th>Design, Follow-up</th>
<th>Sample</th>
<th>Exposure (Definition and Measurement)</th>
<th>Outcome(s) (Definition and Measurement)</th>
<th>Key Findings (Based on Fully-Adjusted Regression Models)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith, 2010</td>
<td>Australia CDAH</td>
<td>Longitudinal, 21 years</td>
<td>$n = 2184$ (53% female) Age at baseline: 7–15.0 years</td>
<td>Breakfast consumption defined as usual breakfast consumption before school (at baseline) and as eating a snack, small meal, or large meal 6–9 a.m. (at follow-up), categorized into four childhood to adulthood breakfast behavior trajectory groups. Child reported. Assessed by a single-item response on a FFQ at baseline and meal pattern chart at follow-up.</td>
<td>Mean difference in continuous BMI and waist circumference (measured height and weight and waist circumference).</td>
<td>Participants who reported skipping breakfast in childhood and adulthood had larger waist circumference ($\beta = 3.74, CI: 0.83, 6.65$) and higher BMIs ($\beta = 1.31, CI: 0.03, 2.59$) than those who reported eating breakfast at both time points.</td>
</tr>
<tr>
<td>Haerens, 2010</td>
<td>Belgium Longitudinal Eating and Activity study</td>
<td>Longitudinal, 3 years</td>
<td>$n = 3716$ (48% female; 98% Belgian) Age at baseline: 10.0 years</td>
<td>Breakfast defined as the number of week and weekend days on which children reported consuming breakfast (never, 1–2 weekend days, 1–5 weekdays). Child reported. Assessed by a supplementary FFQ question asking participants to mark the number of week and weekend days they had breakfast.</td>
<td>BMI z-score (self-reported height and weight). Flemish reference standards.</td>
<td>Breakfast consumption frequency was inversely associated with BMI z-score across four measurement time points ($\beta = -0.03, SE = 0.012, p &lt; .01$).</td>
</tr>
<tr>
<td>Laska, 2012</td>
<td>MN, United States IDEA/ECHO</td>
<td>Longitudinal, 2 years</td>
<td>$n = 693$ (51% female; 86% white) Age at baseline: 14.6 years</td>
<td>Breakfast consumption frequency defined as the percentage of recall days on which participants reported eating a meal called breakfast containing ≥50 cal. Child reported. Assessed by three telephone-administered 24 h dietary recalls (telephone administered) and operationalized as proportion of recalls reporting eating breakfast.</td>
<td>Continuous BMI (measured height and weight) and percentage body fat (digital BIA scale).</td>
<td>Breakfast consumption was inversely associated with BMI and percentage cross-sectionally among males (BMI: $\beta = -5.08, SE = 1.53, p = .001$; PBF: $\beta = -8.82, SE = 2.81, p = .002$) and females (BMI: $\beta = -4.33, SE = 1.62, p = .008$; PBF: $\beta = -7.30, SE = 2.22, p = .001$) but not longitudinally.</td>
</tr>
<tr>
<td>Tin, 2012</td>
<td>Hong Kong, China</td>
<td>Longitudinal, 2 years</td>
<td>$n = 68,606$ (51% female; 100% Chinese) Age at baseline: 9.9 years</td>
<td>Breakfast consumption defined as usually eating breakfast at “home,” “fast food/cafe/restaurant,” or “some other place” (breakfast skipping defined as eating “no breakfast at all”). Child reported. Assessed by questionnaire.</td>
<td>Mean difference in continuous BMI (measured height and weight).</td>
<td>Compared with eaters, baseline breakfast skippers experienced a greater increase in BMI in the subsequent 2 years ($\beta = 0.11, CI: 0.07, 0.16, p &lt; .001$). The effect was stronger among children who also skipped lunch and children who watched ≥2 h of television per day.</td>
</tr>
</tbody>
</table>
### Chang, 2013
United States  
**ECLS-K**  
**Longitudinal**, 3 years  
\( n = 6220 \) (51% female; 66% white, 16% Hispanic, 8% African American)  
Age at baseline: 11.2 years  
Breakfast consumption defined as positive response to the prompt: “At least some of the family eats breakfast together.”  
Parent reported.  
Assessed by computer-assisted telephone or personal interview.  
Likelihood of change in weight trajectory group for nine mutually exclusive weight trajectory groups based on BMI (measured height and weight), category (healthy, overweight, obese), CDC growth charts  
Children who consumed breakfast were more likely to revert from being overweight in the fifth grade to being normal weight in the eighth grade, compared with those who did not (OR: 1.02, CI: 1.0, 1.03).  
There were no significant changes across other weight trajectory groups.

### Drenowatz, 2013
Germany  
**Longitudinal**, 1 year  
\( n = 1495 \) (49% female; 22% migration background)  
Age at baseline: 7.0 years  
Breakfast consumption defined as frequency of child having breakfast before school.  
Parent reported.  
Assessed by questionnaire.  
Likelihood of weight gain compared with loss, defined by a ≥5 percentage point increase or decrease in age- and sex-specific BMI percentile (measured height and weight).  
German reference standards.

### Quick, 2013
MN, United States  
**Project EAT I-III**  
**Longitudinal**, 10 years  
\( n = 1643 \) (54% female)  
Age at baseline: 15.0 years  
Breakfast consumption defined as frequency of breakfast consumption in the past week.  
Child reported.  
Assessed by FFQ with a supplementary question on breakfast consumption frequency.  
Ten-year incidence of overweight (self-reported height and weight, validated by measured height and weight among a subsample).  
CDC growth charts  
Females with higher breakfast consumption frequency during adolescents experienced lower incidence of overweight at 10-year follow-up (OR = 0.91, CI: 0.86, 0.97).  
Increased number of days/week breakfast eaten with family was associated with decreased BMI z-score (\( \beta = -0.04, \text{CI: } -0.07-0.02, p = .027 \)) and PBF (\( \beta = -0.35, \text{CI: } -0.69, -0.02, p = .039 \)).

### Carlson et al., 2012
San Diego County, United States  
**MOVE Project**  
**Longitudinal**, 2 years  
\( n = 254 \) (56% female; 39% white, 48% Latino)  
Age at baseline: 6.7 years  
Breakfast consumption defined as the number of times per week the child ate breakfast with his or her family.  
Parent reported.  
Assessed by questionnaire.  
BMI z-score (measured height and weight) and percentage of body fat (BIA, PBF calculated using Schaefer equation).  
CDC growth charts  
Risk of being overweight at age 5 based on BMI z-score (measured height and weight).  
Dutch reference growth charts (1997) and Cole’s BMI category cutoff for overweight status.

### Kupers, 2014
Netherlands  
**GECKO Drenthe Cohort**  
**Longitudinal**, 3 years  
\( n = 1,366 \) (50% female; 93% Dutch)  
Age at baseline: 2.1 years  
Breakfast consumption defined as the weekly frequency (“How often does your child eat breakfast weekly?”), categorized as “eating breakfast daily” (7/week) or “not eating breakfast daily” (<7/week).  
Parent reported.  
Assessed by questionnaire.  
Risk of being overweight at age 5 based on BMI z-score (measured height and weight).  
Dutch reference growth charts (1997) and Cole’s BMI category cutoff for overweight status.

(Continued)
<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Location Study Name</th>
<th>Design, Follow-up</th>
<th>Sample</th>
<th>Exposure (Definition and Measurement)</th>
<th>Outcome(s) (Definition and Measurement)</th>
<th>Key Findings (Based on Fully-Adjusted Regression Models)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wennberg, 2014</td>
<td>Sweden Northern Swedish Cohort</td>
<td>Longitudinal, 27 years</td>
<td>(n = 889) Age at baseline: 16 years</td>
<td>Breakfast consumption determined by participants' response to the question: “What did you have for breakfast this morning?” and underlining of commonly consumed breakfast items. Responses dichotomized into “Eating breakfast” and “Poor breakfast habits” (breakfast skippers and participants who only reported a beverage or something sweet, (n = 88)) at age 16. Child-reported. Assessed by questionnaire (classroom at age 16, reunion/mail at age 43).</td>
<td>Risk of central obesity at follow-up (measured waist circumference, defined as (\geq 80) cm for women or (\geq 94) cm for men). IDFG guidelines.</td>
<td>Participants with poor breakfast habits were at increased risk of central obesity (OR: 2.18, CI: 1.31, 3.60).</td>
</tr>
<tr>
<td>Zurriaga, 2011</td>
<td>Spain OBICE</td>
<td>Case-control</td>
<td>(n = 1188) (44% female), 437 cases, 751 controls Mean age: 8.8 years</td>
<td>Breakfast consumption measured as frequency of breakfast consumption per week, dichotomized as regular breakfast consumption vs. not. Assessed by two questionnaires asking about frequency of breakfast consumption: one completed by the participants' pediatrician and the other by the children's families as part of a FFQ.</td>
<td>Risk of childhood obesity defined as BMI &gt;95th age-sex BMI percentile (measured height and weight). Fundacion Orbegozo-Sobradillo tables.</td>
<td>Regular breakfast consumption was associated with reduced risk of obesity (OR: 0.5, CI: 0.26, (p = .042)).</td>
</tr>
<tr>
<td>Campos Pastor, 2012</td>
<td>Spain NEP</td>
<td>Cluster randomized trial, one school year</td>
<td>(n = 256) (50% female) Mean age: 13.9 years</td>
<td>Daily breakfast (consisting of a dairy product, fruit, cereal, nuts, and a sandwich with protein filling, either tuna or ham and totaling 275–350 cal) provided by the school in combination with the NEP program compared with NEP only.</td>
<td>Continuous BMI (measured height and weight) and prevalence of overweight/obesity, waist circumference (measured), and fat mass/lean mass measured via BIA. Cole's BMI cutoffs.</td>
<td>Males and females in the intervention group experienced reductions in BMI ((p &lt; .001)) and in waist circumference among females only ((p &lt; .001)). Prevalence of overweight dropped 10.2 percentage points among boys (31.5–21.3) and 7.7% among girls (21.7–14) and the prevalence of obesity dropped 2.4% (7.9–5.5) among boys and 0.8% among girls (4.7–3.9). BMI and waist circumference significantly decreased among children who were normal weight or overweight at baseline ((p = .001)), whereas only BMI decreased among children who were obese at baseline ((p = .02)).</td>
</tr>
</tbody>
</table>

Note: BIA, bioelectrical impedance analysis; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; FFQ, food frequency questionnaire; NEP, Nutrition Education Program; OBIDF, International Diabetes Federation; OR, odds ratio; PBF, percent body fat.
The Influence of Daily Eating Patterns on Weight Status

The greatest number of snacks per day (2.75) and were also the group with the largest increase occurring from 1977 to 2006 (~1.41 additional snacks per day). While energy-dense, nutrient-poor snack foods and beverages are widely available across diverse settings where young people spend time, including schools, corner stores, and recreational facilities [39–41], most snacking occurs in the home [35,37,41]. Since more than two-thirds of calories are consumed in the home, the vast majority of which come from food purchased from stores [1], enabling and encouraging healthy choices at the point-of-purchase could go a long way toward improving the home food environment and diet quality. Such policy efforts, some already underway, include ingredient regulation (e.g., sodium and trans fat), nutrition facts panel updates (added sugars, percentage daily value footnote), and front-of-package labeling.

With regard to snack composition, desserts and sweetened beverages contributed the greatest number of calories to total energy consumed from snacks, despite an observed decrease in dessert consumption from 2003 to 2006 [37]. The second main source of energy from snacking was salty snacks, such as crackers, chips, popcorn, and pretzels, which experienced the largest increase in the past three decades and accounted for the largest increases in snacking occasions through 2006 [37]. While a more recent subgroup analysis of NHANES data from the years 2003–2010 reported no changes in the percentage of daily energy derived from sweet and salty snacks in the full sample, significant declines were observed among children of select race/ethnicity and/or weight-status categories [43]. Specifically, among overweight and obese adolescents, the percentage consuming sweet snacks declined significantly over the study period (59% vs. 50) and was significantly lower than the healthy-weight adolescents in both time periods (2003–2006: 59% vs. 65%; 2007–2010: 50% vs. 64%). In the most recent survey year, overweight/obese adolescents consumed significantly fewer calories from salty snacks than healthy-weight adolescents (253 vs. 295 kcal). Among white children aged 2–5 years and 6–11 years who were overweight/obese, calories from salty snacks declined significantly (age 2–5 years: 192 vs. 134 kcal; age 6–11: 273 vs. 200 kcal). Among black children aged 12–19 years and at a healthy weight, calories from salty snacks also declined significantly (343 vs. 283 kcal). With respect to sweet snacks, significant declines in calories consumed were observed among white children aged 2–5 years who were at a healthy weight (217 vs. 184 kcal) [43]. Assuming overweight and obese children did not underreport consumption, these results suggest that improvements in snack quality, especially among those at highest risk, may be improving and possibly contributing to the leveling trends in obesity and the 201 kcal/day reduction in total calorie intake observed from 2003–2004 to 2009–2010 among 2- to 18-year-olds [44].

Coinciding with the increase in snacking occasions has been an increase in the percentage of energy derived from snacks. In fact, children consumed approximately 168 more calories a day from snacking from 1977–1978 to 2003–2006, reaching 27% of total daily intake in 2006 [37], an estimate which has remained relatively stable since, with 26% of energy (516 kcals) coming from snacks among 2- to 19-year-olds, according to 2011–2012 NHANES data [45]. Consistent with the increase in snacking calories, the largest increase in total energy was found among children ages 2–6 years, who consumed 182 cal more per day over the three decades observed [37]. NHANES 2011–2012 estimates show that 2- to 5-year-old males and females continue to consume 30% and 31% of energy from snacks (relative to roughly 24.5% among 6–11 and 12-19-year-old children) [45]. The increase in calories from snacks paralleled a 113 total calorie increase per day from 1977 to 2006 [37]. Although a small decline in calories per snacking event was observed from 1994 to 2006 among all age groups, the increased energy per snack from 1977 to 2006 was significant, and grams of food consumed per snack event also increased significantly from 1977 to 2003 in all age groups (~50 g more per snack). NHANES 2009–2010 data support these estimates, with nearly 500 cal to daily energy intake, equating to roughly one-quarter of total energy intake (498 kcals; 25.7%) coming from snacks. Independent of beverages consumed as snacks, snack foods contributed 20% (379 kcals) of total daily energy in children. Moreover, total energy intake increased with snacking frequency, with children reporting four or more snacking occasions per day consuming an average 19% more total energy compared with nonsnackers [40]. Given the overall leveling in
obesity rates in recent years, the stable contribution of snacks to total calories suggests that children are consuming less at meals and/or increasing physical activity levels in order to keep calories at a steady or lower rate. A possible decrease in caloric beverage consumption, a behavior possibly not falling into either the meal or snack category, could also be responsible.

**Relationship with Weight Status**

Despite the observed trends in snacking behavior over the past several decades, whether the observed changes in frequency, type, and contribution of snacks to total daily energy intake has contributed to rising obesity rates is a research question lacking a definitive answer. The most recent review of evidence on the relationship between snacking and weight status among children and adolescents was published in 2013 (Larson and Story) and included 2 case control, 23 cross-sectional, and 7 longitudinal studies published internationally between January 2000 and December 2011 [41]. The exclusion of studies with exposure variables that could independently impact adiposity, such as dietary pattern scores/categories, consumption venue, advertisement source, and/or particular foods, left 15 cross-sectional and 2 longitudinal studies looking exclusively at snacking frequency, snack timing, and/or percentage energy from snacks. Of the 15 cross-sectional studies, 3 reported positive associations (one only for snacks consumed after dinner), 8 found no association, and 4 reported negative associations (one only among males in urban areas) between snacking behavior and adiposity outcomes. One of the longitudinal studies found no association, while the other reported an inverse association between snacking frequency and risk of excess adiposity. The five remaining longitudinal studies reported on either dietary pattern adherence ($n=3$) or consumption of specific snack foods ($n=2$), which may independently impact weight status. Two measured adherence to an empirically derived snacking pattern and found null associations; one reported a positive association between adherence to a pattern that combined energy intake and expenditure indices (snacking + sedentary pattern, characterized by energy-dense snacks and television watching). Finally, two found no association between energy-dense snack consumption and adiposity outcomes. Taken together, the results from the longitudinal studies included in the review suggest little evidence for a favorable or adverse impact on adiposity even among those consuming poor-quality snacks.

In light of these inconsistent findings, researchers have continued to investigate the relationship between snacking and adiposity among children. Table 6.4 provides details on studies published since 2012. As with the recent studies on breakfast, the majority took place outside the United States, representing seven unique countries (Norway, China, Korea, Italy, Japan, Greece, and the United States). Overall, findings were evenly split by direction of impact, with three reporting null associations [40,46,47], three reporting inverse associations [48–50], and three reporting positive associations between snacking and adiposity outcomes [51–53]. The majority of the studies were cross-sectional. The two longitudinal studies both reported positive associations between snack consumption and BMI, detailed as follows [51,52].

The first sampled 1504 children (474 first graders and 1030 fourth graders) in Korea participating in the Obesity and Metabolic Disorders Cohort in Childhood registry, which collected data on physical activity, dietary intake, and socioeconomic status through self-administered questionnaires, and measured height and weight annually for 2 years [51]. Dietary intake was recorded for 2 weekdays and 1 weekend day by a 24 h dietary recall, with the frequency of skipping meals and snack intake reported. Physical activity was measured via self-report and quantified as days with moderate physical activity of more than 30 min duration or vigorous physical activity of more than 20 min duration. In a cross-sectional analysis, BMI of first and fourth graders was positively associated with frequent snack consumption ($p = .049$). BMI increased in both groups over time; however, in longitudinal analyses, controlling for energy intake and physical activity, frequent snack consumption ($p = .010$) predicted change in BMI only among fourth graders. The second longitudinal study published since 2012 analyzed data collected from 45,392 participants in the twenty-first-century Longitudinal Survey in Newborns in Japan to identify time-dependent and independent
<table>
<thead>
<tr>
<th>First Author, Year Location</th>
<th>Study Name</th>
<th>Design, Follow-up</th>
<th>Sample</th>
<th>Exposure (Definition and Measurement)</th>
<th>Outcome(s) (Definition and Measurement)</th>
<th>Key Findings</th>
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<tbody>
<tr>
<td>Grydeland, 2012 Norway The HEIA</td>
<td>Cross-sectional</td>
<td>( n = 1103 ) (50% female)</td>
<td>Mean age: 11.2 years</td>
<td>Intake of snacks assessed by four questions; “how often do you eat chocolate/candy, salty snacks, cookies and buns/cakes/pastry,” with seven response categories ranging from “never/seldom” to “twice a day or more.” All variables were recorded into frequency of intake per week and summed. Child-reported. Internet-based questionnaire.</td>
<td>Risk of overweight (measured height and weight). IOTF BMI cutoffs.</td>
<td>Snack frequency was not associated with weight status ( (\beta: 0.97; \text{CI: 0.92, 1.03}; p = .30). )</td>
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<tr>
<td>Guo, 2012 China</td>
<td>Cross-sectional</td>
<td>( n = 4,262 ) (49% female)</td>
<td>Mean age: 11.04 years</td>
<td>Frequency of snacking defined as: “never or occasionally,” “less than once a week,” “1–3 days per week,” “4–6 days per week,” and “everyday.” Child-reported. Questionnaire.</td>
<td>Risk of overweight and obesity (measured height and weight). IOTF BMI cutoffs.</td>
<td>Participants who never or occasionally consumed snacks were at increased risk of excess adiposity (OR overweight: 1.074; CI: 0.904, 1.276; ( p = 0.418 ); OR obese: 1.348; CI: 1.039, 1.748, ( p = 0.025 )).</td>
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<tr>
<td>Jelastopula, 2012 Greece</td>
<td>Cross-sectional</td>
<td>( n = 200 ) (54% female)</td>
<td>Mean age: 11.2 years +/-0.8</td>
<td>Snacking frequency defined as having an afternoon snack daily, sometimes, or never. Child-reported. In-person interviews using a 24-item questionnaire.</td>
<td>Overweight and obesity, mean BMI, and waist circumference (measured height and weight). IOTF BMI cutoffs.</td>
<td>Rates of overweight and obesity were significantly higher among children who never consumed an afternoon snack ((44.7% \text{ overweight and } 25.5% \text{ obese})) compared with children who consumed an afternoon snack daily ((25% \text{ overweight and } 2.5% \text{ obese})) ((p &lt; .001)). Daily afternoon snack consumption was associated with significantly lower BMI ((\beta: –3.020 \text{ kg/cm}^2; \text{CI: –4.410, –1.629}; p &lt; .001)). Consuming a snack daily and sometimes were inversely associated with waist circumference ((\beta: –5.65; \text{CI: –9.28, –2.02}; p = .002; \beta: –4.12; \text{CI: –7.1, –1.13}; p = .007)). (Continued)</td>
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<tr>
<td>First Author, Year Location Study Name</td>
<td>Design, Follow-up</td>
<td>Sample</td>
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<td>Lee, 2014 Korea Obesity and Metabolic Disorders in Children registry</td>
<td>Longitudinal, 2 years</td>
<td>n = 1504</td>
<td>Meal skipping and snack intake. Child-reported. 24 h recalls administered on 2 weekdays and 1 weekend day.</td>
<td>Mean BMI change (measured height and weight).</td>
<td>At 2-year follow-up, snack consumption was positively associated with increase in BMI among fourth graders ($\beta$: 0.278; CI: 0.066, 0.490; $p = .010$) but not among first graders. No association was found between meal skipping and BMI change over 2 years among first or fourth graders.</td>
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<tr>
<td>Bo, 2014 Italy</td>
<td>Cross-sectional</td>
<td>n = 400 (48% female) Mean age: 12.1 years</td>
<td>Percentage of total daily calorie intake from snacks (&lt;15%, 15%–20%, &gt;20%), daily snacking frequency (1, 2, ≥3), and timing of consuming the most caloric snack (morning, afternoon, evening). Parent reported. 24 h dietary recall and a 19-item FFQ.</td>
<td>Mean BMI, BMI percentile, overweight/obesity (measured height and weight). Italian growth charts (overweight/obesity defined as BMI ≥85th percentile based on age- and gender-specific BMI).</td>
<td>Proportion of daily calories derived from snacks, snacking frequency, and evening snacking were positively associated with mean BMI, BMI percentile, and overweight/obesity status. Children consuming 15%–20% and &gt;20% of kcals from snacks had significantly higher risk of overweight/obesity compared with those consuming &lt;15% of daily kcals from snacks (RR: 1.35; CI: 0.58, 3.15; $p = .49$ and RR: 2.32; CI: 1.10, 4.89; $p = .03$, respectively). Relative to children consuming one snack/day, those consuming two snacks were at higher risk of overweight or obesity (RR: 2.20; CI: 1.02, 5.27; $p = .08$), with those consuming ≥3 snacks at greatest risk (RR: 4.17; CI: 1.60, 10.9; $p = .004$). Children consuming the most energy-dense snack in the evening were at higher risk for overweight/obesity compared with those consuming it in the morning (RR: 3.12; CI: 1.17, 8.34; $p = .02$). Snack servings/day did not vary significantly between normal and overweight children (mean [SD] of 1.84[1.0] vs. 1.71[0.9], respectively; $p = .082$).</td>
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<tr>
<td>Hauser, 2014 MA, United States</td>
<td>Cross-sectional</td>
<td>n = 820 (51.7% female) Mean age: 7.6 years</td>
<td>Number of snacks consumed per day.</td>
<td>Overweight (defined as BMI &gt;85th percentile) and obesity (BMI &gt;95th percentile), based on measured height and weight. CDC growth charts.</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Sample Size</td>
<td>Age at Baseline</td>
<td>Follow-up</td>
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<td>Franchetti, 2014</td>
<td>Longitudinal, 5.5 years</td>
<td>n = 45,392 (48% female)</td>
<td>Age at baseline: 0 years (birth)</td>
<td>Follow-up: 4.5 years for breakfast and snack consumption variables and 5.5 years for BMI</td>
<td>Consumption of breakfast, lunch, dinner, and snacks classified as regular, irregular, or no consumption. Parent reported. Questionnaires.</td>
<td>Mean BMI, overweight (≥85th percentile) and obesity (≥95th percentile) (parental reported height and weight at birth).</td>
</tr>
<tr>
<td>Grigorakis, 2015</td>
<td>Cross-sectional</td>
<td>n = 124,113 (49.2% female)</td>
<td>Mean age: 9.9 years</td>
<td></td>
<td>Snack consumption at school during the school day or in the afternoon between lunch and dinner (yes/no) and type of snacks usually consumed (fruits or fruit juice, toast or sandwich, dairy products, salty snacks, and sweets). Child reported with assistance of teachers. Seven-day diet recall questionnaire (closed-question multiple choice format), validated.</td>
<td>Central obesity defined as waist-to-hip ratio ≥0.5 (measured waist and hip circumferences).</td>
</tr>
<tr>
<td>Gugger, 2015</td>
<td>Cross-sectional</td>
<td>n = 2985 (2–18 years)</td>
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<td></td>
<td>Frequency of snacking and nutrient contribution from snacks. One-day 24 h recall from NHANES 2011–2012.</td>
<td>BMI (body weight and height measured), categorized into overweight/obese status.</td>
</tr>
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</table>

Note: BIA, bioelectrical impedance analysis; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; FFQ, food frequency questionnaire; HEIA, HEalth In Adolescence; IOTF, International Obesity Task Force; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; PBF, percent body fat; RR, relative risk.
demographic, social, and lifestyle factors that affect change in BMI across 5.5 years [52]. Snack consumption was classified into regular, irregular, or no consumption. In final, longitudinal models, irregular snack consumption was inversely associated with BMI ($\beta = -0.047, p = .01, CI: -0.083, -0.010$). Though this study did not control for physical activity or energy intake, it did include television hours, sleep duration, and regular meal consumption in regression models. Notably, both studies took place in Asian countries and neither study measured snack composition nor quality. Nonetheless, their findings add to the existing body of evidence.

The recent cross-sectional studies included in Table 6.4 reported null findings in Norway [47] and the United States [40,46], inverse findings in China [48] and Greece [49,50], and positive in Italy [53]. In addition to studies measuring snacking behavior directly, three studies published since 2013 have investigated associations between empirically derived snacking patterns and adiposity outcomes. Two used longitudinal data, one reporting null [54] associations between snacking and adiposity outcomes across eight European countries and the other, conducted in Bogota, Columbia, reporting a positive association [55]. A third cross-sectional analysis of NHANES data reported inverse associations with several of the empirically derived snacking patterns in the United States, despite snacking pattern adherence also being associated with increased energy intake [56]. As a whole, the disparate nature and findings of these studies make it difficult to draw general conclusions about the relationship between snacking and weight status among children.

## EATING FREQUENCY

### Prevalence and Trends

Although breakfast consumption and snacking behavior may contribute to and, therefore, correlate with increased eating frequency, the latter term has been used to encompass all daily eating occasions, regardless of size or composition. Consequently, eating frequency has been considered independently of breakfast and snacking behavior as an exposure variable. Nationally representative US trend data from children aged 2–18 years suggest that the number of daily eating and drinking occasions has increased from 3.9 to 5.1 between 1977–1978 and 2005–2010. Total daily energy intake increased by a net 108 kcal/day over the same time frame (with the greatest increase of 173 kcal/day occurring between 1989–1991 and 1994–1998 and a modest decline of 85 kcal/day occurring between 1994–1998 and 2005–2010), and evidence suggests that changes in daily eating patterns may have contributed [57–59]. Changes in the number of eating occasions accounted for a 2 kcal/day decrease per year from the late 1970s to the early 1990s but were followed by an increase of 69 kcal/day per year through 1998. Between 1977–1978 and 1989–1991, changes in the average portion size per eating occasion accounted for 5 additional kcal/day/year of the annualized increase in total energy intake and a decrease of 31 kcal/day/year of the decline in energy between 1994–1998 and 2005–2010. Changes in the number of eating occasions, on the other hand, accounted for 2 fewer kcal/day/year between 1977–1978 and 1989–1991 but an additional 69 kcal/day/year between 1989–1991 and 1994–1998. The energy density of foods increased over this time period, from 2.0 kcal/g/eating occasion in 1977–1978 to 2.19 kcal/g/eating occasion in 2005–2010. These changes reflect larger increases in the total daily energy from foods (111 kcal/day increase) relative to beverages (4 kcal/day decrease) over the past 30 years, with the number of daily eating occasions responsible for the largest portion of increase of 19 kcal/day/year in total energy intake and a decrease in portion size per eating occasion accounting for a 13 kcal/day/year decrease in the annualized change [60].

### Relationship between Eating Frequency and Weight Status

The first study to investigate the relationship between eating frequency and weight outcomes among children was conducted in the late 1960s, in which participants from a school-based sample were...
assigned to a three or seven meal-per-day condition. Although the two groups had similar total energy intake, children assigned to the three daily meals group gained more weight compared with those assigned to seven meals per day [61]. Since this seminal study, the majority of research has used cross-sectional study designs. A meta-analysis of these studies published in 2013 (Kaisari et al.) systematically assessed the association between eating frequency and excess adiposity in children and adolescents [62]. The analysis included 21 cross-sectional studies representing a total sample size of 18,849 subjects and reported an inverse association between eating frequency and overweight/obesity status. Specifically, children and adolescents who had a higher number of eating episodes per day had a 22% lower probability of being overweight or obese compared with those who had fewer episodes. However, after stratifying the results by sex, the inverse association only held among boys, suggesting possible differences in dietary patterns and behaviors and their effect on overweight/obesity, though the authors caution that publication bias and the significant heterogeneity observed in the results of the selected studies warrant caution in interpreting these findings.

Three longitudinal studies have also investigated the relationship between eating frequency and weight status among children. The first found a positive association between eating frequency and change in BMI z-score among girls (8–12 years at baseline, 11–19 at follow-up) [63], the second reported an inverse association between eating frequency and increase in BMI over 10 years (9–10 years at baseline, 19–20 at follow-up) [64], and the third found a positive association cross-sectionally at baseline and longitudinally at 6- but not 12-month follow-up [65]. A fourth longitudinal study [66], looking specifically at meal frequency in a sample of Norwegian children, reported increased odds of overweight among children who no longer consumed regular meals in seventh grade compared with fourth grade (OR: 3.1; CI: 1.1, 9.0), controlling for sex, socioeconomic status, and physical activity, but not after controlling for fourth-grade weight status (OR: 2.8; CI: 0.7, 11.6). A recent cross-sectional study examined the associations of eating frequency with metabolic risk factors in British children and adolescents and found that eating frequency was positively associated with BMI z-score in adolescents only (p = .004), controlling for total energy intake and physical activity levels. Although eating frequency was inversely associated with total cholesterol and LDL-cholesterol concentrations (p = .01 and .04, respectively) among children, no associations were detected for BMI [67]. On the other hand, an analysis of data collected from a population-based sample of 16-year-old boys and girls (n = 6247) participating in the Northern Finland Birth Cohort 1986 found that adolescents who ate five meals/day (compared with those consuming fewer) were at lower risk for overweight/obesity (OR for boys: 0.47, CI: 0.34, 0.65; OR for girls: 0.57, CI: 0.41, 0.79) and abdominal obesity (OR for boys: 0.32, CI: 0.22, 0.48; OR for girls: 0.54, CI: 0.39, 0.75), after adjusting for later childhood factors [68]. A subsequent analysis suggested that the five meal/day pattern attenuated children’s genetic predisposition toward overweight/obesity, though more research is needed to confirm these findings and to explore interindividual response differences more generally [69].

**DISCUSSION AND CONCLUSION**

Based on the evidence presented in this chapter for each of the three main daily eating pattern-related exposure variables (i.e., breakfast, snacking, and eating frequency) and adiposity-related outcomes among children and adolescents, the evidence supporting a protective effect of breakfast consumption on childhood obesity is most comprehensive and consistent. On the other hand, associations between snacking and eating frequency are less consistently significant and unidirectional. In relating and discussing the relative strength of evidence, it is important to underscore the methodological challenges and limitations of extant literature, inherent and common among all three bodies of literature [66].

First and foremost, the majority of studies on daily eating patterns have employed observational designs and, therefore, regardless of the consistency of results, preclude causal inference. While longitudinal designs address issues of temporality and reverse causality, stronger study designs are
needed to overcome the potential for residual confounding by unobservable or unmeasured variables. However, because prescribed daily eating patterns are difficult to assign and adhere to, in addition to presenting ethical challenges among children, natural experiments and/or innovative methods of data collection and analysis could compensate, in part, for these methodological challenges.

Regardless of study design, a first priority in eating pattern research is developing standardized operational definitions and assessment methods for the daily eating behaviors of interest (i.e., breakfast, snack, eating occasion) [70] and adiposity outcomes of interest (i.e., continuous BMI, BMI percentile, or BMI z-score and reference population/cutoffs). Acknowledging this weakness in current methodology, the Scientific Report of the 2015 Dietary Guidelines Advisory Committee recognized the standardized exposure and outcome assessment methods and the development of operational definitions for meals and snacks as priorities for future research in this area due to the disparate and sometimes conflicting definitions currently in use, which impede comparison across studies [1].

In addition to stronger study designs and the application of standardized primary exposure and outcome definitions, findings from observational studies could be strengthened by employing more precise, valid, and standardized measurements of confounding, effect modifying, and mediating variables. In this regard, two are of top priority: total energy intake and energy expenditure (i.e., physical activity). Because these are the two most proximal determinants of energy balance and possibly associated with or determinants of daily eating patterns, failing to test each as potential confounding and mediating variables renders results less useful. Previous studies have linked breakfast consumption with increased energy intake and/or physical activity, but few have thoroughly investigated the relationship between these outcomes and weight status [71]. Second to energy intake and expenditure, the measurement of meal and snack composition and quality is of utmost priority. Without this information, it is impossible to know whether it is the eating occasion/frequency or content that is impacting adiposity outcomes. Breakfast, in particular, may be a proxy for better overall diet quality and/or linked with other positive health behaviors that are protective against obesity. To this end, controlling for overall diet quality would also be useful. Longitudinal studies should also control for a baseline measure of adiposity. Beyond these essential variables, considering differences by sex, race/ethnicity, and socioeconomic status could shed light on potential factors that could modify the relationship between daily eating patterns and adiposity outcomes. Findings from these analyses could optimally direct the targeting of public health messaging and interventions toward specific subgroups. Finally, in drawing conclusions about existing and future research as a whole, potential publication and funding biases need to be considered and taken into account. Conclusive evidence on associations between the timing and distribution of energy intake across daily eating occasions and adiposity outcomes among children could lend itself to targeted public health messaging, interventions, and campaigns. In the meantime, efforts aimed at improving the quality of foods consumed at every eating occasion, regardless of time of day, place, or quantity consumed, should be continued and prioritized in the fight against childhood obesity.

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The Influence of Daily Eating Patterns on Weight Status


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INTRODUCTION

Large portion sizes of palatable, energy-dense foods were first suggested to be a part of the obesogenic food environment almost two decades ago [1]. Today’s children and adults have ubiquitous exposure to large food and beverage portion sizes in the marketplace, from large single-serving containers and family-value multiple-serving containers found in grocery and convenience stores to food and beverage offerings at fast-food and full-service restaurants [2,3]. The appeal of large food portions to consumers, including families with young children, is enhanced by aggressive marketing efforts for foods high in sugar and fat, as well as by pricing incentives for the purchase of larger portion sizes (i.e., value pricing) [4].

Population-based intake data show increases in portion sizes consumed by US children and adults over the past 40 years [5,6]. Increases in the average portion size consumed have been seen across many different types of categories of foods, with the largest increases seen for pizza, burgers, Mexican food, soft drinks, and salty snacks. Secular trends toward larger portion sizes have not only been seen for foods consumed at restaurants where portions tend to be largest, but also at home. Increases in portion size have also been seen for snacks high in solid fats and added sugars, which are frequently consumed by children [7]. Trends toward large portion sizes in combination with more frequent eating have produced increases in energy intake in the US population over the period when obesity began to emerge as a threat to public health in the United States and worldwide [8]. These and other epidemiological data fueled concerns that large portion sizes have played a causal role in the childhood obesity epidemic [9]. While providing population-representative “signals,” it is important to note that epidemiological studies do not provide causal evidence of portion-size effects on excessive energy intake.

EFFECTS OF PORTION SIZE ON CHILDREN’S FOOD AND ENERGY INTAKE

Much of the research on food portion size in children has focused on preschoolers (age 3–5 years), but has also included children ranging in age from 2 to 9 years. Controlled experiments conducted in laboratory settings have demonstrated that increasing the portion size of palatable energy dense entrées increased children’s intake of those foods by 25%–60% [10]. Increases were observed, despite the fact that children, on average, consumed only two-thirds of the larger portions and reported awareness of the changes in entrée portion size. Further, increased entrée intakes were
not accompanied by appreciable decreases in children’s intake of other foods served at the meal. Consequently, offering larger entrée portions produced increases in total meal-energy intake ranging from 13% to 39% [10]. Studies of portion size conducted outside the laboratory have observed similar effects on intake, although not of the same magnitude [11]. Not all studies, however, have observed portion-size effects and the reasons for these inconsistencies remain unclear [12,13]. In general, however, experimental evidence of portion-size effects in children is consistent with that observed in adults [14].

When faced with larger portion sizes, children tend to increase the average size of each bite taken without appreciable changes to the number of bites taken [15,16]. An increase in the size of bites taken as an effect of larger portions has also been reported in adults [17–19]. In addition, a similar pattern was observed when children aged 4–6 years were allowed to serve themselves a main dish that varied in portion size [20]. Children served themselves larger spoonfuls when there was a greater amount of the main dish available in the serving dish. Collectively, these studies suggest that visual cues conveying information about size and food availability influence subsequent serving and eating behaviors. However, whether there are particular visual parameters (e.g., width of portion) to which children attend that explain these changes in behavior remains unclear [21].

In addition to amorphous foods (e.g., those that can be piled), effects have been demonstrated for unit foods (e.g., those with a distinct shape such as sandwiches and chicken nuggets), possibly due to “unit bias,” as described by Geirer and Rozin [22], where consumption occurs in units and therefore is driven by unit size. Intake-promoting effects of large portions have also been seen with packaged snack foods and beverages. Finally, while most of the research demonstrating intake-promoting effects has involved energy-dense foods, several studies of young children suggest that the effects of portion size are separate to those of food-energy density [13,23], where the combination of the two has an additive effect on energy consumed at snacks [23] and meals [24]. For example, decreasing the energy density of a lunch entrée by 25% significantly reduced energy intake of the entrée by 25% in 3- to 5-year-old children. However, decreasing the portion size of the entrée by 25% did not significantly affect children’s energy intake at lunch [13]. Another experiment [24] showed that when serving 5- to 6-year-old children different portions of an entrée that also differed in energy density (1.3 vs. 1.8 kcal/g), the effect of portion size and energy density were independent but additive.

Given the evidence of intake-promoting effects of portion size, some have investigated whether portion size can be used strategically to increase the intake of healthful foods, such as fruits and vegetables [25]. A number of studies have examined portion size influences on fruit and vegetable intake before and at meals [26–29]. In general, these studies have found that increasing entrée size increases entrée intake and decreases side dish intake (i.e., fruit and vegetable intake) [29]. Alternatively, doubling the portion size of fruit or vegetable side dishes offered to children at meals has produced modest increases in the consumption of those foods, especially fruit, without appreciable changes to energy intake, increasing the relative proportion of meal energy consumed from those healthful foods [26,27]. It is important to point out, however, that the increases observed in those studies were small in absolute terms and food waste was considerable. For instance, a within-subject experimental study of 30 children aged 4–6 years demonstrated increases of 70% and 34% in fruit and vegetable intakes, respectively, at a meal when 75 g portion sizes of each food were doubled to 150 g. In absolute terms, however, offering twice as much only increased intake by ~1/4 c for fruit (41 g increase) and even less for vegetables (12 g increase). These observations underscore the point that increasing portion size may not be an effective stand-alone strategy for promoting vegetable intake in particular, but may compliment other strategies to promote food acceptance in early development, such as repeated exposure and modeling [30,31].

Most experimental studies of food portion size have focused on short-term energy intake at a meal. While the effects on long-term intake among children are not well characterized, the findings of several studies suggest that children do not fully compensate for the intake-promoting effects of larger portions at subsequent eating occasions. One study of 59 low-income Hispanic and African
American 5-year-olds doubled the portion size of three main entrées and an afternoon snack served across a 24 h period [32]. Daily energy intake was 140 kcal greater or 12% higher in the large portion condition than the reference condition. These findings are consistent with several adult studies that demonstrated increases in energy intake over periods ranging from 2 [33] to 11 days [34] when portion sizes of all foods offered were increased.

Taken as a whole, research to date suggests that large portion sizes have intake-promoting effects on children’s eating that may promote excessive energy intake. The extent to which large portion sizes are truly obesogenic for children, however, remains unclear. Experimental studies on portion size have failed to observe an association between children’s susceptibility to portion size and weight status [15,16,32,35,36]. Long-term experimental studies of food portion size effects on weight outcomes in children are not possible for ethical reasons. A few cross-sectional observational studies have documented associations between portion size and child weight status [37–39]. For instance, a study of 784 French children aged 3–11 years found that portion size of pastries consumed was positively related to overweight in 3- to 6-year-old children, while portion size of liquid dairy products was negatively associated with overweight in 7 to 11-year-old children [38]. Observational findings, however, are difficult to interpret because of the inherent confound that heavier children may require larger portions due to greater energy needs. Longitudinal research is needed to understand the relationship between portion size and growth over time taking into account children’s initial weight and energy requirements.

DEVELOPMENTAL AND INDIVIDUAL DIFFERENCES IN HOW MUCH IS ENOUGH

The first study of food portion size in young children suggested developmental shifts in children’s responsiveness to portion size such that intakes among older children were affected by portion size but those of younger children were not [40]. Those findings are consistent with the notion that children become more susceptible to food cues in the environment and less responsive to internal hunger and fullness cues with age. Indeed, caloric compensation (i.e., adjustments in intake in response to changes in the caloric content of a preload) at meals has been shown to decrease [41] and eating in the absence of hunger (i.e., children’s susceptibility to eating when satiated in response to the presence of palatable snack foods) has been shown to increase with age during middle childhood [42]. However, subsequent research demonstrated portion-size effects on meal energy among children as young as 2 years of age [15]. These contradictory findings raise questions about the extent to which children’s responses to food portion size are governed by biological versus situational and learned components acquired through experience. It is interesting to note that children’s perceptions of the amount of fullness produced by a given food are shaped by familiarity with the foods [43]. The extent to which children’s familiarity with foods influences their expectations of fullness and behavior at meals remains unknown. Research is needed to understand how experience influences what children “learn” about the satiating value of foods and food portion sizes.

Dimensions of appetite regulation show significant heritability, including eating rate, eating in the absence of hunger, and satiety responsiveness [44]. There is some suggestion that these heritable traits influence children’s susceptibility to overconsume large portion sizes. In one study, 34 obese and 66 normal-weight African American children were seen in four experimental conditions where all foods at the meal were increased by 150%, 200%, and 250% over a reference condition [35]. Children with lower levels of satiety responsiveness showed greater increases in intake with exposure to large portion sizes. This is similar to one of the first portion-size studies that showed that children who exhibited greater levels of eating in the absence of hunger also showed the largest increases in intake when the portion size of an entrée served at a lunch meal was doubled [16]. It is possible that the relationship between portion size and subsequent eating behaviors may partially be mediated by the brain’s response to visual portion size cues. Recent work suggests that brain responses to large portions of food, particularly in regions involved in inhibitory control (e.g., the
inferior frontal gyrus) and reward processing (e.g., the ventral tegmental area), may influence the relationship between portion size and subsequent eating behaviors. English and colleagues found that 7- to 10-year-old children who were rated as faster eaters showed greater activation in brain reward centers to large portions of food, while children who had lower activation in inhibitory control regions in response to large portions tended to be rated as more emotional and fussy eaters [45]. Additional neuroimaging studies might help to elucidate the mechanisms of portion size on children’s eating behaviors.

ROLE OF PORTION SIZE IN OBESITY PREVENTION AND TREATMENT

Experimental studies of food portion size in children have produced fairly consistent evidence of causal effects on short-term intake. The controlled nature of these studies, however, precludes generalizability to more naturalistic settings in which young children typically eat, such as at home, childcare, school, and restaurants. These settings likely differ in numerous ways that may influence children’s response to food portion size, including children’s familiarity with foods and portions offered as well as social influences on eating. For example, it is well known that social models (e.g., peers, teachers) can influence children’s acceptance of novel and disliked foods [31]. Similarly, social models can facilitate intake in a manner that increases portion sizes and energy consumed [46]. In addition to modeling influences, there is increasing evidence that parents shape portion sizes selected and consumed by young children through their feeding styles and practices. For instance, children of indulgent feeders (i.e., those who show warmth and acceptance in conjunction with a lack of monitoring of child’s behaviors) have been observed to serve and consume larger portions of energy-dense entrées [47]. In addition, an observational study of 154 low-income Hispanic and African American caregivers observed that parents who served themselves larger portions, served their preschool-age children larger portions which, in turn, was closely aligned with the amount that children consumed [48]. Qualitative data reveal that maternal decisions about portion sizes of meals and snacks offered to children are influenced by a variety of factors including the child’s general appetite (e.g., picky eating), preferences, hunger at the time of eating, as well as the perceived healthfulness of the foods and the nutrient needs of the child [49,50].

The most effective method of conveying information to caregivers regarding appropriate portion sizes is unclear, because children and caregivers often inaccurately estimate food portions [51,52]. This is true for the numeric information about portion size on food labels as well as for estimating the portion sizes of foods served and consumed [53–55]. For example, in a study of 120, 8- to 13-year-olds, 39.7% of respondents incorrectly classified the portion size of food images presented on a computer [56]. Complicating poor estimation is the belief held by many adults that the amount they consume represents an average or “medium” portion size [57]. While numeric presentations of portion size (e.g., household measures) are not easily understood, the effectiveness of alternative strategies is unclear. For instance, household items are often used to convey information about portion size in clinical settings (e.g., a deck of cards to approximate 3 oz. of meat). While such aids may improve portion size estimation [58], the effectiveness of these types of aids for communicating information about appropriate portion sizes to caregivers is not known. It is clear that caregivers use a variety of strategies to determine portion sizes offered to young children. In a qualitative study of child snacking, for instance, low-income mothers of preschool-age children portioned snacks by using small containers, subdividing large portions, buying prepackaged snacks, and using hand measurement estimations, measuring cups, and scales [49]. However, the effectiveness of such strategies to convey information about portion size and support healthful portion sizes for young children is unclear.

A number of studies suggest that manipulating subtle size-related cues of the immediate eating environment may shape portion sizes offered to and selected by young children. It has been known for some time that package size influences the amount of food that adults serve themselves
from containers holding multiple servings [59]. Similarly, the portion sizes of individually packaged servings also appear to influence the amount consumed by adults [60,61]. Reducing the unit size of foods (e.g., smaller cookies) has also been shown to reduce portion sizes consumed by children [62]. More recent studies, including studies of children, indicate that other size-related cues in the eating environment may influence portion sizes selected and consumed. For instance, the use of smaller plates, particularly those with wide and color-contrasted borders, may support smaller portion sizes by encouraging smaller servings [63]. A study of 42 predominantly African American elementary school–age children evaluated children’s self-served portion sizes and intake of an entrée and side dishes in a school setting using either child- or adult-size dishware, which represented a 100% increase in the surface area of plates and volume of bowls across conditions [64]. Children were served more energy when using adult-size dishware. Adult-size dishware promoted energy intake indirectly, where every additional calorie served resulted in a 0.43 kcal increase in total energy intakes at lunch. Similarly, using smaller serving utensils may result in smaller portions served without undue burden on caregivers. A small pilot intervention found that the use of smaller plates, along with education about appropriate portion sizes, reduced portions served by caregivers of young children [65]. Another suggested approach to promote appropriate portion sizes during the preschool years is the rule of thumb to offer one tablespoon of food for every year of life. A nutrient content analysis of recommendations for tablespoon per year of age found this strategy met intakes of most vitamins and minerals though it appeared to underestimate the estimated energy needs for children aged 2–5 years [66].

CONCLUSIONS AND PRIORITIES FOR RESEARCH

Young children’s appetites are thought to be strongly driven by internal cues of hunger and fullness (as reviewed in other chapters in this book). At the same time, numerous lines of evidence highlight environmental influences on children’s eating. Evidence to date suggests that young children’s intake at meals and snacks, particularly of highly palatable, energy-dense foods, closely approximates the portion sizes routinely offered to them. Indeed, a recent Cochrane review of 72 studies, published between 1978 and July 2013, concluded that people consume more food when larger portion sizes, package sizes, and tableware are used [14]. While highly controlled studies have characterized an intake-promoting role of large portions on children’s eating, links to weight status remain weak. Longitudinal data are needed to understand the role of portion size in appetite regulation beyond a single day as well as its role in trajectories for growth. An important research need is to understand how to encourage healthy, age-appropriate portion sizes in children. It is unclear whether helping children focus on internal satiety cues is sufficient or effective given the ubiquitous food cues in the modern environment. Recent research on the formation of child feeding habits suggests research opportunities to help caregivers offer smaller portion sizes and engage in healthy portion-size behaviors, such as the use of small plates [67,68]. Another important line of inquiry for research is to identify optimal snack portion sizes. Secular data point to increases in the frequency of eating among both children and adults. There are currently few data to understand the optimal portion size and energy content of snacks relative to meals for young children. Conveying recommendations to the public and to parents of young children regarding appropriate portion sizes is yet another area for research. In particular, research is needed to identify easy to understand and actionable guidance for caregivers of young children.

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8 Role of Satiety Responsiveness in Childhood Obesity

Myles S. Faith and Adam C. Danley

CONTENTS

INTRODUCTION

This chapter summarizes the literature on satiety responsiveness (SR) and its relation to childhood obesity. SR is a form of self-regulation specific to the domain of food intake [1]. Emerging evidence indicates that this is a behavioral mechanism through which young children overconsume calories and gain excess body weight. As described in the fourth section, studies from around the world find that poorer SR is correlated with a risk factor for childhood obesity. Despite this evidence, there has been limited clinical research focused on SR as an intervention target.

This chapter is organized into six sections. In the first two sections, we define SR as a construct and discuss how it is operationalized in studies with children. The third section addresses the extent to which SR is a familial trait and the extent to which genes and home environmental factors contribute to individual differences in this trait. The fourth section reviews evidence for an association between SR and excess child body weight. Cross-sectional and prospective studies from different countries are described. In the fifth section, SR as a potential intervention focus is discussed. It is argued that, to date, a “first generation” of studies has been conducted that includes (1) satiety training laboratory experiments and (2) preliminary intervention studies. These have set the stage for what is needed now: a second generation of treatment and prevention studies guided by basic behavioral science and targeting more diverse populations. The chapter concludes with ideas for future research.

DEFINING SR AS A CONSTRUCT

SR refers to a child’s ability to recognize and adjust eating in response to internal feelings of fullness [2,3]. In colloquial parlance, some children are better “in touch” with feelings of fullness and are more capable of self-regulating their eating in response to what was recently consumed. Children who are better at SR eat proportionally less following a filling meal while those poorer in the trait will continue to eat without compensating for prior food intake. For example, if a child
“overconsumed” at a midmorning snack (perhaps eating an extra 150 kcal from graham crackers), then the perfectly compensating child would make up for it by eating 150 kcal less at lunch. Such a child has strong SR. Peers with poorer SR would not compensate as well and would overeat (relative to their energy needs) at lunch. And because obesity in early childhood can result from small but sustained energy imbalances (perhaps as little as ~50 kcal/day [4]), poorer SR should promote excess weight gain over time. In fact, as discussed later, data from many studies support this prediction. Thus, SR as a construct can be considered a form of self-regulation specific to the domain of food intake. It is highly relevant to children’s everyday living and food choices.

OPERATIONALLY DEFINING SR IN SCIENTIFIC RESEARCH

Most research has assessed SR using the parent-report Child Eating Behaviour Questionnaire (CEBQ) [5]. The instrument has a five-item SR subscale, with higher scores reflecting greater SR (Table 8.1). The CEBQ was developed in the United Kingdom by Wardle and colleagues, using a population-based sample of young twins [5]. The instrument has been used in population-based, community, clinical, and convenience samples across the world [6–10]. Hence, this tool has had a major impact. It also has strong psychometric properties, including reliability and validity [5,11]. As discussed in the next section, a comparable tool for infants has been developed and validated—the Baby Eating Behaviour Questionnaire [12].

SR can also be assessed by a laboratory-preloading paradigm that tests energy (caloric) compensation. Specifically, this protocol assesses children’s ability to adjust ad libitum meal intake following low- versus high-calorie preload snacks (i.e., fixed amounts of a food/drink). The protocol is grounded in the premise that children should eat proportionally less food at an ad libitum meal ~20 min following the higher- compared with the lower-energy preload. This adjustment reflects “compensation.” A particular formula has been used to define compensation ability, that is, the percentage compensation index (COMPX%) [13–15]:

\[
\text{COMPX}(\%) = \frac{\text{Meal}_{\text{low}} - \text{Meal}_{\text{high}}}{\text{Preload}_{\text{high}} - \text{Preload}_{\text{low}}} \times 100
\]

where:

- \(\text{Meal}_{\text{low}}\) = energy intake from the lunch meal following the low-energy preload
- \(\text{Meal}_{\text{high}}\) = energy intake from the lunch meal following the high-energy preload
- \(\text{Preload}_{\text{high}}\) = energy consumed from the high-energy preload intake
- \(\text{Preload}_{\text{low}}\) = energy consumed from the low-energy preload intake

The COMPX% index is a continuous measure. It is scaled such that 100% reflects “perfect” compensation, with progressively lower scores reflecting the tendency to overeat following the high-energy preload relative to the low-energy preload (undercompensation). Progressively higher scores

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**TABLE 8.1**
The SR Subscale of the Child Eating Behavior Questionnaire

1. My child has a big appetite*  
2. My child leaves food on his/her plate at the end of a meal  
3. My child gets full before his/her meal is finished  
4. My child gets full up easily  
5. My child cannot eat a meal if s/he has had a snack just before

*Reverse scored.

Response options: never = 0, rarely = 1, sometimes = 2, often = 3, always = 4.
Role of Satiety Responsiveness in Childhood Obesity

reflect the tendency to undereat following the high-energy relative to the low-energy preload (overcompensation). Hence, lower scores should put children at greater risk for obesity or excess weight gain. An illustration of the formula can be found in the Appendix to this chapter.

In sum, there are two established research methods to assess SR: a brief parent-report questionnaire or a laboratory-preloading paradigm. The latter is considered by some to be a gold-standard assessment, because it is a direct behavioral measurement obtained under controlled laboratory conditions. On the other hand, this very strength is perhaps its greatest limitation. Specifically, it is an intensive protocol that requires much preparation, research staff, and food preparations, and also might not be feasible in younger subjects (e.g., less than 4 years of age). Compared with the parent-report CEBQ, it cannot be implemented on a much broader scale such as population-based research. Even for a smaller-scale clinical intervention that might need to prescreen for youth poorer in SR, the questionnaire may be more feasible. That said, these are two strong measures of the SR construct.

ASSOCIATION BETWEEN SR AND CHILD ADIPOSITY

Studies from many nations have shown that poorer SR, as measured by the parent-report CEBQ, is associated with increased child body mass index (BMI) or obesity status. In one of the first studies conducted, Carnell and Wardle [16] examined a population-based twin study of >10,000 children aged 8–11 years residing in the United Kingdom, as well as a separate community-based sample of 3–5-year-old children (n = 572). Poorer SR was associated with greater BMI z-score in both the younger (r = −0.22, p < .001) and the older samples (r = −0.19, p < .001). In a population-based study of >4000 children aged 4 years old participating in the “Generation R” study (Rotterdam, the Netherlands), poorer parent-report SR was associated with a higher child BMI z-score (r = −.236, p < .001) [17]. In logistic regression models, children who scored high on SR were significantly less likely to be overweight (OR = 0.63) or obese (OR = 0.43). Sleddens et al. [18] examined 135 Dutch children, who were 6 and 7 years of age, from seven primary schools in the Netherlands. Using a translated version of the CEBQ, they found that poorer parent-reported SR was correlated cross-sectionally with higher child BMI z-score (standardized β = 0.24, p = .006). Similar findings have been reported using pediatric samples from Canada, Portugal, and Brazil, among other nations [10,15–17,19–21].

SR also has been linked to greater food intake at meals. Specifically, poorer SR at age 2 years predicted greater total energy intake from a standardized lunch meal provided at children’s homes at age 4 years (r = .43, p = .011) [22]. Lower SR also predicted prospectively greater child BMI z-score (r = −.42, p = .012).

Interestingly, the link between poorer SR and child overweight appears to emerge in infancy. Recent studies from the United Kingdom have examined infants’ SR using the Baby Eating Behaviour Questionnaire [12] (Table 8.2), a three-item parent-report questionnaire that evaluates infants’ propensity to eat in response to fullness. In fact, poorer infant SR at 3 months of age has been associated with significantly greater increases in body weight in the period from 3 to 15 months in a sample of ~1500 infant twins [23]. Interestingly, greater infant standardized weight at 3 months of age was associated with poorer SR at age 15 months as well. These findings support a

| TABLE 8.2 |
| The SR Subscale of the Baby Eating Behavior Questionnaire |
| 1. My baby found it difficult to manage a complete feed. |
| 2. My baby got full before taking all the milk I thought she or he should have. |
| 3. My baby got full up easily. |

*Response options: never = 0, rarely = 1, sometimes = 2, often = 3, always = 4*
bidirectional association between SR and overweight. These are compelling data in need of replication; they suggest that the association between SR and obesity risk emerges in early life. If true, this opens the door to a novel obesity prevention target in the first year of life.

With respect to laboratory experiments, several experiments report poorer energy compensation among heavier children. Johnson and Birch reported a significant negative association ($r = -0.37$) between COMPX% and adiposity in 3–5-year-olds, but among girls only [15]. Thus, heavier girls tended to undercompensate relative to normal-weight girls. Birch and Fisher found that poorer compensation predicted greater 24 h energy intake, which in turn predicted relative weight, in a sample of 4–6-year-old girls [24]. A study of 9–14-year-old boys also reported poorer compensation ability among obese children, compared with normal-weight children [25]. Finally, we found in two independent samples that undercompensation (i.e., a lower COMPX% score) was associated with greater child body fat as measured by dual-energy x-ray absorptiometry [14,26].

**FAMILIAL ORIGINS OF SR**

Behavioral genetics studies indicate that SR, whether assessed by the CEBQ or COMPX%, has a familial component. That is, the trait is correlated among family members. The familial association likely reflects both genetic and environmental influences, although studies have differed with respect to specific heritability estimates depending on how SR was measured. Carnell et al. [6] studied 5435 twin pairs, ages 8–11 years old, whose SR was assessed by the CEBQ [5]. Results indicated that 63% of the variance in SR was due to genetic factors, with the remaining variance accounted for by environmental factors. In a UK population-based twin cohort, the heritability of SR was estimated to be 72% [27]. However a different conclusion was reached by Faith and colleagues [14] who assessed SR using a laboratory-based preloading paradigm [15,28]. They studied a sample of sixty-nine 4–7-year-old same-sex twins recruited from the New York metropolitan area. In this investigation, heritability was estimated to be 0% (i.e., no genetic influence), with all the familial resemblance apparently due to environmental factors. The inconsistent findings between this study and others may be due to measurement issues (i.e., parent-report vs. laboratory observation), age differences (i.e., 8 years and older and infants vs. 4–7 years old), and/or sample size differences (i.e., hundreds of child participants vs. less than 70).

In sum, there is a familial influence on SR although the magnitude of genetic influence is unclear. That said, family membership does matter and there is a resemblance among siblings. Interestingly, no study to date has examined parent–child correlations for the trait. This information could inform novel family-based treatments that attempt to improve SR in both parents and children.

**SR AS A NOVEL INTERVENTION TARGET**

There has been limited intervention research targeting SR in children. However, there have been pertinent laboratory-based experiments and preliminary intervention studies over the past 15 years. We call these studies *Generation-1 SR Training Studies*. These consist of (1) satiety scaling experiments and (2) preliminary SR intervention protocols. Arguably, these studies provide proof of principle that SR can be ameliorated with the right training procedures. We summarize these next.

**Satiety Scaling Experiments**

There is evidence that young children can scale feelings of fullness quantitatively on a continuum, beyond a mere “hungry versus full” dichotomy. This has been studied through experiments using novel pictorial stimuli—or silhouettes—that challenge children to scale how full they feel.

In 2002, we developed the first sex-specific satiety silhouettes for young children for scaling fullness on an ordinal scale [29]. We tested if children—with minimal training—could learn to scale feelings of fullness using this tool. Specifically, children could point to one of five silhouettes, each of which had bellies filled with differing amounts of bubbles to represent fullness (Figure 8.1).
To validate this instrument, we used an imagined eating paradigm in which children were asked to rate how full they would feel in a situation associated with minimal fullness (i.e., before dinner), moderate fullness (i.e., when interrupted in the middle of dinner, or following a small snack), and high fullness (i.e., after a meal). Children did this following a brief training requiring them to discriminate familiar food-related stimuli (e.g., utensils, foods) with varying amounts of objects, as well as to discriminate everyday objects that differed in how empty versus how full they were. Children provided responses and were given feedback during this training.

Following training and during the satiety-scaling challenge, children reported significantly higher fullness levels with the silhouettes across the three imagined eating scenarios. Specifically, average imagined fullness scores were least before dinner, higher for the interrupted meal or following a snack, and highest after dinner. Qualitative data collected in this study further attested to children’s understanding of the experience of fullness. For example, when children were asked to define “fullness,” responses fell into the following categories: the time to stop eating (55%); the time their stomach would be hurting (20%); the time following dinner when ready for bed (10%); after eating a lot (10%); and when they could no longer speak (5%). Integrating all results from this project, we concluded that “young children may be more capable of quantitatively reporting feelings of satiety than is commonly believed, if appropriate experimental materials are used” [29, p. 173].

Keller et al. [30] next developed a satiety silhouette that consisted of a cardboard doll (“Freddie”) with a sliding, retractable ruler that slides along the length of the doll’s belly (Figure 8.2). Children
were instructed to slide the ruler higher up to communicate a greater sensation of fullness following an imagined or actual eating situation. By measuring the distance (i.e., how far the ruler has been moved, in millimeters), one can quantify satiety on a more refined level than the scale originally developed by Faith et al. [29].

“Freddie” was used in an initial study with 4–5-year-old children, who first received training procedures using everyday objects to orient them to the concept of differential fullness. For example, for one training activity (“A Day at the Beach”), investigators poured incremental amounts of sand into clear 16 oz. plastic cups, which simulated pails. The researchers filled up differing amounts representing a small amount of fullness (one-third full), medium fullness (two-thirds full), or large fullness (completely full). Following this and other training activities, children were challenged to rate their fullness with “Freddie” as they imagined eating incremental portions of french fries and fruit salad. Results supported the hypothesis that children can scale feelings of fullness quantitatively. Seventy-two percent of children (8/11) could successfully scale fullness in response to incremental portions of fries, and 90% (10/11) could successfully scale fullness for fruit salad. The authors concluded that “children can be trained to use an analogue scale to quantify differences [in fullness sensations] in proportion sizes of food” [30, p. 233]. In one follow-up study
with 5–6-year-old children studied in a preschool setting, participants successfully used “Freddie” to scale fullness in response to actual food (i.e., 15 mL portions of strawberry yogurt) [31].

Recently, Bennett and Blisssett [32] developed satiety silhouettes that were used with children aged 5 to 9 years of age. They developed the “Teddy the Bear” rating system, a five-level ordinal scale depicting five bears with incrementally greater dark bubbles over their bellies to represent incremental fullness (Figure 8.3). Thus, their ordinal scale was more similar to that of Faith et al. [29] than Keller et al. [30]. Across three studies, children successfully scaled fullness levels during both imagined and actual eating situations. For example, in one of the studies, children rated how full a fictitious teddy bear would feel both before and after a large meal. In fact, children assigned a higher fullness rating following the imagined meal compared with before. In another one of the studies, children rated their own hunger/fullness levels before an actual snack provided in a school setting. Results indicated that higher fullness levels before the snack predicted significantly less meal intake ($r = −.418$, $p = .006$). The authors concluded on page 47 that “the scale may be useful for interventions focusing on improving children’s awareness of hunger and satiety in order to foster healthier eating behavior as well as teaching children at risk for overweight/obesity about the appropriate timing of the initiation and termination of eating episodes.”

In sum, evidence from three studies indicates that—with minimal training—children can use different pictorial silhouettes to communicate quantitatively how full they feel. These tools are yet to be used in intervention studies per se, which might be an opportunity for future research.

**Preliminary SR Interventions**

Using a prepost design, Johnson [33] tested a 6-week intervention designed to foster awareness of internal hunger and satiety cues. Participants were thirty-one 3- and 4-year-old children enrolled in two Denver day-care facilities, of whom 25 completed the program. Intervention components included discussion of hunger and fullness sensations through play skits and videos (e.g., Winnie the Pooh and the Honey Jar); training children to assess their own fullness levels throughout the day by putting their hand on their belly and communicating their satiety (i.e., hungry vs. a little full vs. very full); and pointing to special constructed dolls to communicate how full they feel. The three dolls had clear glass jars as their bellies with varying amounts of salt inside. Specifically, they contained no salt (i.e., empty stomach), a little salt (i.e., a little full), or a lot of salt (i.e., very full). During midmorning snacks, children were prompted at least twice to see if they were still hungry and wanted more food. Additionally, they were prompted to report their fullness levels with the dolls after their snack. The primary outcome was the laboratory-based COMPX% index, as described previously in this chapter. Results indicated that the intervention successfully improved children’s SR. When looking to the breakdown of responders, 68% of children showed improvements in COMPX% scores, 16% stayed the same from baseline, and 16% showed deteriorations. The findings were encouraging.

Boutelle et al. [34] developed an 8-week “children’s appetite awareness training” intervention to reduce overeating in 8–12-year-old overweight children. Youth were trained to recognize and eat in response to internal hunger and satiety cues, using the metaphor of a gas tank in a car. Additionally, children received experiential exercises to identify hunger/fullness levels and had behavioral assignments to hone these skills. The latter included laboratory meals during which members were challenged to recognize and rate hunger levels. Results indicated that this intervention significantly reduced children’s objective and subjective binge-eating episodes, as assessed by a standardized clinical interview. The treatments did not significantly reduce BMI or BMI z-score, although this was not the primary study aim and the intervention duration of 8 weeks may not have been long enough.

In sum, there is proof of concept from two intervention studies that children’s eating regulation can be improved following age-appropriate interventions targeting SR. These investigations, along with the prior satiety scaling experiments, provide a strong foundation for future intervention studies. This is discussed next.
I am really hungry! my belly feels very empty and is rumbling!

I am quite hungry and my belly feels a little empty.

I feel just right, not too hungry and not too full.

I am quite full, but there is still a little room in my belly.

I am not hungry at all! my belly feels very full and i cannot eat any more food!

-Food in Teddy's belly

**FIGURE 8.3** Satiety silhouettes. (From Bennett and Blissett *Appetite*. 78:40–8, 2014.)
RESEARCH GAPS AND OPPORTUNITIES FOR “GENERATION 2 SR INTERVENTION STUDIES”

Given the current state of the science, the timing arguably is right for a second generation of SR interventions for obese or obese-prone youth. Table 8.3 summarizes opportunities for future research, although this list is by no means exhaustive. These opportunities fall into the categories of measurement, sampling, setting, technology, and dose and timing.

SUMMARY

SR is an important type of food intake self-regulation in early childhood. Poorer SR is associated with increased child BMI, body fat, and obesity status. It is associated with increased weight gain in infants. The epidemiological and laboratory studies are compelling. Looking forward, a critical question is whether SR training represents a novel strategic target for childhood obesity prevention and/or treatment. Might interventions training children to “flex their SR muscles” prove effective to improving eating self-regulation and obesity status? Would there be important effect modifiers of such treatments (e.g., child sex, age, or family attributes)? What might be the optimal intervention dose for such approaches, and could innovative technologies support such training? The answers are currently unknown.

That said, “first-generation” experimental and preliminary intervention studies have been encouraging. There is proof of concept. Young children can be trained to scale satiety using

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### TABLE 8.3
Research Opportunities for Generation 2 SR Training Studies

1. **Measurement Opportunities:** Include a broader range of measures that potentially could be secondary outcomes and/or mediators through which the treatment works. Examples include measures of
   a. Global self-regulation from the child development literature
   b. Global self-control
   c. Impulsivity
   d. Executive function parameters (e.g., working memory, task flexibility)
   e. Biological markers of self-regulation or appetite, including genetic markers

2. **Sampling Opportunities:** Study more diverse population attributes. Examples include diversity with respect to
   a. Race/ethnicity
   b. Age (e.g., preschool vs. middle childhood vs. adolescents)
   c. Family membership (e.g., parent involvement in SR training)
   d. Risk status (e.g., children who are high vs. low in obesity risk, or high vs. low in SR based on initial prescreening of children)

3. **Setting Opportunities:** Examining a broader range of settings in which treatments could be provided including
   a. Preschool/school settings
   b. Home-based training
   c. Community settings
   d. Combination of settings

4. **Technology Opportunities:** Leverage new technologies to foster SR. Examples include
   a. The “manometer.” This device incorporates a universal eating monitor-type to provide real-time feedback on children’s eating rate during the course of a meal, and assesses child satiety during the course of the meal. (For details and intervention results, see [35].)

5. **Dose and Timing Opportunities:** Determine the optimal treatment dosage and timing to detect potential intervention effects. Opportunities include experimental variations in
   a. Number of treatment sessions
   b. Number of booster sessions
   c. Follow-up duration
age-appropriate silhouettes, as demonstrated in different laboratories. Two initial SR interventions successfully improved child eating outcomes [33,34]. These provide a foundation for what might evolve into a second generation of SR intervention studies that use larger samples and more comprehensive measurement batteries, assess markers of self-regulation, and examine more diverse samples of children. Advances in basic behavioral and biological research should strengthen such intervention studies.

APPENDIX

To illustrate the COMPX% formula and its calculation, consider an experiment in which children consume a low-energy preload of 3 kcal and a high-energy preload of 159 kcal, across two laboratory visits. Imagine a child within this study who consumes exactly 456 kcal at lunch following the low-energy preload and 300 kcal at lunch following the high-energy preload. Plugging these values into the formula yields \[
\frac{(456 - 300)}{(159 - 3)} \times 100, \text{ or } \text{COMPX} = 100\%.
\]
Had this child consumed 800 kcal rather than 300 kcal following the high-energy preload (with all else the same), this would have yielded \[
\frac{(456 - 800)}{(159 - 3)} \times 100, \text{ or } \text{COMPX} = -220.51\%.
\]
But had this child consumed only 150 kcal following the high-energy preload (with all else the same), this would have yielded \[
\frac{(456 - 150)}{(159 - 3)} \times 100, \text{ or } \text{COMPX} = 196.15\%.
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Role of Satiety Responsiveness in Childhood Obesity

9 Food Reward and Appetite Regulation in Children

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OVERVIEW OF BRAIN REGULATION OF APPETITE AND EATING BEHAVIOR

Eating is necessary for survival, and humans have powerful biological systems that help to maintain an adequate nutrient supply [1]. These systems involve cross talk between the brain and the rest of the body. The body sends messages to the brain about its energy needs, and the brain responds to these needs through a number of pathways that regulate food intake, energy expenditure, and energy storage in a biological process called energy homeostasis [2–4]. The hypothalamus is the central orchestrator of energy homeostasis. Its interactions with other brain regions and with the periphery help to ensure an adequate energy supply. The arcuate nucleus (ARC) and ventral medial nucleus (VMN) in the hypothalamus have a high density of neurons that respond to peripheral hormones, including leptin, insulin, and ghrelin [5]. The ARC contains two subsets of neurons that play opposing roles in appetite regulation. Pro-opiomelanocorticotropin (POMC) neurons are anorexigenic (i.e., suppress appetite), whereas neurons that coexpress neuropeptide Y (NPY) and agouti-related peptide (AgRP) are orexigenic (i.e., stimulate appetite) [3]. Arcuate POMC and NPY/AgRP neurons send projections to other areas in the hypothalamus, including the dorsomedial (DMN) and paraventricular (PVN) nuclei of the hypothalamus and the lateral hypothalamic area (LHA), as well as other brain regions involved in regulating energy homeostasis [5]. POMC is cleaved into anorexigenic peptides, including α-melanocyte stimulating hormone (MSH) and cocaine- and amphetamine-regulated transcript (CART). When POMC neurons are activated, α-MSH is released into the PVN, where it acts on melanocortin-3 and 4 receptors to promote satiety. In contrast, NPY/AgRP neurons activate orexigenic signaling via NPY receptors and inhibit anorexigenic signaling via melanocortin receptors [5–7].

While the hypothalamus primarily regulates the homeostatic drive to eat, other brain regions, such as the ventral tegmental area (VTA), striatum, orbitofrontal cortex, amygdala, hippocampus, and insula, control motivation-reward systems associated with the hedonic drive to eat. Dopamine and opioid are neurotransmitters that play an important role in the regulation of hedonic feeding behavior. Dopamine receptors, D₁ and D₂, are located in various brain regions, including the nucleus
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The reward-associated mesolimbic dopaminergic neurons in the VTA project to the dorsal striatum and NAc to regulate the reward value of food. Cortical regions, including the PFC, help regulate impulse control and inhibit the motivation for rewarding signals arising from the dopaminergic reward circuitry.

HORMONES INVOLVED IN REGULATION OF APPETITE AND REWARD

The body produces a number of hormones that help regulate appetite. Long-term energy stores are reflected by circulating levels of leptin, a hormone that is secreted by adipose tissue in proportion to body fat mass [3,8]. Insulin is produced by the β-cells in the pancreas, and plasma insulin, like leptin levels, parallel overall levels of adiposity [5]. Insulin and leptin act on neurons located in the hypothalamus, particularly in the ARC, to suppress appetite. In addition, both insulin and leptin decrease reward signals that are triggered by the striatum and other components of the brain reward circuitry [3,5,10].

During periods of hunger, the stomach produces the hormone, ghrelin, which stimulates food intake. Ghrelin levels rise before consuming a meal and decline after eating, which suggests that ghrelin plays an important role in hunger and meal initiation [5,11,12]. Ghrelin activates NPY/AgRP neurons and inhibits POMC neurons located in the ARC nucleus of the hypothalamus [12]. In addition, ghrelin stimulates the reactivity of the striatum and other reward-related brain regions, which drives food-seeking behavior [13–15]. After a meal is consumed, the gut releases appetite-suppressing hormones, including glucagon-like polypeptide-1 (GLP-1) and polypeptide YY (PYY), which provide satiety signals to the hypothalamus and hindbrain to reduce food intake [16–19].
FOOD REWARD AND ITS ROLE IN FEEDING BEHAVIOR

The drive to eat palatable foods, typically those rich in fat and sugar, has a strong biological basis and exposure to palatable foods can stimulate eating even in the absence of an energy deficit. This is likely because food (particularly energy-dense food) is a natural reward that influences neurochemical systems to reinforce food intake [20,21]. The neurobiological basis for food reward has been demonstrated in a number of studies, which show that foods dense in sugar and fat can stimulate the release of neurotransmitters, including dopamine, opioids, serotonin, and cannabinoids, that enhance feelings of pleasure and reward [9,22,23]. The involvement of dopamine in food reward has been associated with the motivational salience or “wanting” of food as opposed to the “liking” of food, which is thought to primarily involve opioid signaling within the NAc [24]. Neuroimaging studies in children and adults have shown that exposure to palatable food cues, including the sight and smell of food, leads to the activation of reward-related circuitry and an increased subjective “wanting” of the food [25–31]. The current environment with ubiquitous exposure to palatable food and food-related cues is likely promoting food-seeking behavior. This may be particularly relevant to children and adolescents, who are the target audience of many food-related advertisements [32].

CHILDHOOD OBESITY: EFFECTS ON NEUROENDOCRINE APPETITE AND REWARD CIRCUITS

Emerging evidence suggests that high levels of adiposity may promote overeating behavior due to obesity-associated alterations in the neural pathways that regulate appetite, reward, and cognitive inhibitory control. Neuroimaging studies provide a way to noninvasively study the neural circuitry involved in the regulation of feeding behavior in humans. A commonly used paradigm for probing body-weight-related differences in neural circuitry is to expose people to pictures of highly palatable food items (and nonfood objects as a control). The majority of work in this area has shown that obese individuals compared with lean individuals exhibit greater activation in reward-related brain areas in response to food cues [28,29,31,33,34]. To date, findings in the small number of neuroimaging studies performed in children are in keeping with the results observed in adults [25,30,35]. Greater brain activation within reward-relevant regions has also been shown to predict weight gain in adolescent girls [36] supporting the theory that hyperresponsivity to food cues may be a risk factor for overeating [9,36–38].

Additional work has shown that obesity is related to hyporesponsiveness in the hypothalamus after the consumption of food [39,40] or glucose drinks [40–42], suggesting that appetite signaling in response to nutrient ingestion may be disrupted by obesity. Obese adults compared with lean adults also exhibited less postprandial activation in the dorsolateral PFC, a region involved in cognitive inhibitory control [43,44]. Additional evidence from preclinical and clinical studies suggests that obese individuals have a reduction in dopamine signaling, including decreases in striatal dopamine receptor (D2R) density and in dopamine release [45–47]. These findings are in keeping with functional magnetic resonance imaging (fMRI) studies showing that obese adolescent girls have a reduction in the striatal response to the receipt of food [48,49]. Some posit that a weakened reward response to food consumption could stimulate overeating in an effort to compensate for the reward deficit. This mismatch between the high expectations associated with the food cue and the weakened reward response to food consumption could perpetuate a vicious cycle of overeating and obesity [48,50,51].

Taken together, current evidence suggests that obesity is associated with an enhanced sensitivity to conditioned food stimuli that predict reward (e.g., the smell of apple pie or the sight of chocolate cake), but a decreased sensitivity to satiety and reward signaling after actual food consumption, as well as impairments in cognitive inhibitory control over appetitive behavior. Future work is necessary to determine whether these obesity-associated alterations in neural circuitry are reflective of adaptations to the obese state or if they antecede and possibly play a role in the development of obesity.
ENERGY-DENSE DIETS: EFFECTS ON NEUROENDOCRINE APPETITE AND REWARD CIRCUITS

Most of what we know about the effects of consuming diets rich in sugar and fat comes from experimental studies in animal models with limited studies in children. Mounting evidence suggests that consuming a high-fat diet can cause inflammatory damage within the hypothalamus, which leads to impaired leptin and insulin signaling and an increased susceptibility to obesity [52,53]. Chronic consumption of high-fat, high-sugar diets has also been shown to affect the reward centers in the brain, including a reduction in the expression of D2R [46] and decreased dopamine content in the striatum [54]. Moreover, when rats are given repeated but intermittent access to foods high in sugar, fat, or both, they develop binge-eating behavior and alterations in the reward circuitry [20,45,55].

Currently, there are few human studies on the effects of chronic intake of energy-rich diets on brain circuits involved in the regulation of feeding behavior. However, one fMRI study showed that normal-weight adolescents who reported frequent ice cream consumption had lower activation in the striatum in response to the receipt of small tastes of milk shake [56]. These findings support animal studies suggesting that chronic exposure to energy-dense foods can lead to a reduction in dopamine signaling [55]. Another fMRI study reported that adolescents who habitually consumed the soft drink, Coke, when compared with nonsoft drink consumers, had greater brain activation to Coke logo ads in the posterior cingulate and decreased activation in the ventrolateral PFC when anticipating the receipt of Coke. The investigators interpreted these findings to suggest that habitual soft drink consumption may promote increased responsiveness within brain regions encoding salience toward brand-specific cues, as well as hyporesponsiveness within inhibitory brain regions while anticipating intake of the soft drink [57]. Thus, it appears that consumption of diets high in fat and/or sugar could lead to alterations in the brain circuitry that regulate reward and cognitive control over feeding behavior.

DIFFERENT TYPES OF SUGAR: EFFECTS OF FRUCTOSE VERSUS GLUCOSE ON NEUROENDOCRINE AND APPETITE RESPONSES

Fructose and glucose are both monosaccharides with the same number of calories, but their differential effects on the neuroendocrine circuits involved in appetite and reward processing may affect feeding behavior [58–61]. When compared with glucose, fructose may be a weak suppressor of appetite due to attenuated stimulation of the purported satiety hormones, insulin, leptin, and GLP-1 [19,62–64]. Moreover, fructose is sweeter than glucose and, in contrast to glucose, very little fructose circulates in the bloodstream due to the complete extraction of fructose into the liver [65]. These differences in fructose versus glucose may help explain their differential effects on brain appetite and reward pathways. Animal studies have shown that the central administration of fructose activates appetite-signaling pathways in the hypothalamus and increases food intake, whereas glucose inhibits hypothalamic appetite-signaling pathways and decreases food intake [61]. Similarly, neuroimaging studies in humans also show differential brain responses to glucose compared with fructose ingestion [58,60]. Relative to fructose, ingestion of drinks containing glucose resulted in a greater reduction in hypothalamic cerebral blood flow (CBF), a marker of neural activation in healthy young adults [59]. The acute ingestion of fructose relative to glucose was also shown to increase brain activation to food cues in the orbitofrontal cortex, visual cortex, and ventral striatum (brain regions involved in attention and reward processing) and led to greater hunger and motivation for immediate food rewards [58]. These studies provide potential insights into epidemiological evidence linking fructose consumption to overeating behavior in healthy adults [66,67]. However, future work is necessary to determine the neuroendocrine effects in children of consuming different types of sugar as well as the effects of obesity and other metabolic conditions on these responses and the long-term effects of fructose intake on neuroendocrine pathways. Moreover, future studies are necessary to
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determine neuroendocrine and appetite responses to combinations of fructose and glucose, such as high-fructose corn syrup or sucrose, as they are commonly consumed in the real world.

DEVELOPMENTAL PROGRAMING: EFFECTS OF PRENATAL ENVIRONMENT ON NEUROENDOCRINE APPETITE AND REWARD CIRCUITS

Human and animal studies provide compelling evidence that the nutritional and metabolic conditions that an individual is exposed to in utero can shape long-term susceptibility to obesity and other metabolic diseases [5,68,69]. Epidemiological and cross-sectional studies show an association between fetal exposure to maternal overnutrition (through maternal obesity, diabetes, or high-fat feeding during pregnancy) and increased risk for obesity during childhood and adult life [70–72]. While some of this risk is likely attributable to genetic susceptibility, studies in siblings demonstrate that the risk is in excess of genetic factors alone. For example, children who were born after their mother developed diabetes (i.e., these children were exposed to diabetes in utero) were at higher risk for developing obesity and diabetes than their siblings who were born before their mother developed diabetes [73–75]. Other studies demonstrated that offspring who were born after their mothers lost a significant amount of weight via bariatric surgery had a lower risk for developing obesity than their siblings who were born before maternal surgery [76,77]. These data show a disproportionate risk of obesity in siblings born to the same mother under different in utero conditions and provide support for independent effects of the intrauterine environment on programing risk for obesity [78].

Animal models are helping to uncover potential mechanisms that underlie these early-life programing effects [5,78–81]. For example, preclinical studies show that fetal or newborn exposure to various models of maternal overnutrition can “program” hypothalamic appetite circuitry to favor orexigenic pathways in offspring. These changes in brain appetite circuitry lead to increased food intake and obesity in offspring [79,82–85]. In addition to affecting hypothalamus appetite circuits, fetal exposure to maternal high-fat, high-sugar feeding during pregnancy has also been shown to disrupt the development of brain reward pathways and increase the offspring’s preference for energy-dense food [86–88].

Lactation has also been identified as a critical period for developmental programing [86,89–92]. Studies in mice have shown that maternal high-fat feeding during lactation causes a reduction in the number of projections from POMC neurons to the PVN in the hypothalamus and a predisposition for obesity and diabetes in offspring [91]. Additional studies have shown that exposure to high-fat, high-sugar diets during lactation leads to hyperphagia and a preference for energy-dense foods in offspring [86,89,92].

CONCLUSIONS

In light of the current childhood obesity epidemic and the high rates of relapse associated with current obesity treatments, it is important to understand the neural systems that regulate feeding behavior and how these systems are affected by environmental factors. Future work is needed to determine the effects of specific interventions, such as diet and physical activity, on neural pathways implicated in feeding behavior. These studies are particularly relevant during childhood and adolescence because these are critical time periods when the brain is highly plastic and susceptible to metabolic and external influences. Moreover, preventive measures that begin early in pregnancy and continue throughout lactation may be important for improving the metabolic health of offspring and reducing the rising rates of childhood obesity.

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Food Reinforcement and Childhood Obesity

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INTRODUCTION

Children are often drawn to sweet and fatty treats such as cake and ice cream. We can imagine a typical child, Johnny, who is willing to walk several blocks for an ice-cream cone. Food reinforcement describes how motivated one is to obtain food and is measured by observing how strongly a behavioral response is supported by the reinforcer, that is, how much work a child will perform to obtain an ice-cream cone. What choice might Johnny make if he could walk to the store to buy ice cream or eat a piece of fruit at home? Would he engage in the extra work for the ice cream, or settle for the easily available fruit? This choice could help us determine how reinforcing ice cream is for Johnny. Increased food reinforcement is associated with obesity in infants [1], in addition to obesity and weight gain in children [2] and adolescents [3]. The strong association between obesity and food reinforcement impacts research in childhood obesity and should be considered in weight-loss programs for children.

DEVELOPMENT OF FOOD REINFORCEMENT

Food reinforcement is innate and present at birth [4] and is biologically preestablished to increase the behaviors it rewards. While some foods require multiple feeding attempts for an infant or child to find them acceptable, sugary and fatty foods do not require prior learning, and only a taste of
these foods by infants may develop into preferences that continue into adulthood [5]. Infants show stereotypical and automatic responses to specific tastes, with sweet foods eliciting a smile prior to bottle or breast-feeding [6]. As an infant or toddler, Johnny may have first tasted ice cream, activating primary brain reward centers signaling a pleasant taste and laying the groundwork for his high motivation to eat ice cream. Infants who have an increased bottle sucking rate gain more weight at 12 and 24 months [4]. This research suggests that even in infants, motivation to eat is present at early ages and may represent initial problems with high food reinforcement. While food is intrinsically rewarding, there are individual differences in the motivation to eat, which are characterized by the concept of food reinforcement [7].

**Measuring Food Reinforcement in Children**

Food reinforcement is assessed in the laboratory by allowing children to play a computer game for food [7]. Reinforcing value is the quantitative measure of a person’s food reinforcement or their motivation to obtain food [7]. In the game, each mouse click corresponds to a unit of work, and the number of clicks corresponding to a portion of food, or the behavioral cost of the food, can be manipulated. To measure reinforcing value, the work required to earn a portion of food needs to increase in difficulty, so that there are a range of maximum work values to distinguish between individuals with high and low food reinforcement. Each time a portion of food is earned, the work required for the next portion increases in a progressive schedule of reinforcement. In addition to a behavioral task in which children click a button for access to food, a questionnaire has also been developed and used in children [2]. A series of questions asks a child to indicate whether he or she prefers to click a handheld counter for food or for an alternative activity. The alternative activity remains at a constant, low behavioral cost (i.e., 20 clicks), while the preferred food increases in behavioral cost until the child is no longer willing to click for the food and chooses the alternative reinforcer.

The reinforcing value of food can be measured in an absolute sense, with no available alternatives, or in a relative sense, with an available alternative. While candy may be highly reinforcing to children, when ice cream is available, the motivation to eat candy may be low compared with ice cream. While most studies examine the relative reinforcing value of food, there may be important developmental considerations for measuring absolute food reinforcement, that is, if a young child is unable to consider two options simultaneously. Alternative reinforcers can include other types of food or nonfood activities. To measure relative reinforcing value, the alternative has an increasing behavioral cost (i.e., the work for each food portion increases) that matches the target reinforcer. The alternative can also be held at a constant behavioral cost to measure substitution between the food and alternative. Substitution describes a situation in which the behavioral cost of the food becomes too high and the child switches to the lower-costing alternative. Both the reinforcing value of food and the nonfood alternatives are important, as having high food reinforcement may be offset by having high reinforcing value for nonfood alternatives [8], such as children foregoing food and enjoying an alternative, such as reading or puzzles. Substitution may be especially important when trying to help a child decrease their energy intake by switching to lower-calorie, or low energy-dense healthy foods, from their usual intake of high-fat, high-sugar, energy-dense foods.

In our laboratory, research on food reinforcement in 8- to 12-year-old children uses the same procedure as adults [8,9]. A slot machine–type game is played in which various shapes change with a click of the mouse and matching shapes indicate a point is earned. Generally, the relative reinforcing value of food is measured with the available alternative being a nonfood reinforcer, such as reading materials or puzzles [8]. The game is structured to have very low reinforcing value itself, that is, children and adults do not want to play the game without the promise of a reward. This paradigm has recently been extended to preschoolers [10] and 9- to 12-month-old infants [1] by establishing developmentally appropriate measures. When measuring food reinforcement in preschoolers, task novelty may increase responding, so computer monitors are masked and only a small sound indicates that the child earned a portion of food [10]. The only study that has examined food
reinforcement in preschool-age children looked at the relative reinforcing value of a target food versus an alternative food [10]; no research has examined the relative reinforcing value of food versus nonfood activities in children this age.

To measure food reinforcement in infants, our laboratory has set up a different series of reinforcement schedules. With older children, we traditionally double the work requirements after each reinforcer is earned; while with infants the work requirements only increase by one response across schedules (e.g., FR1,1,2,2,3,3,3…15,15) to control for the limited attention span and physical abilities of infants [1]. Infants need to first learn the button-reward contingency prior to measuring the reinforcing value of food, which is accomplished by using an audio clip of a cartoon-type sound when they properly click the mouse button. When the infant has learned the contingency, the experimenter then places a plate of food on the table and encourages the child to press the button to receive a food portion. Both the experimenter and the mother will observe the child to determine when the child no longer wants to play for food. The research in infants assesses the absolute reinforcing value of food and an alternative activity (e.g., 10 s blowing bubbles) in separate sessions. Pilot work has been done to assess relative reinforcing value with two concurrently available activities, but has not been successful in developing a task appropriate for infants. A reinforcing ratio can be calculated by determining the proportion of responses for food versus the total responses for both food and the alternative activity.

**FOOD REINFORCEMENT IS ASSOCIATED WITH ENERGY INTAKE, OBESITY, AND WEIGHT GAIN IN CHILDREN**

Studies in 8- to 12-year-old children have shown greater responding for food in overweight (body mass index [BMI] percentile ≥85) versus nonoverweight children [8], and a significant positive correlation between responding for food and greater BMI z-scores in preschoolers [10]. Higher food reinforcement is also related to greater energy intake in the laboratory for children [8] and preschoolers [10] and usual energy intake in children [11]. Recent research has examined differences in the reinforcing value of snack foods in children with different flavor profiles [11], with sweet-tasting or high-sugar foods having higher food reinforcement than savory or salty-tasting foods [11]. However, the reinforcing value of these different foods was highly correlated and loaded onto one factor in a factor analysis, rather than representing three different values [11].

Research has also shown that food reinforcement is associated with weight gain in children [2] and adolescents [3]. In adults, increased food reinforcement leads to increased energy intake [12], which can produce excess weight gain. In a sample of 7- to 10-year-old children, responses on the food reinforcement questionnaire showed that the higher reinforcing value of food predicted greater weight gain, BMI gain, and fat gain in children after 1 year [2]. This has been replicated in adolescents, as those with higher food reinforcement had greater weight gain over 2 years [3]. Johnny’s high food reinforcement has led to overconsumption of food and enough weight gain for him to be considered obese.

**FACTORS THAT ACUTELY INFLUENCE FOOD REINFORCEMENT**

**Sensitization and Satiation**

The reinforcing value of a food can change over time, either growing, reducing, or staying the same with the effect depending in part on the dose and individual sensitivities. The increase in the reinforcing value with repeated exposure is called sensitization, and may describe why the motivation to eat some foods increases with repeated eating bouts. The opposite of sensitization is satiation, or a decrease in reinforcing value with repeated consumption. Temple and colleagues have shown that the reinforcing value of food can increase with repeated exposure to preferred snack foods based on dose and obesity status, as the reinforcing value of larger doses of preferred food sensitizes for
obese persons, while the reinforcing value of large doses of preferred foods is reduced with repeated exposures for leaner persons [13,14]. Adults who gained the most weight over a year were also more likely to show a pattern of sensitization to food than those who gained less weight [15]. Research on how trajectories of reinforcing value shift over time is just beginning, but it may help illuminate both how the reinforcing value of food develops and, perhaps, methods of reducing the reinforcing value of food. To date, only snack foods, rather than entrées, have been studied and there is no research on the optimal intervals between eating bouts to enhance either sensitization or satiation.

**Restriction and Deprivation**

Research shows that food reinforcement and the motivation to eat increases as a function of food deprivation, as individuals are often willing to work harder to obtain food and consume larger quantities of food when hungry [16]. Restriction is a common practice that parents use to control the types of foods their children consume, in addition to the portion sizes of those foods [17]. Usual restriction practices attempt to control intake of high-fat, high-sugar foods, including snacks such as ice cream and potato chips. Fisher and colleagues [17] studied preschool-age children in a day-care setting, and showed that the restriction of a snack food acutely increased energy intake for that food. For 2 weeks, the children were offered two foods during their normal snack time, one of which was offered for 5 min and then removed. The restricted food had greater consumption and more requests for it from the children during the snack period. This research was recently extended, showing that food reinforcement moderated this effect, as children with higher food reinforcement consumed more of the restricted food than other children [18]. Due to Johnny’s weight gain, his parents may attempt to control his energy intake by restricting ice cream to the weekend. However, this may only increase his attempts to eat ice cream and how much he wants to eat when it is available.

**Factors That Moderate the Effect of Food Reinforcement in Children**

**Alternative Reinforcers**

Overweight or obese children are more motivated to work for food and have higher response rates in a food-reinforcement task than their lean peers [8]. Not only do obese children respond more for food than lean children, but they also responded less for the nonfood alternative than their lean peers [8]. Typically, when given the option to work to obtain either a preferred or less preferred food, a child will choose to work for the preferred food [19]. However, when the behavioral cost of the preferred food is increased (i.e., when the child has to work harder to obtain the preferred option), he or she opts for the less preferred alternative, which has a lower behavior cost [19]. Problems of high reinforcing value are compounded when alternatives are less reinforcing, which may prevent children from being able to both decrease energy intake and find alternative activities to engage in that are unrelated to food. In adults, having alternative reinforcers that are similar to the reinforcing value of food is protective against weight gain over 1 year [20], and a recent study in adolescents has shown that 42.4% of children at risk for weight gain with high food reinforcement did not gain weight over 2 years [3], suggesting some protective factors are present in children that may moderate the impact of food reinforcement on weight changes.

**Reinforcement Pathology**

While high food reinforcement predicts increased energy intake and BMI [8], individuals with the highest energy intake and BMI often are also low in self-control, specifically in delay of gratification [21]. *Delay of gratification* describes the preference for a choice between smaller immediate rewards and larger delayed rewards, made famous through Walter Mischel’s marshmallow task [22]. This task offered children one marshmallow now or two marshmallows later and measured how long the children were able to wait for the larger reward. A more recent and precise approach to measure delay of gratification is the delay discounting task, in which choices are made between small immediate rewards and large delayed rewards across increasing time points [23]. The term
Reinforcement pathology describes an individual with both high food reinforcement and high delay discounting [21,23]. Adults with reinforcement pathology consume more calories during a buffet-style eating task [24] and are more obese [25].

Reinforcement pathology may be especially important to consider in children, as the ability to delay gratification is not fully developed until late in adolescence/early adulthood [26], leading to an increased difficulty with delaying gratification in children [27,28]. In children, difficulty in delaying gratification is associated with weight gain [29,30] and diminished weight-loss treatment success [31]. A recent study examined discordant for weight (i.e., one lean and one obese) adolescent sibling pairs [32], and found that siblings with larger differences in both delay discounting and food reinforcement also had the greatest differences in BMI z-score [32]. This study suggests reinforcement pathology may be a primary behavioral processes contributing to obesity in children, and highlights the importance of considering a child’s ability to delay gratification for food as well as their food reinforcement when helping children regulate energy intake.

**INTERVENTION APPROACHES TARGETING FOOD REINFORCEMENT**

The research reviewed so far paints a clear picture of the association between high food reinforcement, increased energy intake, and weight gain in children and adults. When designing interventions to help children lose weight, food reinforcement, and the processes that influence it, should be an important consideration. Reducing the reinforcing value of unhealthy foods for children with high food reinforcement could facilitate the regulation of energy intake. However, food is a primary reinforcer and present at birth, so reducing food reinforcement is a difficult task. To date, methods for reducing food reinforcement involve targeting behaviors that moderate the influence of food reinforcement on energy intake and BMI. Intervention approaches that manipulate these factors can be incorporated into obesity treatment to reduce the impact of high food reinforcement in obese children.

**Manipulating the Behavioral Cost of Food**

Children’s attempts to gain access to food are related to both their food preferences and the effort required to obtain the various food choices, as constraints on the preferred food encourages a switch to the less preferred alternative [19]. This suggests that increasing the behavioral cost of preferred but unhealthy foods and keeping the behavioral cost of healthy foods low may help to improve food choices. Even if the child still finds the unhealthy food highly reinforcing, manipulating behavioral cost may be one way to attenuate the effect of higher food reinforcement. Previous research shows that fruits and vegetables, in addition to nonfood activities, are acceptable alternatives, or substitutes, when the unhealthy snack increased in behavioral cost [33]. Thus, interventions that require children to work harder to obtain unhealthy foods may help encourage substitution of unhealthy foods with healthier low-calorie foods.

One common practice in weight-loss programs is advising families to use stimulus control [34]. This strategy involves removing or hiding unhealthy foods in the home and making healthy foods and activities more accessible. Families may hide their cookies in a high cabinet and place a bowl of fruit on the kitchen table. Some may even hide their televisions or place their sneakers by the door to make exercise more accessible. These types of strategies involve increasing the behavioral cost of participating in unhealthy behaviors and lessening the behavioral cost of the healthy habits, to encourage participation in these new, healthier behaviors.

**Strategies to Lessen Impact of Food Deprivation and Restriction**

A necessary component of weight-loss programs is the requirement to maintain a negative energy balance by reducing normal energy intake. This makes it unlikely for a child to be able to regulate their body weight without some periods of food deprivation or restriction of unhealthy but reinforcing foods, which may cause an increase in the motivation to eat [35]. This becomes especially problematic if a child eats unhealthy foods when they are deprived, potentially increasing the
reinforcing value of those foods. While short-term food restriction does not increase the reinforcing value of a food [16], restriction increases consumption of the restricted food especially in children who are high in food reinforcement [18].

Interventions may make use of strategic food deprivation and restriction procedures to lessen their acute effects on food reinforcement. For example, allowing children limited but frequent choice of unhealthy foods in a portion-controlled manner may be useful in reducing the effect of food restriction. Reducing periods of food deprivation with healthy low-calorie snacks, or scheduling them to occur prior to a healthy meal, may attenuate the effect of food deprivation of the reinforcing value of food or increase the reinforcing value of healthy foods.

Using Food Variety to Increase Reinforcing Value of Healthy Foods
Food variety increases energy intake [36] and responding for food [37], and may be used to increase the reinforcing value and consumption of healthier foods and reduce the consumption of unhealthy foods. Increasing the variety of healthy low-calorie foods, such as fruits, vegetables and low-fat dairy, while reducing the variety of unhealthy foods that children have access to during snacks and meals could significantly improve their eating habits. Research shows that reducing the variety of unhealthy food increases the efficacy of family-based weight-loss interventions for both children and their parents [38].

Providing Reinforcing Alternatives to Food
The decision to eat is often a choice between food and some other behavioral alternative or reinforcer, and the value of food may depend on the alternatives concurrently available [39]. Providing children with reinforcing nonfood alternatives may reduce choices for food-related activities and energy intake. The availability of cognitively enriching activities (e.g., books, musical instruments) predicted greater success in a weight-loss treatment among children with low food reinforcement [31]. This suggests that finding reinforcing nonfood alternatives may be difficult for obese children as research also shows that obese individuals find food more reinforcing than other pleasurable sedentary activities [40].

Improving Ability to Delay Gratification
Targeting improvements in children’s ability to delay gratification may be another way to curb the effect of high food reinforcement. Obese children often have difficulty delaying gratification for food [41], and interventions that incorporate training on how to resist the immediate gratification of food may benefit children attempting weight loss. Mischel and colleagues [22,42,43] have an extensive program of research on techniques to improve children’s delay of gratification, including teaching children to divert attention away from tempting foods and imagining the tempting foods as abstract nonconsumable objects (e.g., a scoop of chocolate ice cream resembles mud) [22].

A new technique to help individuals delay gratification, episodic future thinking, has been shown to decrease energy intake and impulsivity in children [44]. Episodic future thinking involves vividly imagining or preexperiencing autobiographical details while mentally simulating a future event [45]. This technique is thought to increase the value of delayed outcomes during decision making [46] and steer individuals toward choices with long-term benefits [47]. The ability to think about episodic future events emerges between 3 and 5 years old [48], so children can be taught to imagine themselves in the future as a technique to delay gratification when they are tempted to make a less healthy food choice.

CONCLUSION

Food reinforcement is an important factor to consider in childhood obesity and interventions to both prevent obesity and help children lose weight. There are multiple factors that impact food reinforcement and these can be used to improve weight-loss interventions. We might help Johnny lose weight
by teaching him delay of gratification techniques, offering a large variety of healthy foods, ensuring the availability of nonfood alternative reinforcers in his home that are more accessible than food, and allowing a small number of portion-controlled unhealthy foods. Combining a variety of techniques that target food reinforcement may be especially important to help children regulate their energy intake.

REFERENCES

INTRODUCTION

Understanding childhood obesity is of the utmost importance today, given its precipitous, progressive, and persistent upward trajectory starting at a young age. More than 10% of 6–23-month-olds and 20% of 2–5-year-olds are either overweight or obese, with ≈70% remaining so in adulthood [1,2]. Due to the recalcitrant nature of obesity, prevention rather than treatment is key, with breast-feeding identified as a cornerstone of any prevention program. This is supported by the recommendation from a presidential task force of breast-feeding as a strategy to reduce pediatric obesity [3]. Universal breast-feeding is also supported by the Centers for Disease Control and Prevention [4], the World Health Organization [5], the American Academy of Pediatrics [6], and the American College of Obstetricians and Gynecologists [7], to name just a few. These recommendations reflect findings from seven systematic review/meta-analyses conducted using 81 studies spanning from 1970 to 2010 [5,8–13]. A review performed in 2015 of the best available evidence observed that results from all available meta-analyses indicated a reduction of 12%–24% in the prevalence of overweight/obesity in children who were breast-fed compared with those who were not breast-fed (odds ratios ranging from 0.76 to 0.88) [13]. Further, the American Academy of Pediatrics stated there is a “15%–30% reduction in adolescent and adult obesity rates if breast-feeding occurred during infancy compared with no breast-feeding” [6].

This chapter will focus solely on a single question: Is breast-feeding protective against obesity? However, it would be remiss to exclude the far-reaching benefits of breast-feeding beyond that of obesity prevention. Probative data exist showing clear associations between breast-feeding and reductions in the incidences of respiratory, allergen, gastrointestinal, and infectious-related morbidity in infancy, saying nothing of the effects of bonding and nurturing between mother and infant, and at this time it is still recommended as the preferred feeding choice of mothers [14–17]. Furthermore, a recent review reported that breast-feeding provides protection from future diabetes
risk (34% reduction) while modestly improving IQ (2.2–3.5 points) [5,18,19]. This chapter will cover four broad topics that currently exist in the breast-feeding literature. The first area discussed is some of the current debate on how the literature was gathered and interpreted to come to the recommendation that breast-feeding reduces obesity. A second area will discuss the presence of nonnutritive molecules in breast milk. Building on this topic, both animal and human studies are presented that demonstrate a mechanism of action for nonnutritive molecules exerting a harmful outcome in offspring. Lastly, new and innovative study designs are discussed that advance the field forward by overcoming some of the inherent problems in conducting true randomized controlled studies in humans.

DEBATE AS TO WHETHER BREAST-FEEDING PROTECTS AGAINST OBESITY

HANDLING OF DATA AND ADEQUATE CONSIDERATION FOR PUTATIVE CONFOUNDERS

Given the biological plausibility that breast-feeding protects against pediatric obesity, along with the preponderance of the evidence and near-universal belief that breast-feeding has this effect, it would appear that the case for breast-feeding protecting against pediatric obesity risk is resolved. However, some have begun to challenge not only the recommendations but also the very evidence on which these recommendations were made [20–23]. In 2008, a critical assessment of the interpretation and handling of the data in the World Health Organization’s 2007 report on “evidence of the long-term effects of breast-feeding: systematic reviews and meta-analysis” with respect to obesity was published [23]. The authors stated “while breast-feeding may have benefits beyond any putative protection against obesity, and benefits of breast-feeding most likely outweigh any harms, any statement that a strong, clear and consistent body of evidence shows that breast-feeding causally reduces the risk of overweight or obesity is unwarranted at this time” [23]. A major criticism made was in the selection or exclusion of data that may have led to an artificial inflation in the observed association between breast-feeding and reduced obesity risk. In fact, the authors brought into question the “reliability and reasonableness of the data extraction process itself” and went as far as to suggest that an independent assessment be performed.

Another issue raised by the authors is the lack of appropriate control of presumed confounders, with maternal body mass index (BMI) being especially relevant [13,20,23]. The Department of Maternal, Newborn, Child and Adolescent Health of the World Health Organization [5] reviewed the role of breast-feeding in obesity prevention, examining 71 separate studies providing 75 different estimates on the associations between breast-feeding and the risk of becoming overweight/obese. It appears that maternal BMI was collected and considered for study analyses in approximately 65% of the studies, while in the remaining studies, maternal BMI was either not collected, ambiguously obtained, or not considered at all in the analyses. The failure to consider maternal BMI and/or poor collection (i.e., retrospectively relying upon maternal recall or poor description in the methodological design) may partly explain the large range in the individual study odds ratios of 0.28 (95% CI: 0.09; 0.84) to 1.83 (95% CI: 0.53; 6.28). Failure to control for maternal BMI among breast-feeding mothers may also explain why some have concluded that there is no causal link between the duration of breast-feeding and childhood overweight/obesity, or that, at best, breast-feeding provides a modest level of protection [20–22,24]. Yet another potential confounder that is underappreciated and not commonly reported is the “length” of time that the breast-feeding took place. Oftentimes, breast-feeding is handled as a dichotomous variable, a yes or no proposition, with no regard to the length of time that the child was breast-fed. Interesting results by O’Tierney, which were part of the Helsinki Birth Cohort Study (n = 12,345), reported that infants who either breast-fed for <2 months or >8 months had the highest BMI and body fat at 60 years of age [25]. Both of the confounders presented, maternal BMI and length of breast-feeding, only highlight the difficulty and idiosyncratic complexities in categorizing a seemingly simple question, “did you breast-feed your child?”
Epidemiological evidence against breast-feeding’s beneficence

Epidemiological data have also brought into question the role of breast-feeding in reducing obesity. The Promotion of Breast-feeding Intervention Trial (PROBIT) is the largest randomized trial ever conducted with the expressed purpose of understanding the role that breast-feeding plays in reducing obesity and blood pressure [26]. The cluster-randomized trial for breast-feeding promotion was conducted in 31 Belarusian hospitals (n = 17,046). Given that it is unethical to randomize infants to breast-feeding or formula, the authors employed a “cluster-randomized” study design where an entire hospital/clinic was exposed to the intervention based on the Baby-Friendly Hospital Initiative, which supports and promotes breast-feeding [26]. What is important to keep in mind is that the “Baby-Friendly Initiative” is not to increase initiation of breast-feeding, but rather to support the continued practice and duration of breast-feeding in mothers who choose to initiate breast-feeding. Infants from both groups (control and experimental) were followed longitudinally with serial weight, waist/hip circumferences, and tricep/subscapular skinfolds (measures of body composition) taken over the first 6 years of life (81% were followed to their sixth birthday). The authors reported no effect on BMI or adiposity (reduction in skinfold thickness) between the groups.

Presence of nonnutritive molecules in breast milk

A logical first question to ask to help understand the purported decrease in obesity risk in breast-fed infants is what evidence exists for biological plausibility? It was long thought that the primary function of breast milk was the delivery of macronutrients (protein, fat, and carbohydrates) for sustenance and immunologic primers for protection against infection and that the compositional makeup of breast milk was generally homogenous [27]. It is only now being recognized that human breast milk is a biological product generated by women with markedly varying genotypes, phenotypes, and diets, and is therefore highly variable in composition. Failure to appreciate the heterogeneity of breast milk has led to substantial gaps in our understanding, especially with regard to the effect of maternal habitus (weight and adiposity) on the composition of her breast milk, which in turn affects her infants’ health. Starting in the mid-2000s, data began to emerge that showed that breast milk is composed of a myriad of appetite-regulating hormones (leptin, ghrelin, and peptide YY), cytokines (IL-6, IL-10, TNF-α), growth factors (IGF-1 and VEGF), and metabolic hormones (adiponectin and resistin) [27–29]. In all likelihood, these “analytes” are crucial players in setting early metabolism and appetite regulation, with leptin and adiponectin the most understood. In humans, breast milk leptin concentration is inversely related with weight-for-length z-scores, BMI-for-age z-scores, and delta BMI in the first month of life [30,31], while adiponectin levels are inversely related with weight-for-height and BMI in the first 2 years of life [32,33]. Animal models have demonstrated a cause and effect relationship when oral leptin supplementation is given to lactating dams, with their offspring having protection against overweight/obesity later in life [34]. What is especially important to keep in mind is the potential role that breast milk cytokines, chemokines, and metabolic hormones have on future obesity risk. We do not yet know the exact role and function of all these bioactive nonnutritive substances, though there is support for an impactful and significant role.

Associations between maternal BMI and nonnutritive molecules in breast milk

A review by Andreas and colleagues on the effects of maternal BMI on bioactive nonnutritive substances (e.g., insulin, glucose, leptin, adiponectin, ghrelin, resistin, obestatin, peptide YY, and glucagon-like peptide 1) in breast milk sheds light on the importance of maternal BMI when examining associations between breast-feeding and obesity risk [35]. After taking into account the best available evidence, they found a consistent relationship between maternal BMI and breast milk leptin; however, there was no clear evidence supporting an association with breast milk adiponectin, ghrelin, insulin, peptide YY, and resistin [35]. Admittedly, most of the studies included were
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“proof of concept” studies, lacking rigorous study design, with inadequate sample size, poor to no standardization of sampling collection (whole milk expressions vs. fore milk vs. hind milk, time of day), and varying immunoassay methodologies (radioimmunoassay [RIA] vs. enzyme-linked immunosorbent assay [ELISA]) to determine breast milk hormone concentration levels. The review only highlights a need for more definitive well-designed studies in a field ripe for investigation. Indeed, another review investigating the biological determinants of future obesity risk and their association with mode of feeding (breast vs. formula) in infancy concluded that, “in all likelihood the mechanisms are complex and involve synergistic interactions between endocrine effects and factors that alter both inflammatory and oxidative stress in the infant” [36]. Though emergent, the role that maternal BMI has on the compositional makeup of nonnutritive molecules in breast milk is just now being appreciated, with little to nothing known of its associations with infant obesity risk.

A new and exciting component of breast milk beyond that of the molecules listed is human milk oligosaccharides (HMOs). HMOs are unconjugated glycans that serve as prebiotics and the metabolic substrate for the microbiota [37]. In a small proof of principle study, Alderete and colleagues reported at 6 months a 1 µg/mL increase in fucosyl-di sialyl lacto-N-hexaose, and lacto-N-neotetraose was associated with 0.04% higher (p = .03) and 0.03% lower (p < .01) whole body fat (by dual-energy x-ray absorptiometry) [38]. Though emergent, these findings support the hypothesis that differences in HMO composition in breast milk play a significant role in early growth and body composition.

PROPOSED MECHANISMS

Animal Studies

Interesting data exist in both animal cross-fostering studies and a uniquely designed human study suggesting the importance of maternal BMI and/or metabolic health for healthy and appropriate breast milk composition. Both lines of study provide windows into the future that will elucidate important mechanistic pathways that are yet to be discovered. For example, these animal studies allow manipulations not ethically possible or feasible in human studies, and are often essential to understand the basic underlying mechanisms of treatments such as breast-feeding. Using a cross-fostering design, Gorski and colleagues examined the effects of the postnatal environment (i.e., breast-feeding) on offspring obesity and insulin resistance using a diet-induced obesity rat model [39]. In the obese diet–induced dams, breast milk insulin at 7 days was significantly higher (128%) compared with the diet-resistant dams, though no differences were observed in breast milk leptin. Interestingly, pups from obesity-prone dams cross-fostered to obesity-resistant dams remained obese in adulthood but improved their insulin sensitivity, while pups from obesity-resistant dams cross-fostered to obesity-prone dams had increased adiposity and decreased insulin sensitivity in adulthood. These findings are suggestive that maternal obesity affects the compositional makeup of a mother’s breast milk, which in turn affects her offspring’s obesity and overall metabolic health. In another cross-fostering study design using a mouse model, obese-prone dams had four times as much breast milk leptin as nonobese dams at 18 days [40]. Genetically fixed obese pups fostered to obese dams were 26% heavier than obese pups fostered to nonobese dams. Similarly, nonobese pups fostered to obese dams were 22% heavier than nonobese pups fostered to nonobese dams [40]. Taken together, these cross-fostering studies provide good evidence that breast milk composition differs by the obesity status of the mother, and pups, either obese prone or obese resistant, are significantly heavier if fostered to an obese prone mother versus a nonobese or obese-resistant dam.

Human Studies

Several human studies have reported increased breast milk glucose and insulin concentrations from diabetic mothers compared with nondiabetic mothers [41,42], providing an opportunity to test the
effects of breast milk composition on infant outcomes, namely, by comparing diabetic mothers who breast-fed with those who formula fed. As previously stated, it would be unethical to randomize human offspring to either breast-feeding or formula; however, an ingenious study design provided insight into the association between breast-feeding and infant obesity using a pseudorandomized study design [43]. Plagemann and colleagues enrolled 112 diabetic mothers (\( n = 29 \) who had gestational diabetes; \( n = 83 \) who had type 1 diabetes) prospectively and followed them for the first week of their infant’s life [43]. For mothers who could not breast-feed, or stopped within the first week of life, their infant was given banked nondiabetic milk. Of note, the banked milk was from “nondiabetic” mothers (no mention was reported on maternal BMI). The findings were startling: a significantly positive correlation was observed between the volume of breast milk ingested (i.e., milk from their diabetic mother) and the risk of being overweight at 2 years of age (odds ratios 2.47; 95% CI: 1.25; 4.87). This study demonstrates that breast milk from diabetic mothers may increase the risk of obesity and diabetes later in life. Though far from conclusive, this study suggests that all breast milk is not the same and that maternal habitus/metabolic health plays a crucial role in determining the “quality” of her breast milk.

**INNOVATIVE STUDY DESIGNS**

Some beliefs, practices, dogmas, and ideologies are thought of so highly that they become sacrosanct, thus allowing *ipse dixit* to dominate the discussion rather than letting empirically driven, scientifically derived evidence be the prevailing driver [44]. Unfortunately, the claim that breast-feeding causes a reduction in obesity risk has entered the lexicon as proved by science and is factually untouchable. This persistent and impassioned belief has recently been called a myth by some and contemptuously challenged by others [13,20–22,45–47]. The proposition that “mothers who breast-feed prevent obesity in their offspring” must be based on the evidence, with more weight given to randomized controlled clinical trials than observational studies, no matter how well designed. For practical, ethical, and theoretical reasons it is impossible to have true randomization in breast-feeding studies, with few observational studies controlling for known confounders by maintaining tight controls. To date, almost all breast-feeding studies are observational in nature without controls and are purely associational in nature. This leads to a fallacy of presumption known as *cum hoc*, where it is assumed that because two events occur together (breast-feeding and less obesity), they must be causally related. Randomized controlled studies are essential for causal inference, but in the realm of breast-feeding and human obesity, are nigh impossible to carry out. The two following examples are forward thinking and advance the field forward.

Most breast-feeding studies have a multitude of methodological shortcomings that are either hard to control or impossible to eliminate. Colen and Ramey employed a unique sibling comparison using 25 years’ worth of data from the National Longitudinal Survey of Youth [45]. Three models were used for analysis: Model 1 used the complete sample (between families), Model 2 included data only within siblings, and Model 3 examined discordant siblings (one sibling was breast-fed while the other sibling was formula fed). The findings were intriguing: Model 1 indicated that breast-fed children were protected not only for weight (i.e., lower) but other measured outcomes (asthma, hyperactivity, parental attachment, behavioral compliance, math and reading scores, vocabulary, intelligence, and scholastic competence). Model 2 showed similar results; however, Model 3 indicated that breast-fed siblings had, on average, only a 0.14 kg/m\(^2\) smaller BMI than their formula-fed sibling. Colen et al. (2014) concluded that many of the “purported benefits attributed to breast-feeding, chiefly obesity prevention, may be primarily due to selection pressures into infant feeding practices along key demographic characteristics, such as ethnicity, socioeconomic status, education, and other yet identified confounders” [45]. This is an important consideration when understanding and interpreting the results of studies currently in the field.

More creative study designs that employ both animal and human designs are needed, such as packet randomized experiments (PREs), a framework that improves causal inference when
randomization is not possible [48]. Briefly, in a PRE using an animal model (e.g., mice) of obesity, mice would be randomized to human breast milk obtained from breast-feeding mothers of varying physiological (adiposity and diabetes), sociological (education, rural vs. urban, socioeconomic), and genetic confounders that human-correlational studies (which currently dominate the literature) either cannot remove or are almost impossible to control. By randomizing mice to human milk, three sources of confounding present in human studies can be removed: (a) external/environment factors (e.g., rural vs. urban, smoking vs. none, high crime neighborhoods), (b) genetics (all mice have the same mother), and (c) maternal factors (e.g., diet, obesity status, diabetes). At this time, unique study designs that go beyond that of simple associations such as PREs are badly needed if we are to understand how maternal BMI affects human breast milk, which in turn affects her offspring. The field in general sorely needs “outside the box thinking” to resolve an important and pressing health issue.

CONCLUSIONS

This chapter focused solely on the evidence investigating the role of breast-feeding in reducing overweight/obesity risk in pediatric populations. Current evidence linking breast-feeding to reduced risk for developing obesity is inconclusive at this time. In fact, when taking into account the obesity status of the mother, data from both animal and human studies have demonstrated increased obesity in offspring nursed from either obese or diabetic mothers. Though a controversial topic, we must demand the highest scientific evidence and rigor if we are to advance the field and ultimately improve the lives of children specifically, and public health as a whole. Important questions we need to ask ourselves are where do we go from here, and what are the key issues moving forward. The most pressing issue is increasing the number of mechanistic-based studies in the science of lactation and its association with infant outcomes, while understanding the role for the maternal habitus (obesity and metabolic status). The underlying principles are important and allow for proper context (e.g., ethnicity, duration, mixed feeding) in understanding the beneficial role that breast-feeding has in obesity prevention. By understanding this role, breast-feeding can be used as a vehicle for improved health in the offspring.

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Section III

Individual and Environmental Factors Contributing to and/or Associated with Childhood Obesity
INTRODUCTION

The developmental origins of health and disease (DOHaD) is a burgeoning field of research that suggests that perturbations occurring during critical periods of early life play a significant role in shaping a person’s long-term risk of obesity and negative health outcomes [2]. Although the concept of “developmental programming” most commonly refers to adverse exposures during intrauterine life, factors at the time of conception have also been implicated. As the opening quote suggests, parental health status before conception may powerfully shape child health and obesity risk. This chapter reviews prenatal exposures that may increase a child’s long-term susceptibility to obesity and adverse health outcomes. We consider several potential prenatal risk factors, including poor maternal health status, complications during pregnancy (e.g., gestational diabetes, hyperglycemia), gestational weight gain (GWG; excessive or inadequate), prenatal nutrition, activity, smoking, and other potentially adverse exposures. Our review draws primarily from observational studies in humans. Other chapters review epigenetic mechanisms (Chapter 14), environmental factors (Chapters 19 and 20), and intervention research using life course prevention approaches (Chapters 32 and 33).
MATERNAL HEALTH STATUS

Several lines of research have shown that maternal obesity before and during pregnancy has an independent, adverse impact on offspring weight and health outcomes during every life stage—from birth through adulthood [3]. Such associations have been reported in several studies with effect sizes ranging from small to moderate [4]. Linear relationships are generally observed with higher maternal preconception weight related to higher offspring weight outcomes. A within-family analysis of the US population found that the risk for having a high birth weight baby, which itself is a risk factor for later obesity, increased by 1.3% for mothers who were overweight before pregnancy and 3% for mothers who were obese [5]. Greater risks have been observed for the offspring of mothers with extreme (body mass index [BMI] >50 kg/m²) prepregnancy obesity [6]. A small number of studies have explored the relationship between maternal obesity and other offspring outcomes beyond adiposity, such as insulin sensitivity, glucose levels, lipids, and type 2 diabetes; findings generally indicated significant associations between maternal obesity and poorer offspring metabolic health [3]. Maternal prepregnancy obesity may also impact child neurological functioning. A systematic review on the topic [7] found associations between maternal obesity and several adverse child neurodevelopmental problems, including lower childhood IQ, attention-deficit/hyperactivity disorder, schizophrenia, and eating disorders, which have also been associated with child obesity; however, the review also noted several limitations in the literature.

Initially, the associations between maternal obesity and adverse offspring health outcomes were studied as evidence for a genetic underpinning of obesity risk. While shared genes partially mediate these associations, an abundance of human evidence, supported by extensive data from experimental animal studies, now suggests that intrauterine exposure to an obese intrauterine environment, per se, programs offspring obesity risk by influencing appetite, metabolism, and activity levels [4]. Nevertheless, the moderate size effects observed to date suggest that other early-life exposures may play a role in shaping child health outcomes.

GESTATIONAL WEIGHT GAIN

The National Academy of Science Institute of Medicine (IOM) has formulated specific recommendations based on maternal prepregnancy BMI for GWG ranges that are associated with optimal maternal-child health outcomes. However, approximately 35% of normal-weight women and 60% of obese women gain more than recommended [8]. In both normal-weight and overweight/obese women, excessive GWG is an established risk factor for obesity and obesity-related comorbidities in offspring. Meta-analyses have found that excessive GWG significantly increased the risk of offspring overweight/obesity [9,10]. One meta-analysis concluded that at least 21% of the risk for childhood overweight was related to excessive GWG [10]. Given the high prevalence of excessive GWG, many offspring, particularly in the United States, are exposed to this obesity risk factor.

Although inadequate GWG is comparably far less common in the United States (~24%), it too has been linked with future offspring weight status, but the magnitude and direction of this association remain unclear. Two, large-scale observational studies have reported significant U-shaped associations between maternal GWG and child weight outcomes [11,12] with both inadequate and excessive GWG linked with later offspring obesity risk. By contrast, two meta-analyses [9,10] concluded that inadequate GWG was associated with a small decrease in the risk of later childhood obesity. Studies of pregnant women during times of famine have also reported mixed effects. A series of studies examining the effects of famine in the Dutch population found small and weak positive associations between exposure to famine during pregnancy and later obesity in female (but not male) offspring [13]. By contrast, research on the effects of the Leningrad famine found no significant effects of intrauterine exposure to famine and later offspring metabolic health [14]. The extent of a nutritional “mismatch” in the intrauterine versus postnatal environment may underlie these mixed findings. Offspring exposed to inadequate GWG but adequate or excessive postnatal feeding may exhibit “catch-up growth” or
a compensatory acceleration in the rate of growth that may lead to later obesity and chronic diseases [15]. However, overall, the potential adverse effects of excessive GWG appear more robust than those of inadequate GWG in predicting subsequent child obesity and metabolic risk.

**PRENATAL NUTRITION**

Studies of the effects of GWG commonly infer effects on “overnutrition” or “undernutrition” during pregnancy and effects on long-term child obesity, but only a few human studies have objectively measured prenatal nutrition in relation to postnatal child weight and health outcomes. One study measured maternal macronutrient intake (using a food frequency questionnaire) at 32 weeks of gestation and child adiposity (assessed using dual-energy x-ray absorptiometry [DEXA]) at 10 years of age in 5593 mother/child dyads [16]. There were no significant associations between maternal prenatal protein, fat, and carbohydrate intake and offspring adiposity or lean mass at ages 9 and 11 years. Another study of two prospective UK cohorts reported an association between low carbohydrate intake (using a food frequency questionnaire) during early pregnancy and gene methylation that was linked with higher offspring weight (DEXA measured) [17]. Other work has suggested that the ratio of carbohydrate to protein intake during pregnancy was the key risk factor for later abnormal glucose homeostasis and high blood pressure in offspring [18]. Macronutrient components (rather than total macronutrient content only) may more consistently relate to offspring obesity. Two studies have reported that higher maternal sugar intake during pregnancy was predictive of higher offspring weight at birth and 6 months [19], and at 5 years of age [20]. Moreover, some evidence points to a role for maternal fat intake in shaping later offspring health outcomes [20]. Overall, however, linkages between maternal prenatal dietary intake and child obesity and health have been equivocal and are not well understood. The scant research in this area limits conclusions that can be drawn. Prospective assessments with validated, repeat measures of maternal dietary intake during pregnancy are needed to move the field forward.

**MATERNAL PHYSICAL ACTIVITY**

The American College of Obstetricians and Gynecologists (ACOG) recommends that pregnant women engage in at least 30 min of moderate exercise each day on most, if not all, days of the week for uncomplicated pregnancies. While light and moderate leisure time and occupational physical activities have been shown to improve several maternal health outcomes, including decreasing the risk of preeclampsia, hypertension, and gestational diabetes (GDM) [21], far less is known about the potentially protective effects of maternal physical activity on child health. Sufficient evidence exists that shows that prenatal physical activity does not increase the risk of low birth weight [21]. Some observations studies have reported that prenatal physical activity reduced the occurrence of offspring neural tube malformations [22]. Evidence in animal studies has suggested potential associations between higher activity levels during gestation and improved vasomotor function in offspring. However, similar to prenatal diet, there is a clear need for research in humans, using objective, repeat measures of physical activity and objectively measured child adiposity and health outcomes.

**PREGNANCY COMPLICATIONS**

GDM is another widely accepted risk factor for the development of obesity and chronic disease in offspring. Several studies have shown that fetal exposure to maternal diabetes during gestation conveys a risk of several short- and long-term health problems in offspring, including obesity, type 2 diabetes, and metabolic syndrome in children, adolescents, and adults [23]. Exposure to GDM has also been linked with birth trauma, respiratory distress syndrome, and neonatal death. An analysis of data from nine studies of diverse populations showed that by age 3–16 years, the mean offspring BMI z-score was 0.28 higher for the offspring of women with diabetes compared with controls [24]. In a series of longitudinal studies of Pima Indians, most of the increased prevalence of childhood
type 2 diabetes occurring over a 30-year time frame was attributable to increased exposure to maternal diabetes during pregnancy [25]. Other long-term, prospective research has shown that the adolescent offspring of mothers who had diabetes during pregnancy (regardless of type) had a significantly higher prevalence of impaired glucose tolerance (19.3% vs. 2.5%, respectively) and obesity (50% vs. 20%, respectively) than the age- and sex-matched controls [26]. Females born with obesity had an increased risk of later obesity and a doubled risk for delivering an obese infant themselves [27]. These findings suggest that prenatal exposure to diabetes could form the basis of transmission of obesity and health risks from parent to child to grandchild and beyond, creating a vicious cycle to fuel the obesity epidemic for decades to come.

Maternal gestational hypertension and preeclampsia are also significant risk factors for offspring hypertension, stroke, and cardiovascular disease, independent of maternal weight status and a range of potential confounders [28]. Using data from 6343 9-year-old participants in the Avon Longitudinal Study of Parents and Children, both preeclampsia and gestational hypertension were associated with elevated systolic and diastolic blood pressures in the 9-year-old offspring, after adjustment for parental adiposity [29]. A number of other studies have reported that offspring exposed to preeclampsia and gestational hypertension had an increased risk of depression and other psychiatric and psychological problems in adulthood [30].

Overall, a preponderance of evidence suggests that pregnancy complications may exert programing effects on later offspring health. In examining the effects of pregnancy complications on offspring health outcomes, studies typically “adjust” or remove the potential confounding influences of maternal obesity and excessive GWG. However, these (and other) risk factors commonly co-occur, are intertwined and, when combined, appear to exacerbate the observed adverse programing effects on child health and development [31].

MATERNAL MENTAL HEALTH

Maternal stress and depression may also play a role in programing adverse child health outcomes. In a review of nine studies, chronic maternal depression was associated with greater risk of child overweight [32], independent of a range of potential confounds. In several retrospective reports, maternal depression during pregnancy was independently associated with neonatal distress, reduced orientation and motor activity, and disrupted sleep; and longer-term effects have been observed on child neurobehavioral outcomes, including disruptive social behavior and depression [33]. Unfortunately, treatment with antidepressant medications during pregnancy also has been related to adverse long-term effects on gross motor function and language development in offspring [34].

Similarly, prenatal maternal stress and anxiety also appear to negatively impact child cognitive development, particularly if the exposure occurs early in pregnancy [35]. Moderately severe stress during pregnancy (i.e., a natural disaster) was independently associated with lower cognitive and language abilities at five and a half years of age in one Canadian study [36]. Other work has found that high levels of cortisol in mothers during the third trimester of pregnancy was negatively related to offspring cognitive skills, independent of family and postnatal factors [37]. However, most studies examining the effects of maternal mental health on offspring outcomes have only followed children through infancy. Additional long-term studies are needed with systematic follow up of women through pregnancy along with careful quantification of the degree, duration, and timing of depression, stress, and antidepressant exposures, using standardized, structured assessments of infants and children, and measurements of obesity and metabolic function.

FAMILIAL AND SOCIODEMOGRAPHIC FACTORS

Sociodemographic disparities in obesity risk are well documented, with familial-level factors, such as lower income and education levels, black race, and Hispanic ethnicity, all placing individuals at higher risk for the development of obesity. Unfortunately, sociodemographic disparities also exist
for the preconception and prenatal risk factors reviewed in this chapter. The prevalence of maternal preconception obesity is higher in non-Hispanic black and Hispanic white women compared with non-Hispanic white [8]. Similarly, the risk for GDM is higher for several ethnic groups compared with non-Hispanic white mothers. Also, smoking during pregnancy is more prevalent among low-income and disadvantaged mothers. The most disadvantaged mothers are also more likely to be exposed to pesticides and toxic metals and to experience higher stress from financial challenges and life events. The reasons behind social disparities in prenatal exposures are complex and implicate a wide range of socioeconomic factors (e.g., income, education, social status) and disparities in both nutritional exposures (i.e., food availability, food security, and diet quality) and physical activity opportunities. Since socially disadvantaged populations are exposed to more risk factors, both during fetal life and after birth, developmental programing effects may serve to exacerbate health disparities from one generation to the next. Future social epidemiology research must consider whether and how the social–environmental conditions of pregnant women perpetuate social disparities in chronic disease.

NEW DIRECTIONS

This is an exciting time for research in maternal–child health and disease prevention. As reviewed earlier, the evidence in support of the DOHaD is compelling, but there are many caveats in the field requiring future research, and more work is needed to bridge the gap between animal and human studies. There are also several new avenues of inquiry on the horizon.

CHILD HEALTH OUTCOMES

Extensive research has consistently documented associations between several prenatal exposures and the risk of offspring obesity. However, far more work is needed to identify whether and how prenatal exposures impact a range of other offspring health outcomes, including insulin resistance, hypertension, dyslipidemia, adverse neurodevelopmental outcomes, and asthma.

CHILD FOOD PREFERENCES

Emergent research suggests that prenatal nutrition may be indirectly linked to offspring obesity through the influence of prenatal flavor exposures on the offspring’s later food preferences [38]. Flavors of the mother’s diet can be transmitted to the fetus through amniotic fluid, and the fetus has the ability to detect the flavors present in the womb, which may influence the offspring’s later flavor and food preferences. In an interesting study, mothers who were randomized to drink carrot juice daily during their last trimester of pregnancy or first 6 months of lactation had infants who showed higher preferences for carrot-flavored cereal at 6 months when compared with infants whose mothers only consumed water during pregnancy and lactation [39]. Longitudinal studies that span the prenatal and postnatal periods should continue to explore how interactions between pre- and postnatal flavor and food exposures influence children’s dietary patterns and obesity risk and whether long-term flavor and food preferences and, ultimately, health status can be altered by manipulating prenatal dietary exposures.

PATERNAL PRECONCEPTION HEALTH

Much research in DOHaD has focused on maternal influences on offspring outcomes. However, paternal health at the time of conception may also influence offspring development. Paternal obesity is among the strongest risk factors predicting offspring overweight [40]. Other research suggests that paternal history of smoking and/or diabetes may increase offspring susceptibility to metabolic disease. The extent to which these paternal–child health associations are due to shared genes or
adverse exposures remains unclear. Data from animal models indicate that paternal obesity may negatively impair sex hormones, basic sperm function, and molecular composition, which may perturb embryo development and increase subsequent offspring disease [41]. Similar to other DOHaD research, the majority of data surrounding paternal obesity and offspring health have come from rodent models. New epidemiologic cohorts that provide repeated biological and behavioral data on fathers are needed to inform whether and how paternal health and related behaviors before and at the time of conception may influence fetal and child health.

**Preconception Period**

It is difficult to study the preconception period, given that approximately half of pregnancies are unplanned and that there is no readily available source of recruitment for women planning pregnancy. It is also difficult to separate preconceptual from pregnancy-specific influences on the risk of adverse health outcomes in children. As noted earlier, most women who enter pregnancy overweight remain overweight during pregnancy and may also experience excessive GWG and pregnancy complications. However, the relative impact of adverse exposures at the time of preconception versus during pregnancy remains unclear. Without prospective studies of mothers and fathers during the entire pre- to postnatal period, the optimal targets and timing for interventions remain unknown. There is a strong need for new cohort studies of families that begin before conception and follow offspring through childhood.

**Microbiome**

Fascinating research has been uncovering linkages between deviations in gut microbiota composition and the risk of obesity; specific groups of gut bacteria appear to harvest energy from food more efficiently than others and are more common in the guts of individuals with obesity versus those of normal weight status [42]. In maternal–child studies, exposures during pregnancy (e.g., maternal obesity, excessive GWG) and during the neonatal period immediately after birth (e.g., breast-feeding, vaginal delivery) appear to influence the infant microbiome and may be critical for programing child immune function and gut–brain energy-sensing systems [43]. Alterations in maternal microbiota composition during pregnancy may be transferred to infants in utero, impact the fetal gut, and exert significant effects on offspring immune and metabolic programing and later risk of disease [44]. As most of the work in this area has been done in animals, with limited studies during developmental periods (see Chapter 21), the time is ripe for human microbiome studies in the time surrounding pregnancy and early childhood.

**Epigenetic Mechanisms**

The field is at the budding stages of identifying and understanding the complex epigenetic mechanisms by which preconception and intrauterine exposures impact offspring development (Chapter 14). Pathways likely differ depending on the type, timing, and duration of exposure(s) and, importantly, on the interactions with postnatal life. Further mechanistic work with humans is needed that includes a range of offspring health outcomes but also assessments of behaviors that may be amenable to intervention. Berkowitz et al. [45] found that women who were obese before pregnancy (vs. normal weight) were more likely to have offspring who exhibited an obese eating style (large mouthfuls of food and increased caloric intake per minute during a test meal) at 4 years of age. These findings were consistent with the altered hypothalamus regulation of eating behaviors illustrated in animal models [46]. Further mechanistic work (likely through randomized controlled trials and interventions) is needed to better understand the application of findings from animal models to human systems (central nervous system [CNS], hypothalamic, metabolic) and behavior (eating, activity, smoking) and in relation to offspring health outcomes.
SUMMARY

Although much investigation has already occurred in the area of DOHaD research, the science itself is still in its infancy. It remains for researchers to tackle key questions and translate knowledge into effective interventions to reduce childhood risk of obesity and disease burden. Our review suggests several potential prenatal targets for intervention, including maternal prepregnancy overweight, GWG, pregnancy complications, and smoking. However, long-term experimental studies in humans will be needed to determine whether and in whom altering/improving preconceptual and intrauterine environments reduces offspring risks of obesity and chronic disease. To date, prenatal intervention studies with long-term follow up of offspring weight and health outcomes are few and far between, and the optimal intervention window (before, during, and/or after pregnancy) remains unclear. The best window for intervention may not be the same for all pregnancies, ethnicities, cultures, and health-care systems.

Many of the preconceptual and pregnancy risk factors for adverse intergenerational effects correlate with socioeconomic status, race, and gender. This points to the need for societal changes rather than solely individual-level interventions. Research in health disparities and the DOHaD field provides a rationale for public health policies to improve preconceptual and pregnancy care for women and men across all levels of society. As Richardson and colleagues [47] poignantly urged, the DOHaD research findings should not be used to blame individual women. Societal-level changes are needed to support interventions that ultimately empower all women and men of childbearing age to engage in health behaviors to protect the health of future generations.

REFERENCES


INTRODUCTION

As the worldwide prevalence of obesity increases, it is critical to elucidate the genetic basis for obesity and its associated cardiometabolic complications. The pediatric population is uniquely positioned to provide insights into the genetics of obesity, as the effect of environment on disease state is less manifest than in adults.

In this chapter, an overview is provided of the various methodologies for investigating the genetics of childhood obesity. This is followed by a description of the key genetic studies of obesity in both adults and children, as adult studies provide the foundation for genetic obesity studies in children. Finally, the known monogenic and polygenic obesity syndromes are described.
METHODS FOR STUDying THE GENETIC COMPONENTS OF CHILDHOOD OBESITY

TWIN, ADOPTION, AND FAMILY STUDIES

It is well established that obesity has a complex and multifactorial pathogenesis, including interactions between environmental, behavioral, and genetic factors. Over the past several decades, increasing evidence has supported a substantial inherited component of human obesity risk. The first investigations linking genetics with obesity included studies in monozygotic and dizygotic twins, and in many cases occurred years prior to the identification of specific variants associated with the trait. While one of the earliest twin studies estimated a heritability of 70% for body weight and 65% for waist circumference [1], subsequent studies have produced more varied estimates, with heritability of fat mass ranging from 70% to 90% in monozygotic twins and 35%–45% in dizygotic twins [2–9]. Of note, these heritability estimates can vary greatly when additional factors including physical activity, age, and other exposures are considered. For example, higher heritability for body mass has been reported in adolescents and young adults compared with older adults [10].

In addition to twin studies, adoption and family studies have also contributed to the evidence for the heritability of obesity. During the same time period as the early twin studies, an adoption study showed that the body size of adopted children was more highly associated with that of their biological parents than their adopted parents, across multiple measures of body size and anthropometry [11]. Further, studies within different racial and/or ethnic populations have shown variation in the heritability rates of body size, with estimates of heritability of approximately 35% or less in Caucasian and Asian populations, compared with rates of 50% or more in Pima Indians and South Sea Islanders [12]. Despite the variability in study reports, the heritability of obesity is now generally accepted to be between 40% and 70%, with a typical estimate of around 50% [9,13]. Thus, approximately half of the variation of body mass within a population is attributable to genetic factors. In the case of the “common” form of diet-induced or exogenous obesity, it is also clear that inheritance is not in a predictable pattern and instead is complex, indicating the likely presence of multiple responsible genes and gene networks, many of which likely have not yet been identified.

LINKAGE STUDIES

As one of the earlier methodologies to evaluate the genes underlying disease states, linkage analysis has been very effective in identifying disease-causing genetic variants for single-gene conditions. In these studies, the genomes of multiple affected relatives are mapped using genetic markers to identify specific segments of DNA inherited more often together than would be expected by chance. The shared loci are then further analyzed to identify individual genes responsible for the disease phenotype. When applied to the evaluation of obesity, linkage studies have been successful in identifying the single-gene mutations responsible for monogenic obesity syndromes. In particular, several studies have reported that mutations in the leptin gene, identified from analysis of a region on chromosome 7q31, are responsible for severe forms of obesity, as discussed later in this chapter [14].

In contrast to the monogenic forms of obesity, the utilization of linkage analysis in common, polygenic phenotypes has proved less successful. While linkage analysis has repeatedly identified several loci associated with the so-called common forms of obesity, no genes have been identified as of yet in these regions of haplotypic sharing and there is significant variation between the results of individual studies [9,15]. This is generally due to the low power of linkage analysis to detect the effects of variation in common genes that confer only modestly increased obesity risk, as well as variations in study groups and methods. As analysis continues on larger study populations, the detection of associated loci and the possible identification of genes using linkage analysis can be refined, and can be complemented with newly available high-throughput sequencing technologies.
CANDIDATE GENE STUDIES

In candidate gene studies, potential genes are selected for association analysis based on a known or hypothesized role in a disease phenotype. Candidate genes are considered to be either functional or positional. Functional candidates are dependent on current knowledge of the disease, as they are identified through products or mechanisms that are known to be involved in the disease process. Positional candidate genes are identified through their proximity to genomic loci that have been associated with disease pathology in previous linkage or association studies as well as animal models. Large numbers of candidate genes for obesity have been published; however, many initially suggestive results demonstrated no association in additional studies [2]. As this method is based on the pathophysiological mechanisms of obesity, of which much remains unknown, there has been limited success in identifying risk genes, and the genes that have been identified appear to carry a small effect [2,15]. These studies further reveal that the genetic causes of obesity are complex and potentially involve a large amount of genes with various effect sizes. They also demonstrate the need for discovery-focused evaluations of the genetic factors associated with obesity.

GENOME-WIDE ASSOCIATION STUDIES AND META-ANALYSES

Since 2005, research into the genetic basis of human obesity has been largely driven by the development and utilization of genome-wide association studies (GWAS) and in particular the HapMap Project, which developed an extensive catalog of sequence variations along the human genome [16]. GWAS use high-throughput methodology to span a large set, often millions, of common variants (single-nucleotide polymorphisms [SNPs] or single-nucleotide variants) across the entire human genome. This method allows for an untargeted, non-hypothesis-driven approach to reveal associations between specific disease phenotypes and common variants within the genome. Several large GWAS have been conducted within the fields of human obesity and metabolism; the general approach has been to compare common variant frequencies within obesity versus normal-weight controls. This has led to the identification of robust associations between numerous genetic loci and obesity and obesity-related traits. To date, dozens of established loci have been identified for body mass index (BMI) and waist-to-hip ratio [9,17–23]. A discussion of the most important of these is found in the following section of this chapter.

As GWAS are non-hypothesis-driven and have been successful in implicating genetic loci within complex, multifactorial disease processes, these robust associations are widely accepted within the research community, and are thought to offer an advantage over the linkage and candidate studies. The majority of these studies have been conducted in populations of European descent; however, recent GWAS have expanded the focus to include other ethnic populations as well as evaluating differences between sexes, pediatric populations, and longitudinal cohorts to identify potential effects by age [18,22,24–28].

Recently, meta-analyses of GWAS have become more common. Following analyses of individual GWAS datasets, statistical approaches to meta-analysis provide sufficient power to detect subtle genetic variants for common traits. By using imputation within the analyses, the number of common variants is computationally increased, which allows for a more extensive evaluation of a specific variant across the genome. In addition, meta-analyses overcome the effect of multiple testing of markers with borderline significance and thus reduce statistical noise. See subsequent sections of this chapter for more details.

MISSING HERITABILITY, RARE VARIANT–COMMON DISEASE HYPOTHESIS, AND NEXT STEPS

Despite the significant advantages that GWAS provide for our understanding of the genetic basis of obesity, there are a few particular drawbacks. The SNPs identified by GWAS are considered to be tag SNPs. They tag a causative variant in a particular region but are not causal themselves. Thus,
the key causal factors have yet to be identified. Further, while many loci have been identified, it is estimated that GWAS results account for only 10% of the heritability of obesity. This is in contrast to the nearly 50% heritability reported in twin and family studies. The missing heritability not identified by current GWAS methods is a topic of current debate and research. One theory for the missing heritability centers on the rare variant–common disease hypothesis. GWAS methods are based on the common disease–common variant hypothesis, in which the genetic components of a complex disease are thought to be attributable to the additive effect of a moderate number of common variants, each of which explain only a small proportion of the heritability. In contrast, newer methods to study rare variants, including new microarray chips that will evaluate SNPs with minor allele frequencies as low as 0.5%, as well as larger sample sizes have emerged [29,30]. One of the most recent modalities to effectively address the missing heritability issue was reported in 2015 and utilized a new method to impute a large sample of SNP arrays. Approximately 17 million imputed variants, including common and rare alleles, were generated to evaluate the heritability of height and BMI and demonstrated that the heritability of BMI is likely to be 30%–40%, producing a smaller range of missing heritability than has previously been described [31].

In addition, several other methods of study have been identified to explain the missing heritability. Currently, copy number variants (CNVs), which are the products of large segments of genetic material that have been replicated or deleted, have been implicated in the heritability of obesity and association studies have identified such multiple loci [32]. Emerging research also focuses on the effect of epigenetic mechanisms, which include DNA methylation, histone modification, and microRNA, on the heritability of obesity. Currently, the association of DNA methylation and obesity is being studied using whole-genome sequencing. Finally, the effects of epistasis, or gene–gene interaction, in which variants of different genes may interact and contribute to the heritability of obesity, have been hypothesized and the methods to evaluate these interactions genome wide are under development [9,15].

**RESULTS OF SPECIFIC PEDIATRIC GENETIC STUDIES**

**FTO Locus and Obesity Risk in Adults and Children**

To date, the genetic locus most strongly associated with adult BMI using GWAS is within the fat mass– and obesity-associated (FTO) gene, despite only explaining less than 2% of the predicted genetic component of obesity attributable to this trait [33]. Notably, this common variant was initially identified in a GWAS of type 2 diabetes (T2D) [34]; however, it was ultimately found that the incremental increase in T2D risk attributable to the variant in FTO was conferred by increased BMI [18]. FTO was actually the second obesity locus to be identified by GWAS [18], and has been widely replicated [35]. Not all initially suggestive GWAS results demonstrate such consistency. Indeed, unlike FTO, the first such obesity locus identified, within insulin-induced gene 2 (INSIG2) [36], has not produced such consistent associations in subsequent studies [37].

Studies have also demonstrated age-dependent variations between BMI and variations harbored within FTO. A meta-analysis was conducted of associations between the FTO locus (rs9939609) and BMI in eight European cohorts of children whose ages ranged from early infancy to 13 years. An inverse relationship was found between BMI and the obesity-associated allele of FTO in infancy; in contrast, a positive association was noted between BMI and the obesity-associated allele of FTO in early childhood, corresponding to the approximate time of adiposity rebound [38]. Thus, the adult obesity–associated allele of FTO was related to a lower BMI during the period of infancy peak BMI and a higher BMI during the period of adiposity rebound [38]; this may be explained by variations within FTO altering the characteristics of the BMI trajectory. Another longitudinal study noted that the peak association between the FTO locus and BMI occurred by age 20 years, after which the association diminished [39]. The FTO risk allele has also been shown to demonstrate dynamic physiological changes during adolescence, including an association with higher BMI, fat mass index, and
leptin concentrations during early puberty, followed by a nadir of these associations mid-puberty, and an eventual strengthening of these associations toward the completion of puberty [40]. These temporal associations highlight the likely complex physiology of this genetic variation with excess adiposity.

The mechanism whereby the risk allele of FTO is associated with obesity remains unclear, but there are some suggestions that it affects the central regulation of energy balance. FTO encodes 2-oxoglutarate-dependent nucleic acid demethylase, which is expressed in the appetite-regulating centers of the brain [41]. Rodent studies demonstrate that overexpression of FTO results in obesity [42], while a knockout of FTO protects against obesity [43]. Indeed, in a mechanistically focused study of 2726 Scottish children aged 4–10 years, those with the common obesity risk allele of FTO had significantly higher weight and BMI. In a subset analysis (n = 97), the risk allele was significantly associated with increased fat mass and increased energy intake but did not show associations with resting energy expenditure [44].

Notably, environmental changes over time have also been found to modify genetic risk factors. A gene-by-birth cohort interaction was identified for the rs993609 variant of the FTO gene within the longitudinal Framingham Heart Study, such that there was a strong linear correlation between the risk allele and BMI for individuals born after 1942, while no significant relationship existed for those born prior to 1942 [45]. This finding illustrates that some genetic variants may only contribute to obesity risk under specific adverse circumstances.

Although GWAS have yielded a large number of genomic signals, and there are a number of lines of evidence for FTO encoding a protein involved in the pathogenesis of obesity, these reports only represent a genomic signal and not necessarily, as often presumed, the localization of a culprit gene. This is because gene expression can be controlled locally or over large genomic distances; indeed, most regulatory elements do not control the nearest genes and can reside tens or hundreds of kilobases away. A paper published in Nature in March 2014 revealed that the signal within FTO was actually an embedded enhancer for the neighboring IRX3 gene [46]; indeed a follow-up study in the New England Journal of Medicine in 2015 suggested that this enhancer drove the expression of two other genes, IRX3 and IRX5 [47]. It remains to be determined how IRX3 and IRX5 mechanistically mediate the risk of obesity in children specifically.

RESULTS OF GWAS AND META-ANALYSES IN ADULTS

The first GWAS meta-analysis of BMI in adults was conducted in nearly 17,000 European individuals and noted the strongest associations for adult BMI within the FTO locus, along with an association between BMI and a locus near the melanocortin-4 receptor [MC4R] gene, well known to cause severe monogenic childhood obesity [48]. Although this GWAS was initially performed in adults, the identified MC4R association was confirmed in both adults (n = ~60,000) and children ages 7–11 years (n = ~6,000) from the Avon Longitudinal Study of Parents and Children (ALSPAC). In these children, each additional copy of the risk allele was associated with a difference in BMI of 0.10–0.13 z-score units, which was approximately double the effect size noted in adults [48]. These seminal results demonstrate that GWAS could be used to determine obesity associations both in adults and in children.

The Genetic Investigation of Anthropometric Traits (GIANT) consortium was formed soon thereafter to conduct large-scale meta-analyses of multiple GWAS. The initial meta-analysis combined 15 GWAS from over 32,000 individuals of European ancestry to investigate the association between BMI and about 2.4 million SNPs that were either genotyped or imputed [49]. The SNPs from the most significantly associated loci were then further studied through de novo genotyping in approximately 45,000 additional individuals, along with SNP analyses in over 14,000 individuals who were genotyped in other GWAS studies. Six more genes were identified through the GIANT consortium meta-analysis that were found to be reproducibly associated with BMI, including: transmembrane protein 18 (TMEM18), potassium channel tetramerization domain–containing 15 (KCTD15), glucosamine-6-phosphate deaminase 2 (GNPDA2), SH2B adaptor protein 1 (SH2B1),
mitochondrial carrier 2 (\textit{MTC\textsubscript{H}2}), and neuronal growth regulator 1 (\textit{NEGR1}) \cite{49}. With regard to potential mechanistic roles for the newly identified loci, the GIANT consortium noted that \textit{SH2B1} is involved in leptin signaling and that \textit{SH2B1-null} mice are obese \cite{50}. \textit{MTC\textsubscript{H}2} is thought to function in cellular apoptosis through the encoding of a mitochondrial carrier protein \cite{51}. \textit{NEGR1} is thought to be involved in the outgrowth of neurons \cite{52}.

Notably, a follow-up study by the GIANT consortium of the established SNPs in a pediatric cohort (ALSPAC Study, using BMI information from age 11 years) demonstrated significant and consistent associations between BMI and variants around \textit{TMEM18}, \textit{KCTD15}, and \textit{GNPDA2} \cite{49}.


Follow-up studies to confirm the significance of the BMI-increasing alleles included both adults and children and found a 1.016- to 1.203-fold increase in the overall odds of obesity \cite{53}. Furthermore, for 23 of the 32 SNPs, the specific BMI-increasing allele noted in adults also increased the BMI in children and adolescents. Notably, these 32 BMI loci were found to explain only 1.45% of the interindividual variation in BMI, with each additional risk allele increasing BMI by 0.17 kg/m\textsuperscript{2} \cite{53}. In terms of function, the consortium considered that amid the newly found loci, mutations in \textit{POMC} are a known rare cause of human obesity \cite{54}, and \textit{GIPR} encodes a receptor for gastric inhibitory polypeptide \cite{55}, suggesting a potential mechanistic link between incretin secretion and the obesity phenotype.

Another GWAS meta-analysis was conducted in 2013 to investigate loci associated with BMI in individuals of African ancestry. Thirty-two of the thirty-six variants established in individuals of European ancestry were confirmed in the African sample. Furthermore, robust associations with BMI were noted at two additional loci: \textit{GALNT10} and \textit{MIR148A-NFE2L3}, along with a suggestive association at \textit{KLHL32} \cite{28}. These results indicated that BMI loci are likely shared across populations, but also underscored the need for further research to investigate ancestry-specific differences, including in children.

In 2015, the GIANT consortium conducted a GWAS and meta-analysis of BMI in over one-third of a million individuals from 125 studies derived from different ethnicities. The study found genome-wide significance for 97 BMI-associated loci, of which 56 were novel. These loci have been found to account for about 2.7% of variation in BMI \cite{56}. The GIANT consortium then performed fine mapping, a form of follow-up genotyping, post-GWAS, enabling the identification of candidate genes and causal variants with a greater degree of certainty \cite{57}. Notably, fine mapping identified a single SNP at \textit{FTO} (rs1558902). Further studies are needed to elucidate the specific causal genes and pathways \cite{56}, including in the pediatric population.

**RESULTS OF CANDIDATE GENE STUDIES, GWAS, AND
META-ANALYSES IN CHILDREN AND ADOLESCENTS**

The results of adult GWAS and meta-analyses have paved the way for genetic studies in the pediatric population. Candidate gene studies of 25 SNPs from 13 obesity loci previously reported in adults were performed in just over 6,000 children of European ancestry. Fifteen of the SNPs demonstrated at least nominally significant association to BMI, representing 9 of the 13 tested loci, including: \textit{INSIG2}, \textit{FTO}, \textit{MC4R}, \textit{TMEM18}, \textit{GNPDA2}, \textit{NEGR1}, \textit{BDNF}, \textit{KCTD15}, and 1q25; however, no associations were noted for \textit{MTC\textsubscript{H}2}, \textit{SH2B1}, 12q13, and 3q27 \cite{58}.

In 2010, 15 of 16 known adult obesity–susceptibility loci tested in children and adolescents from the European Youth Heart Study were found to have directionally consistent associations with BMI (including \textit{NEGR1}, \textit{SEC16B}, \textit{LYPLAL1}, \textit{TMEM18}, \textit{ETV5}, \textit{GNPDA2}, \textit{TFAP2B}, \textit{MSRA}, \textit{BDNF},
MTCH2, BCDIN3D, NRXN3, SH2B1, FTO, MC4R, and KCTD15) [59]. To increase statistical power, a meta-analysis was performed of 13 of the variants using previously reported data (n = 13,071 children and adolescents using cohorts from the Children’s Hospital of Philadelphia and ALSPAC). All 13 variants were found to have directionally consistent associations with BMI as previously reported in adults, and 9 were found to be significant, with the greatest effect in the TMEM18 variant. Interestingly, effect sizes for BMI were stronger in children and adolescents than in adults for the variants near TMEM18, SEC16, and KCTD15 [59].

The first GWAS of pediatric and adolescent obesity was conducted in 2010 in a combined analysis of French and German cohorts (n = 1138 extremely obese children and 1120 normal/underweight controls). In addition to previously identified genes (FTO, MC4R, and TMEM18), two new loci were discovered within SDCCAG8 and TNKS/MSRA in association with extreme obesity (BMI 97th to 99th percentile). For each loci, the odds ratios for early obesity were marginal, at approximately 1.1 per additional risk allele [60].

A larger-scale North American–Australian–European GWAS meta-analysis was performed by the Early Growth Genetics (EGG) consortium in 2012, incorporating just over 5500 cases of European ancestry (with BMI ≥95th percentile for age) and in excess of 8000 controls (with BMI <50th percentile for age) [26]. Two loci were identified that demonstrated a genome-wide significant combined p-value: near OLFM4 on 13q14 and within HOXB5 on 17q21. These signals were also tested within the GIANT meta-analysis of adult BMI [53] and also yielded directionally consistent associations.

A GWAS of BMI trajectories from ages 1 to 17 years was conducted in 2015 using repeated measures from the ALSPAC cohort (n = ~8000) and the Western Australian Pregnancy Cohort Study (n = ~1500). Replication analyses were performed for regions achieving genome-wide significance (p < 5 × 10^-8) using the Northern Finland Birth Cohort of 1966 (n = ~4000). Genome-wide significant associations were found for three loci previously identified in GWAS of adult BMI (FTO, MC4R, and ADCY3) and for one known pediatric obesity loci (OLFM4) [61]. Furthermore, a novel association was found between BMI at 8 years of age and SNPs near the FAM120AOS gene, with effects starting around 2 years of age [61]; however, this effect was not present in the replication cohort, possibly due to potential differences in genetic profiles or generational factors between the cohorts. The function of the FAM120AOS gene is currently unknown, but it is near to other genes implicated in severe childhood obesity (NINJ1) [62], along with the development of bone and the differentiation of adipocytes (PHF2) [63].

**KNOWN GENETIC OBESITY SYNDROMES**

Current research in obesity genetics leverages next-generation high-throughput sequencing technology to use whole-exome and whole-genome sequencing approaches, along with epigenetic investigations, to further define the genetic causes of obesity. Before these techniques were available, the identification and sequencing of candidate genes in syndromic forms of obesity provided valuable genetic and molecular information in defining the neuroendocrine contribution to obesity. The most well-characterized molecular signaling pathway related to obesity is the hypothalamic leptin–melanocortin pathway [64]. The syndromic forms of obesity involving mutations in the constituents of this pathway, along with other syndromic forms of obesity, are individually rare. Despite this, they have provided valuable insight into genetic and molecular explanations for obesity.

**MONOGENIC OBESITY SYNDROMES AFFECTING THE HYPOTHALAMIC LEPTIN–MELANOCORTIN PATHWAY**

**Congenital Leptin Deficiency**

Mouse models provided the lead for a monogenic form of obesity in humans. Ingalls and colleagues described a new mutation in what they called the obese (ob) gene in 1950, when they identified mice in their laboratory that quickly grew to four times the weight of normal mice [65]. Subsequently,
positional cloning of the mouse ob gene and its human homolog identified the ob locus as a highly conserved area that encoded for a secreted protein product [66]. Mouse studies further demonstrated that the ob gene product leptin was deficient in ob/ob mice, and that this secreted protein served an endocrine function in controlling fat stores in the body [67]. A later study in two severely obese children from the same consanguineous family provided the first genetic evidence that leptin was also important for energy balance in humans, and strongly suggested leptin deficiency was causative of their severe obesity [68]. Phenotypically, patients with congenital leptin deficiency have a normal birth weight, and then experience rapid weight gain in the first few months of age, causing severe obesity characterized by intense hyperphagia. Other associated abnormalities include endocrine manifestations such as hypothalamic hypothyroidism, abnormal pubertal development due to hypothalamic hypogonadism, and immunological manifestations with decreased T cell numbers and impaired function, leading to increased risk of infection [69]. Treatment with recombinant human leptin through daily subcutaneous injections has been shown to reduce body weight and fat, further confirming leptin’s role in the regulation of body weight and appetite in humans [70]. Daily treatment has also been shown to alleviate the other endocrine and immunological manifestations of congenital leptin deficiency [69].

**Leptin Receptor Deficiency**

Patients with congenital leptin receptor deficiency are phenotypically similar to patients with congenital leptin deficiency. The prevalence of pathogenic leptin receptor gene (LEPR) mutations in one study in a cohort of subjects with severe, early onset obesity not associated with developmental delay was 3% [71]. Mouse models first demonstrated leptin receptor deficiency as a cause of obesity using genetic mapping and genomic analysis in the diabetes (db) mouse to discover LEPR [72]. Ensuing studies in humans showed elevated mean levels of leptin in obese subjects compared with normal-weight controls, suggesting possible insensitivity or resistance to leptin in these obese individuals [73]. Follow-up investigations not only discovered mutations in the human leptin receptor gene, but also showed that a functional leptin receptor is required for sexual maturation and the secretion of growth hormone and thyrotropin, in addition to the regulation of body weight [74].

**Inactive Leptin**

More recently, individuals have been identified who harbor mutations in the leptin gene that lead to the production of a functionally inactive protein product. Thus, these individuals have apparently high levels of circulating leptin, suggestive of resistance, but nevertheless respond to exogenously administered recombinant leptin therapy [75].

**Complete Pro-Opiomelanocortin (POMC) Deficiency**

The POMC gene is expressed in the arcuate nucleus. POMC-expressing neurons are activated by both leptin and insulin and produce peptide hormones such as alpha-melanocyte-stimulating hormone (α-MSH) that induce satiety. Patients with complete POMC mutations are phenotypically characterized by severe early-onset obesity, adrenal insufficiency, red hair pigmentation, and mild hypothyroidism [76,77]. The phenotypic manifestations are due to a lack of multiple POMC-derived ligands, including adrenocorticotropic hormone (ACTH), which promotes cortisol synthesis, and α-MSH, which modulates the production of skin and hair pigments.

**Prohormone Convertase 1/3 Deficiency Due to Mutations in Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1) Gene**

The PCSK1 gene encodes a neuroendocrine-specific prohormone convertase 1/3 (PC1/3). Patients with a deficiency in PC1/3 present with early onset childhood obesity, hyperphagia, small-intestinal dysfunction, diarrhea, pituitary hypofunction including adrenal, gonadotropic, somatotropic, thyrotropic, and vasopressin insufficiency, and disordered glucose homeostasis [78–80]. PC1/3 acts on a range of substrates, including enteric hormones, proinsulin, proglucagon, and POMC, which
explains how PC1/3 deficiency causes severe obesity along with other endocrine and gastrointestinal pathologies related to a deficiency in the active forms of these substrates.

**Human Melanocortin-4 Receptor (MC4R) Deficiency**

After processing by PC1/3, POMC-derived ligands α-MSH and β-MSH act on melanocortin receptors in the paraventricular nucleus to promote satiety. MC4R mutations can present as either dominant or recessive causes of hyperphagic obesity because this receptor plays a key role in the control of eating behaviors in humans [81]. Indeed, MC4R mutations were behind the first dominant form of monogenic obesity to be described, and they are also the most common form of monogenic obesity, occurring in 3%–6% of subjects with severe childhood obesity [82]. Phenotypically, patients with MC4R variants are hyperphagic, obese, and hyperinsulinemic. Studies have demonstrated that mutations in MC4R are inherited in a codominant pattern, with mutations causing a complete loss of function, producing a more severe phenotype [82].

**Other Notable Genetic Mutations in the Hypothalamic Leptin–Melanocortin Pathway**

With rapid advancements in sequencing techniques, several other genes have been discovered that are also associated with syndromic hyperphagic obesity and specifically related to the hypothalamus downstream of MC4R-containing cells in the paraventricular nucleus. A full discussion of these genes is beyond the scope of this text; however, it should be noted that in addition to the genetic syndromes already described, deficiencies in the single-minded homolog 1 (SIM1) gene, brain-derived neurotrophic factor (BDNF), which is encoded by the neurotrophic tyrosine kinase receptor type 2 (NTRK2) gene, and its associated tyrosine kinase receptor (TRKB) all cause severe monogenic hyperphagic obesity [83,84]. In addition, mutations in the SH2B1 gene causing a deficiency in SH2B1 have been identified as a monogenic cause of obesity related to leptin signaling with a phenotype of severe obesity, insulin resistance, and behavioral abnormalities [85].

**Other Known Genetic Obesity Syndromes**

**Albright Hereditary Osteodystrophy (AHO)**

AHO is characterized phenotypically by obesity, multihormone resistance, short stature, brachydactyly, subcutaneous ossifications, and mental deficits such as developmental delay. AHO is caused by dominantly inherited inactivating mutations of a G protein alpha subunit (Gαs) that couples receptors to the stimulation of adenylyl cyclase and the generation of cAMP. Maternal inheritance of this trait is referred to as pseudohypoparathyroidism type 1a (PHP1a) and paternal inheritance is classified as pseudopseudohypoparathyroidism. When the trait is inherited maternally, patients demonstrate all the characteristics of AHO plus obesity and multihormone resistance. Multihormone resistance is not seen with paternal inheritance. Obesity is a more prominent feature of PHP1a and severe obesity is a specific characteristic [86]. Parent-specific inheritance effects suggest that the imprinting of Gαs in central nervous system (CNS) regions and tissues acts as an important mediator of energy metabolism related to obesity [87].

**Bardet–Biedl Syndrome (BBS)**

BBS is a ciliopathic, genetically heterogeneous disorder inherited autosomal recessively and characterized phenotypically by the main features of obesity, retinal dystrophy, renal dysfunction, postaxial polydactyly, hypogonadism, and genitourinary malformations, with several other secondary features. Diagnosis is based on clinical features. Currently, there are 16 known genes for BBS (BBS1–16), which account for ~80% of BBS cases [88]. Unlike the other disorders described in this chapter, BBS can be caused by multiple genetic mutations affecting several proteins; however, the exact pathophysiologic mechanism of obesity in BBS is incompletely understood. Mouse studies have demonstrated a possible explanatory mechanism namely, leptin resistance resulting from abnormal LEPR trafficking and attenuated LEPR signaling in the
hypothalamus [89]. However, this mechanism has not yet been definitively established as the cause of obesity associated with BBS.

In addition to BBS, several other disorders involving ciliary genes highlight the connection between obesity and abnormal ciliary function. Included in this class of disorders is Alström syndrome caused by mutations in the ALMS1 gene, Carpenter syndrome caused by mutations in the RAB23 gene, morbid obesity in humans and mice arising from homozygous mutations in the ciliary protein 19 (CEP19) gene, and a homozygous mutation in the TUB gene associated with retinal dystrophy and obesity [90,91].

Prader–Willi Syndrome (PWS)

PWS is characterized phenotypically by hyperphagic obesity (in early childhood), decreased fetal movement, hypotonia, cognitive deficits, short stature, hypogonadotropic hypogonadism, and small hands and feet. It is the most common obesity syndrome, and PWS is genetically characterized by a deficiency of one or more paternally expressed imprinted transcripts within chromosome 15q11–q13. Most cases of PWS are caused by deletion of a critical segment on the paternally inherited copy of chromosome 15q11.2–q12, while the remaining cases are caused by uniparental disomy, with the loss of the entire paternal chromosome 15 and the presence of two maternal copies [92]. The exact cause of hyperphagic obesity in PWS patients is unknown. Recently, a deletion of the HBII-85 class of small nucleolar RNAs (snoRNAs) was shown to be associated with hyperphagia, obesity, and hypogonadism in a 19-year-old patient in which previous testing for PWS was negative [93]. In this patient array, comparative genomic hybridization was used to identify a microdeletion at chromosome 15q11–q13 that encompassed the noncoding snoRNAs (including HBII-85). The findings were significant, suggesting the role of a particular family of noncoding RNAs in the regulation of energy, growth, and reproduction. Patients with PWS have also been found to have elevated levels of fasting plasma ghrelin, a gastrointestinal peptide involved in regulating appetite, though the importance of this finding to obesity in PWS remains unknown [94].

CONCLUSIONS

There has been significant progress in the development of various genetic technologies, but each strategy is associated with inherent weaknesses. Computational genetic studies of obesity have helped further unravel the heritability of obesity. Strides continue to be made using the results of large GWAS and meta-analyses, both in adults and in children. However, much work remains to be done to reveal the missing heritability of obesity, as only 10% of obesity heritability is currently explained by the results. Transethnic analyses are needed in order to investigate the effects of ancestry on genetic composition. Additionally, more functional studies are needed to translate genetic association into causation.

Furthermore, studies of specific monogenic and polygenic obesity syndromes have enriched our understanding of the complex neuroendocrine mechanisms that govern both energy intake and energy expenditure. As populations expand and unique phenotypes continue to emerge, a concerted effort is needed between clinicians and scientists alike to identify and characterize new syndromes. Taken together, these pediatric genetic studies can inform efforts for obesity prevention and treatment starting in early childhood.

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INTRODUCTION

The prevalence of obesity and associated disorders including type 2 diabetes is increasing globally at an alarming rate. While genetic variations in a number of genes have been linked to obesity (see Chapter 13), to date, single-nucleotide polymorphisms and copy number variations explain only a fraction of the risk of obesity and metabolic disease in humans [1]. However, there is now substantial evidence from both human and animal studies that the quality of the early-life environment before and after birth can affect susceptibility to obesity and associated metabolic disorders in later life [2]. Experimental studies show that the developmental environment can alter later phenotype by changing the epigenetic regulation of genes, and this chapter focuses on the evidence that perinatal influences such as maternal nutrition can alter epigenetic processes, leading to persistent phenotypic changes and an increased risk of childhood obesity.

DEVELOPMENTAL INFLUENCES ON LATER HEALTH AND DISEASE

Some of the first evidence that developmental influences play a substantial role in “programming” later health and disease came from follow-up studies of men whose mothers were exposed to famine in pregnancy during the Second World War; measurements taken in young adulthood showed that maternal famine exposure mid-pregnancy was associated with later obesity [3]. Subsequent longitudinal studies in 25,000 UK men and women related infant size at birth to later coronary heart disease and associated disorders in adulthood. People who were small or disproportionate (thin or short) at birth, or whose infant growth faltered, had high rates of coronary heart disease, raised blood pressure and cholesterol levels, and impaired glucose tolerance [4]. Large effects were particularly seen if restricted fetal and infant growth was followed by increased childhood weight gain. Replication of the initial findings in further studies worldwide has led to wide acceptance that low rates of fetal growth are associated with cardiovascular disease in later life. In the original UK studies, the relations between smaller size at birth and an increased risk of ill health and adult disease extended across the normal range of infant size in a graded manner, but with an increase at the highest birth weights. Maternal obesity is one of the drivers of high birth weight, and subsequent
research has shown that maternal obesity is also associated with premature mortality in the offspring from cardiovascular disease and associated disorders [5].

These observations have led to the hypothesis that obesity, coronary heart disease, type 2 diabetes, and other noncommunicable disorders (NCDs) originate through developmental plastic responses made by the fetus and infant as part of a prediction of the subsequent environment to which it anticipates that it will be exposed. Critical periods in development result in irreversible changes; if the environment in childhood and adult life differs from that predicted during fetal life and infancy, the developmental responses may increase the risk of adult disease. Evolutionary considerations and experimental findings in animals strongly support the existence of major developmental effects on health and disease in adulthood [6]. The preservation of this “programming” phenomenon across species and within the normal range of fetal growth suggests a physiological rather than a pathological basis to the developmental influences on later health. The policy implications of these concepts are now under serious consideration: the 2011 High-Level Meeting of the United Nations General Assembly on the Prevention and Control of NCDs noted that maternal and child health is inextricably linked to NCDs and their risk factors, and stressed the importance of taking a life course approach to addressing NCDs [7].

DEVELOPMENTAL INFLUENCES ON CHILD ADIPOSITY

In humans, famine exposure during pregnancy [3], maternal smoking, obesity [8], and gestational diabetes [9] are all associated with an increased risk of obesity in later life, as reviewed in Chapter 12. In the UK Southampton Women’s Survey (SWS), we have demonstrated the associations of preconception, pregnancy, and early postnatal factors with childhood adiposity, determined using dual x-ray absorptiometry (DXA) at birth, and at ages 4 and 6–7 years. Using the US Institute of Medicine gestational weight gain categorization, excessive gain was associated with greater offspring fat mass at age 6–7 years [10]. Additionally, low maternal vitamin D status in pregnancy was associated with greater postnatal adiposity gain [11]. Early-life risk factors for greater adiposity in childhood, identified in the SWS, often coexisted, such that excess gestational weight gain and a shorter duration of breast-feeding were more common in obese mothers, and smoking during pregnancy was related to lower vitamin D status. Examining the combined impact of five early influences (maternal obesity before pregnancy, excessive gestational weight gain, smoking during pregnancy, low maternal vitamin D status, and a short duration of breast-feeding), we found strong positive associations between the number of early-life risk factors and child fat mass at both 4 and 6–7 years of age [8]. In parallel with the effects on fat mass, an increasing number of early-life risk factors was also associated with strong graded increases in the risk of being overweight or obese in childhood, according to the International Obesity Task Force definitions; when compared with children who had no perinatal risk factors, the relative risks of being overweight or obese among children who had four or five risk factors were 3.99 at four years and 4.65 at six–seven years. These findings are similar to those of an earlier US study [12], which showed that preschool children whose mothers had excess gestational weight gain and smoked during pregnancy, who were breast-fed for less than 12 months, and who slept for less than 12 hours per day in infancy had a predicted obesity prevalence of 29%, compared with 6% of children who had none of these risk factors. Importantly, these marked differences were found to persist (28% compared with 4%) when the children were aged 7–10 years [13].

DEVELOPMENTAL ADAPTATIONS AND CHILDHOOD ADIPOSITY

Our SWS studies have provided evidence that prenatal developmental adaptations play important roles in the human propensity to deposit fat [14]. Among primates, human neonates have not only the largest brains but also the highest proportion of body fat. If placental nutrient supply is limited, the fetus faces a dilemma: should resources be allocated to brain growth or to fat deposition for use
Childhood Obesity

as a potential postnatal energy reserve? We hypothesized that resolving this dilemma operates at the
level of umbilical blood distribution entering the fetal liver. In uncomplicated third-trimester SWS
pregnancies, we used ultrasound to measure blood flow perfusing the fetal liver or bypassing it via
the ductus venosus to supply the brain and heart [14]. Across the range of fetal size and independent
of the mother’s adiposity and parity, greater liver blood flow was associated with greater offspring
fat mass measured by DXA, both in the infant at birth and at age 4 years. In contrast, smaller pla-
centas less able to meet fetal demand for essential nutrients were associated with a brain-sparing
flow pattern. This led us to propose that humans have evolved a developmental strategy to prioritize
nutrient allocation for prenatal fat deposition when the supply of conditionally essential nutrients
requiring hepatic interconversion is limited, switching resource allocation to favor the brain if the
supply of essential nutrients is limited. Facilitated placental transfer processes for glucose and other
nutrients evolved in environments less affluent than those now prevalent in developed populations,
and we proposed that in circumstances of maternal adiposity and nutrient excess these processes
now also lead to prenatal fat deposition [14].

This proposal suggests that there may be two groups of broad developmental paths to childhood
obesity. A “low” path is associated with maternal famine exposure or macronutrient deficiency,
micronutrient deficiency (e.g., vitamin D insufficiency), smoking (itself associated with both toxic-
cant exposure and low micronutrient status), and placental pathology; the infants are thin at birth
but gain adiposity progressively during the infancy and preschool periods, such that they become of
above-average adiposity by childhood. Conversely, a “high” path is associated with maternal obe-
sity, excessive pregnancy weight gain, and gestational diabetes; the infants have average adiposity
at birth and remain adipose during the infancy, preschool, and childhood periods.

**MOLECULAR MECHANISMS LINKING DEVELOPMENTAL
INFLUENCES WITH LATER OBESITY**

It has been argued that the associations between fetal or infant growth and later adult disease
could represent the multiple (pleiotropic) effects of genes transmitted from mother to child.
The Early Growth Genetics consortium, however, showed only a small genotypic contribution
to birth weight [15]. Epigenetic processes, including DNA methylation, modification of the
histone proteins that package DNA, and noncoding RNAs, play a central role in regulating gene
expression. DNA methylation typically involves the transfer of a methyl group to a cytosine
immediately 5’ to a guanine (so-called CpG dinucleotides, where p denotes the intervening
phosphate group), creating 5-methylcytosine (5mC) [16]; non-CpG methylation is, however, also
prevalent in embryonic stem cells [17]. Across the genome, CpG frequency is biased toward
promoter regions, where they may occur in clusters termed **CpG islands**, which are mostly
unmethylated. Lower-density CpG promoter sites tend to be hypermethylated. Methylation at
CpG islands is typically associated with genes that require long-term repression; such genes
include imprinted genes that are preferentially expressed from one parental chromosome, those
located on the inactive X chromosome in female mammals, and those only requiring expression
in germ and not somatic cells [18].

The traditional view has been that DNA methylation is linked to gene silencing. However, the
effect of methylation on gene expression is potentially dependent on factors such as CpG density,
gene product function, and site of methylation; for example, gene body methylation is not associated
with gene repression [19,20]. The different epigenetic processes do not act in isolation but interact in
a coordinated fashion; for example, inactive CpG island promoters are generally not methylated but
are instead marked by lysine trimethylation on histone H3. Whether DNA methylation is a cause or
a consequence of repressed gene expression is still under debate; some of the proposed mechanisms
for methylation-associated gene silencing include disrupted transcription factor binding preventing
RNA polymerase activity, the recruitment of methyl-binding proteins that in turn attract other
repressor complexes, and the transcription of noncoding RNAs.
DNA methylation is a stable epigenetic mark that is transmitted through mitotic DNA replication and cell division, leading to the suggestion that epigenetic processes could be an important mechanism by which the environment alters long-term disease risk. Consistent with this suggestion, the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) study has recently found that maternally mediated *in utero* environmental influences and gene–environment interactions are a more important source of variation in neonatal genome-wide methylation patterns than fixed genetic variation, as reflected by DNA sequence polymorphisms [21].

Evidence from experimental studies in animals indicates that early life is a critical period when appetite and the regulation of energy balance are programmed, with lifelong consequences for the risk of excess adiposity. Variations in maternal diet have, for example, been linked to alterations in metabolism and body composition in the offspring [22]. Experimental studies show that the developmental environment induces an altered phenotype through epigenetic mechanisms, including changes in DNA methylation, histone modification, and noncoding RNAs [6]. The father’s diet can also have an effect on the epigenome and phenotype of the offspring. Male mice fed a low-protein diet prior to mating showed widespread modest changes in the methylation (10%–20%) of the DNA of their offspring compared with control offspring, including a substantial increase in methylation at an intergenic CpG island 50 kilobases upstream of the PPARα gene [23]. Similarly, in rats, a paternal chronic high-fat diet led to pancreatic β-cell dysfunction in the female offspring [24]. Experimental studies of paternal environmentally induced intergenerational effects are an area of increasing research interest; for example, a recent study in marine tubeworms has shown that transgenerational adverse paternal effects can be stronger than maternal effects [25].

A classic example of maternal nutrition influencing DNA methylation in mammals is in the agouti mouse model, where coat color is influenced by the methylation status of the 5’ end of the *Agouti* gene. Differences in the mother’s intake of dietary methyl donors and cofactors (including folic acid, vitamin B12, betaine, and choline) were shown to alter DNA methylation of the *Agouti* gene and induce differences in the coat color and adiposity of the offspring [26]. DNA methylation changes induced during development are highly gene and CpG specific [27], and methylation of individual CpG dinucleotides in gene promoter and intergenic regions alters gene expression. Such “tuning” has potential adaptive value and fitness advantage because it adjusts the phenotype to current circumstances and/or matches responses to the environment predicted to be experienced later [6]. When the phenotype is mismatched to the later environment—for example, from inaccurate nutritional cues from the mother or placenta, or from rapid environmental change through improved socioeconomic conditions—the risk of NCDs increases. Evidence is accruing that endocrine or nutritional interventions during early postnatal life can reverse epigenetic and phenotypic changes induced, for example, by an unbalanced maternal diet during pregnancy [28]. Elucidation of epigenetic processes may permit perinatal identification of individuals at risk of later NCDs and enable early intervention strategies to reduce such risk.

**EPIGENETIC CHANGES AS A CONSEQUENCE OR CAUSE OF OBESITY**

While DNA methylation states at particular loci have been associated with a range of disorders, it is generally unclear whether the methylation changes occur before disease symptoms or afterward as a consequence of the disease. A large epigenome-wide association study with replication in two independent cohorts reported that methylation levels at three CpGs in the first intron of the hypoxia inducible factor 3 alpha (*HIF3A*) locus were positively associated with adult body mass index in whole blood and adipose tissue from Caucasian subjects [29]. The finding has since been replicated by an independent group of researchers [30]. The authors of the original observation considered three possibilities that could explain the association between *HIF3A* methylation and adiposity in adults: (1) that a confounding factor (such as environment) independently affects both *HIF3A* methylation and adiposity, (2) that increased *HIF3A* methylation causes increased adiposity, and (3) that increased adiposity causes increased *HIF3A* methylation. The *HIF3A* genotype
was associated with HIF3A methylation but not adult body mass index, and using a Mendelian randomization approach [31], Dick et al. suggested that adiposity most likely results in HIF3A hypermethylation [29]. However, in this context, Mendelian randomization assumes the genotype can affect the phenotype only through DNA methylation and not through other biological pathways, an assumption of unknown applicability for the HIF3A genotype.

Given the evidence that developmental pathways to obesity begin before birth, we used a multi-ethnic Asian mother–offspring cohort (the GUSTO cohort) to examine if HIF3A gene methylation levels in umbilical cord tissue are associated with birth size and adiposity [32]. Taking account of sex, ethnicity, cellular composition of umbilical cords, and interactions between ethnicity and cellular composition, the analyses showed that the link between HIF3A DNA methylation with weight and adiposity can be detected at birth. The association was limited to measures of adiposity (i.e., weight, BMI, and skinfolds) and not other determinants of birth size or putative proxies for gestational quality such as gestational age and birth length. Although pertaining to the same three CpGs within the HIF3A gene that were previously reported, these findings were derived from a different tissue (umbilical cord vs. blood and adipose), in a population-based cohort (rather than a study population of metabolic disorders and controls), and at a different stage in the life course (neonates vs. adults). The findings point away from established obesity as a cause of HIF3A hypermethylation [32], and suggest that prenatal factors may influence HIF3A methylation as well as adiposity; however, despite the extensive data collected in the GUSTO study, no responsible prenatal factor could be definitively identified. Nonetheless, as the association between HIF3A methylation and adiposity is detectable so early in life, HIF3A may be a potential biomarker of metabolic trajectory.

HUMAN STUDIES OF EPIGENETIC PROCESSES AND CHILDHOOD ADIPOSY

While epigenetic processes operating in early development have been implicated in growth and later body composition, until recently there has been little direct evidence for the proposition in humans. Studies using candidate gene approaches have shown associations between DNA methylation in cord blood leucocytes (e.g., in the IGF2-imprinting control region in 24 infants) and childhood adiposity [33]. Using Sequenom MassARRAY, we measured the methylation status of 68 CpGs 5’ from five candidate nonimprinted genes in umbilical cord tissue DNA from healthy neonates [34]. Methylation varied greatly at particular CpG sites. For 31 CpGs with median methylation ≥5% and a 5th to 95th percentile range ≥10%, we related methylation status to the maternal pregnancy diet and to the child’s body composition at age 9 years; greater methylation of two CpGs within the retinoid X receptor alpha (RXRA) promoter measured in the umbilical cord was robustly associated with greater adiposity [34]. The associations reflected clinically important shifts in body composition; from the lowest to the highest quarters of the distribution of RXRA methylation, mean fat mass rose from 4.8 to 6.6 kg (17.3%–21.3% body fat). Regression analyses including sex and neonatal epigenetic marks explained >25% of the variance in childhood adiposity. The findings were replicated in a second independent cohort. In these human studies, associations were also observed between levels of RXRA methylation and mothers’ carbohydrate intake [34], supportive of the concept that nutritional conditions in early pregnancy can affect a child’s adiposity in later life.

As DNA methylation and gene transcription are often tissue specific, it is not possible to extrapolate how the level of methylation in the umbilical cord may affect expression in adipose or other tissues and/or whether such epigenetic alterations are causally involved in the development of fat mass. However, for a number of imprinted and nonimprinted genes, there is evidence that methylation levels are similar across a range of conceptual tissues, including buccal, brain, eye, intestine, liver, lung, muscle, and umbilical cord blood, despite the fact that these cell types arise from different germ layers [35,36]. It may be that an early environmental challenge could leave an imprint on the epigenome that is detectable across tissue types.

Another area of uncertainty arises from data showing that some DNA methylation marks can be dynamically regulated in response to postnatal environmental stimuli, raising questions about the
stability of developmentally induced epigenetic marks over time. One study that examined DNA methylation stability over time in children found that the methylation levels of the genes MAOA, DRD4, and SLC6A4 was highly dynamic between the ages of 5 and 10 years [37]. An example of dynamic regulation relates to the induction by acute physical activity of hypomethylation in the peroxisome proliferator–activated receptor gamma coactivator 1 alpha (PGC1α) promoter in muscle tissue [38]. In contrast, in DNA from peripheral blood cells, Clarke-Harris et al. reported year-on-year stability of the methylation levels of a different group of seven CpG sites within the PGC1α promoter in children 5–14 years of age [39]; this suggests that for these CpG sites methylation levels are set up in early life and their stability is maintained. Moreover, seven of the PGC1α promoter CpG sites analyzed at age 5–7 years were predictive of adiposity in the children at ages 9–14 [39], providing further evidence that developmentally induced methylation marks may be significant contributors to later obesity risk. The differences in the stability of the PGC1α methylation between the two studies may reflect differences in the location of the CpGs or tissue-specific differences between blood and muscle (PGC1α has a muscle-specific transcript). Whether the changes in methylation in response to exercise occur on top of a developmentally induced methylation change is also not known.

EPIGENETICS IN SEVERE CHILDHOOD OBESITY

Much of the research to date has examined the role of epigenetic processes in potentially mediating variations in child adiposity across the range in general population samples of children. To examine whether severe childhood obesity is associated with differential DNA methylation, we studied DNA methylation profiles in whole blood from 78 obese children (mean BMI z-score: 2.6) and 71 age- and sex-matched controls (mean BMI z-score: 0.1) [40]. Using the Infinium HumanMethylation450 BeadChip array, comparison of the methylation profiles between obese and control subjects revealed 129 differentially methylated CpG (DMCpG) loci associated with 80 unique genes that had a greater than 10% difference in methylation. Undertaking pathway analysis of these DMCpG loci, the top pathways enriched included developmental processes, immune system regulation, regulation of cell signaling, and small GTPase-mediated signal transduction. The associations between the methylation of selected DMCpGs within the FYN, PIWIL4, and TAOK3 genes and childhood obesity were then validated using sodium bisulfite pyrosequencing in individual subjects. Three CpG loci within FYN were hypermethylated in obese individuals, while obesity was associated with lower methylation of CpG loci within PIWIL4 and TAOK3. Using logistic regression models, a 1% increase in methylation in TAOK3 multiplicatively decreased the odds of being obese by 0.91, and a 1% increase in FYN methylation multiplicatively increased the odds of being obese by 1.03 [40]. The findings provide further evidence that childhood obesity is associated with specific DNA methylation changes.

CONCLUSION

Research has demonstrated that during prenatal development, responses to a range of environmental stimuli are likely to “program” the risk of obesity and associated metabolic disorders. Subsequent environmental exposures during infancy, childhood, and adult life may modify or condition this later risk of obesity. This life course approach is central to the concept of the “developmental origins of health and disease.” Development, growth, and metabolism are influenced by a combination of genetic, epigenetic, and environmental factors. Experimental studies indicate that environmental factors in early life, including nutrition, stress, endocrine disruption, and pollution, induce altered body composition in ways that are influenced or mediated by epigenetic mechanisms. These mechanisms include DNA methylation, covalent modifications of histones, and noncoding RNAs, and increasing evidence implicates similar mechanisms in the developmental programming of childhood obesity. This evidence suggests that efforts to improve
the nutrition of young women before and during pregnancy will be central to future strategies to achieve the primary prevention of childhood obesity [41].

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15 Parent- and Family-Level Factors Associated with Childhood Obesity

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INTRODUCTION

Many factors have been associated with the development of childhood obesity. The socioecological model [1] suggests that the closest level of influence to the child besides individual-level factors such as biology, epigenetics, and genetics, is the microsystem that involves interpersonal relationships with parents and family. Parents are responsible for the home environment and control what foods are available, provide opportunities for physical activity, model important eating and activity behaviors, set limits and behavioral expectations, create a socioemotional environment that shapes the child’s socialization and growth, and influence the overall family functioning in the home. As such, parents are critical to the overall growth and development of the child, as well as to the development of obesity and obesity-related behaviors. Their participation is also essential to the success of the child’s efforts in weight control interventions [2,3]. The goal of this chapter is to highlight the parent- and family-level factors that influence the development of childhood obesity and obesity-related behaviors through a number of different mechanisms.

There are a few caveats that are necessary to consider while evaluating the influence of parent-and family-level factors on the development of childhood obesity. First, it is important to recognize that parents and children can influence each other’s behaviors, reflecting a bidirectional relationship [4]. As shown in Figure 15.1, specific parenting practices and other broader parent- and family-level factors can influence the child, but may also be shaped by the child’s own behaviors and weight status. However, much of the work in this area is cross-sectional and does not take into account the bidirectional nature of the parent–child relationship. Additionally, the role and influence of parents
and family need to be considered in the context of child development, where many of the influences may be stronger when children are younger and more dependent on their parents and weaken as the child transitions into adolescence and adulthood. As a result, much of the work reviewed in this chapter will focus on preschool and grade school children, on whom the influence of parents may be more pronounced.

Using Figure 15.1 as a framework for the relationship between parent and child behaviors, we will first address specific parenting practices and behaviors that can affect child eating, activity, and sedentary behaviors and ultimately weight status. We will then review the effect of general parenting style, a broader level of parenting that can set the tone for child development and socialization, on child outcomes. In particular, we will examine how general parenting styles can influence or moderate the effect of specific parenting practices on child eating and activity behaviors. Finally, we will address family functioning and how the overall functioning of the family as a unit can influence the development of childhood obesity and obesity-related behaviors.

**SPECIFIC PARENTING PRACTICES AND BEHAVIORS**

Parenting practices are considered to change based on the context, or in this case, the child’s and parent’s traits and behaviors. Specific parenting practices are the most proximal parent-level factor to the outcome of interest (childhood obesity) [5] and can directly address the child’s eating behaviors, physical activity behaviors, and sedentary behaviors that ultimately affect weight status. Some of the more commonly studied parenting practices and behaviors are described in the following sections.

**ENCOURAGING CHILDREN TO EAT PAST SATIETY**

One of the most commonly studied feeding practices includes encouraging children to eat beyond satiety (i.e., to “clean their plate”) [6]. This practice can have a direct effect on the child’s energy balance. Parents often encourage their child to clean his or her plate because they are concerned about the quality and quantity of the child’s intake or because they were taught to clean their own plate. This is particularly salient during the toddler and preschool years, when children’s growth trajectories naturally slow down and dietary consumption decreases proportionally. However, encouraging children to “clean their plate” may lead to overeating and a loss of attention to internal satiety and hunger cues that help a child to naturally self-regulate his or her caloric intake [7]. Similarly, directly prompting, encouraging, or reminding a child to eat (e.g., “take another bite,” “finish your peas”) has been associated with higher child weight, faster rates of eating, and longer durations of eating [8–10]. Overweight mothers in particular may prompt their child to eat more often [10], further increasing their child’s risk of obesity. As a result, it may be beneficial to allow some children,
particularly young children who are developing eating habits and are not yet overweight, to respond to internal cues of hunger and satiety and self-regulate their caloric intake, rather than prompt them to clean their plate [11].

**Using Food as a Reward and for Emotion Regulation**

It is natural for family members to use food as a reward, as it is a primary reinforcer and can almost always motivate children. Some parents will use this feeding behavior to encourage children to finish their plate or eat an undesired food, such as vegetables. Other parents use food as a reward for participating in an uncomfortable event (e.g., visiting the dentist) or for celebrations (e.g., getting good grades or winning a competition). However, this behavior can have some undesired consequences, such as lower satiety responsiveness and greater caloric intake [6]. Using food as a reward can also increase the value of the reward food (typically dessert) and decrease the value of the required food (often vegetables) [12,13], which ultimately undermines the intention of the parent to get the child to eat the required food. By offering food when the child is sad, bored, or stressed, particularly high-energy density sweet or salty foods, parents may also alter the child’s ability to respond to internal cues of satiety and be more responsive to emotional cues that trigger a person to eat [14].

**Restricting Access and Overtly Controlling a Child’s Intake**

Restricting a child from a desired high–energy density food (e.g., potato chips) may increase the child’s desire for that food. However, restricting access to these foods may also prevent weight gain and promote disordered eating behaviors or cognitions. The literature regarding controlling feeding behaviors and restriction reflects this quandary. A number of studies suggest that restricting a child’s intake is associated with greater caloric intake when the child has free access to the restricted food and weight gain [15–17]. However, not all studies show a relationship between restriction and weight gain [18,19]. Recent studies suggest that restriction may be a response to a child’s weight status or disinhibited eating behaviors [20,21]. Because of the concern that parents have regarding their child’s weight, they could be using restriction to limit the child’s intake of excess calories. Restriction may also be beneficial in limiting a child’s intake if he or she is an impulsive eater or is highly stimulated by external food cues. Therefore, the use of restriction may have some benefits depending on the individual child and his or her responsivity to food in the environment.

**Exposure and Availability of Foods**

Studies have shown that frequent exposure to an unfamiliar food can result in increased consumption, liking, and preference for that food [22,23]. Exposing children to healthy foods over time and making them available in the home has been associated with greater consumption of these foods [24]. Furthermore, increasing the accessibility of these foods (e.g., by precutting fruits and vegetables, putting them on a lower shelf in the refrigerator, or putting them on the counter top in plain sight) has also been shown to increase their consumption [25]. On the other hand, covertly limiting the availability of unhealthy snack foods by not buying them and bringing them into the house will decrease the likelihood that children will eat these foods; if these foods are not available in the home, children cannot eat them and must choose another healthier option. Several studies have demonstrated that decreased availability of these foods in the home leads to decreased snack intake [26,27], and it appears that in teenagers, healthy food availability is more strongly correlated with fruit and vegetable intake than restriction of unhealthy foods [28].

**Portion Size**

Research shows that children as young as 2 years old and adults will often respond to external food cues and consume more calories when given larger portion sizes [29–31]. Interestingly, in one study
of preschool children, those who were allowed to serve themselves and determine their own portion size ate 24% less of the entrée than when someone else provided them with a large portion on their plate [30]. While this technique may be effective in young children who are not overweight and are not stimulated by food, it may not be effective in older children who are overweight or highly responsive to food stimuli. These factors have yet to be explored. Nevertheless, the size of a portion can influence a child’s caloric intake, and if left unchecked, can lead to excess weight gain.

**Modeling**

According to social cognitive theory [32], individuals learn behaviors by observing the behaviors of others. Initial research shows that modeling healthy eating and activity behaviors can result in healthier habits among children [33]. Children who have parents who eat fruits and vegetables [34,35] and have low dietary fat intake [36] are more likely to report similar behaviors themselves. Several researchers have also demonstrated that preschool children will more quickly accept and consume a novel food when an adult is eating something similar [37] or a teacher makes an enthusiastic comment about the targeted food [38]. Unfortunately, parents or adults who model negative behaviors can have the same effect on a child, as is seen with the development of emotional eating, snacking, and body dissatisfaction [33]. The power of modeling is demonstrated in weight control programs where parents are the primary agent of change [39,40]. Research also suggests that parent weight change is one of the best predictors of child weight change in a behavioral weight loss program [3].

Parent modeling of physical activity behavior has also been thought to influence child and adolescent physical activity behavior [41,42]. However, several reviews suggest that parent physical activity in and of itself may not be significantly related to child and adolescent physical activity [43–45], and a more recent meta-analysis suggests that there might only be a small effect of parent modeling of physical activity on child physical activity [46]. Instead, the type of support that parents provide may be a stronger moderator of child physical activity (see the following section, “Access to and Support for Physical Activity Opportunities”) [46].

With regard to sedentary activity, research shows that children watch more television when their parents watch television frequently [47–49] and when there are few rules regarding the amount of time that they are allowed to watch television [48–50]. Setting up guidelines and boundaries as to when and how much television can be viewed may help to decrease this activity and the associated caloric intake that happens when watching television [51]. Given the potential influence of parent modeling, parents who actively engage their children in other healthy activities may be able to shape these behaviors at an early age and work toward developing healthy habits.

**Access to and Support for Physical Activity Opportunities**

Parents who enroll their child in sports and increase the availability of physically active opportunities often have children who are more physically active [52]. Parents can also influence their child’s participation in physical activity by providing the appropriate support for this behavior. Parental support comes in a variety of forms, including informational (i.e., providing physical activity advice), emotional (i.e., letting the child know that the parent cares about his or her physical activity by watching the child’s games), appraisal (i.e., direct prompts or verbal encouragement), and instrumental support (i.e., providing transportation to recreational facilities). Several studies have demonstrated that parental instrumental support is associated with higher physical activity among girls and boys [53]. Other types of parental support, particularly emotional and positive appraisal or encouragement, have also been associated with increased child physical activity behavior [43,54]. This type of support may lead to increased child self-efficacy and confidence to engage in physical activity, which has also been a positive correlate to physical activity in children and adolescents [45]. Thus, increasing access to and support for physical activity behaviors may be useful in tipping the energy balance toward a lower, healthier weight status.
TELEVISION ACCESS

Research consistently shows that children watch more television when they have televisions in their bedrooms [47,50]. This is associated with increased calorie consumption [55,56] and has been attributed to mindless eating while the child’s attention is focused on the screen rather than what he or she is putting in his or her mouth [57]. In one of the only longitudinal studies evaluating correlates of television viewing, the number of meals eaten while watching television was significantly associated with the amount of time children at age 6 and 12 years were watching television [58]. The amount of time spent watching television was also associated with overweight status at both 6 and 12 years of age. Efforts to reduce screen time have demonstrated a decrease in caloric intake [51] and may be an effective way to decrease weight [59].

GENERAL PARENTING STYLE

General parenting style is often thought of as a higher-order construct [60] that embodies the overall socialization goals parents have for their child and provides the social and emotional context for child rearing [61]. As such, it provides the backdrop or emotional context in which children interpret the specific parenting practices that parents use. Parenting style, then, represents how a parent delivers an intervention, while specific parenting practices, such as restriction, describe what a parent does. There are four classic parenting styles that are each defined by varying levels of emotional involvement, warmth, and support as well as demands for self-control, discipline, and maturity [62,63]. The authoritative parenting style is characterized by high levels of warmth, support, and involvement, as well as discipline and demands for self-control, and is often considered the optimal parenting style. Several cross-sectional studies have found an association between the authoritative parenting style and lower body mass index (BMI) in children and adolescents [64,65]. On the other hand, more authoritarian parenting styles that show little warmth and affection but use high levels of behavioral control defined by psychological control (characterized by the use of coercion, guilt induction, shame, love withdrawal, and possessiveness) have been associated with increased BMI z-scores [66]. Our own longitudinal study found that children of authoritarian parents (high demandingness, low responsiveness) had almost a fivefold increase in odds of being overweight [67]. At this time, an intervention that targeted general parenting behaviors for families with children with behavioral problems found a decreased rate of obesity three to five years later, despite not having targeted any weight-related eating and activity behaviors during the intervention [68].

The authoritative parenting style has also been associated with greater consumption of fruits and vegetables [69–71], more frequent physical activity behavior in children [69,72], and greater weight loss during treatment [73]. However, general parenting style is more often thought to moderate the effect of specific parenting practices, such as feeding practices, on child eating and activity behaviors or weight [74,75]. In one study, van der Horst and colleagues found that parents who limited their child’s consumption of sugar-sweetened beverages in the context of an authoritative parenting style had children who drank fewer calories than children whose parents used an authoritarian parenting style [74]. Therefore, a higher-order general parenting style may be important to consider when examining the impact of specific parenting practices and behaviors on child outcomes. Our work suggests that it is the emotional responsiveness parents display that is particularly associated with decreased child weight status [67]. Parental displays of warmth and sensitivity may work via their effects on increasing the child’s ability to regulate negative emotions, work cooperatively with the parents, and have greater psychosocial functioning [76]. This emotional connection and responsiveness may create a supportive environment in which the child can develop the confidence to explore behaviors and test boundaries while becoming an independent being. Consequently, children may be able to develop greater self-regulation across several domains, including eating and physical activity. Nevertheless, creating an environment with some behavioral expectations and boundaries may also be needed to guide children in the development of healthy eating and activity behaviors.
As such, specific parenting practices delivered within the context of an authoritative parenting style may result in optimal outcomes for the child.

In contrast to research on parenting style and eating, cross-sectional evidence regarding general parenting and physical activity report inconsistent results. Some studies suggest that more permissive approaches are associated with greater child engagement in moderate-to-vigorous physical activity [53], while other studies suggest that an authoritative parenting style is associated with increased physical activity in the child [77]. Interestingly, findings from longitudinal studies indicate that authoritative parenting is a positive predictor of physical activity [72,78], but the same relationship was not significant in others [79]. Because of the relatively few studies conducted in this area and the variability in outcomes, additional research in this area using consistent definitions of parenting style and longitudinal designs need to be conducted.

Studies regarding sedentary behavior and parenting are much fewer. The majority of the studies focus on television viewing. In two longitudinal studies, it appears that authoritative parenting is inversely related to sedentary behavior [72,78]. However, as with physical activity outcomes, further research needs to be conducted in this area.

FAMILY FUNCTIONING

In addition to parenting style, family functioning is another higher-order construct that can influence child development and childhood obesity risk. Family functioning refers to the structural/organizational properties and the interpersonal interactions of the family group, such as how they problem solve, communicate, adopt roles, adapt to each other, display warmth and closeness, and demonstrate behavior control [80]. Overall, poor family communication [81] and lower family functioning [82,83] were associated with higher BMI in youth. In a few studies using videotape assessments of family meals, positive qualities during mealtime (e.g., group enjoyment, higher relationship quality and interpersonal involvement, and warmth/nurture) were associated with reduced prevalence of child overweight/obesity, while negative qualities (e.g., hostility, being indulgent and permissive, and inconsistent discipline) were associated with a higher prevalence of child overweight/obesity [18,84]. Interestingly, it appears that mothers of overweight/obese children may use more maladaptive behavioral control strategies, particularly a permissive feeding style, which may contribute to their child’s obesity risk.

With regard to eating behaviors, higher family functioning is associated with greater fruit and vegetable intake, family meals, and breakfast consumption [85–87]. Positive communication about the food and reinforcement for eating appropriately was associated with these more positive family functions [84]. However, in families where there is a discordant-weight sibling pair, mothers showed more interpersonal involvement with the lower-weight child, more maladaptive feeding control behaviors (authoritarian) with younger children with low restraint during eating and overweight, and permissive feeding control behaviors with older children with low restraint and overweight [88]. Thus, parents seem to respond to the characteristics of the child, and overall family functioning may be altered as a result.

With regard to activity levels in children, most studies show a positive association between higher family functioning and physical activity [87,89,90]. Recent research also suggests that the gender of the child and parent may be a moderator of this relationship [87]. Overall, the creation of more positive interactions and family functioning in the home setting appears to support positive health behaviors in children. As seen with some of the research around eating behaviors, the degree to which child characteristics or traits contribute to how the family functions remains to be seen.

SUMMARY

In summary, there are a number of parent- and family-level factors that play a role in the development or maintenance of childhood obesity. Specific parenting practices such as prompting the child to eat or turn off the television can directly influence the eating and activity behaviors of
children. Other behaviors such as providing a healthy food environment, access to physical activity opportunities, and modeling of healthy behaviors also influence the child’s behaviors. Furthermore, higher-order constructs of parenting style and family functioning may act to moderate the specific parenting practices and behavioral strategies that parents use and make them more palatable for children, ultimately reducing obesity risk. From this body of work, we can see that parents can potentially have great influence on their child’s development and health. However, we must realize that parents often respond to child behaviors, temperament, and body size [20,21,91,92], and while certain parent behaviors (e.g., restricting food) may have a positive outcome for some children, they may result in greater food intake in others (e.g., those with low inhibitory control and high food responsivity) [93,94]. Additional factors such as parent and child gender, parent weight status, and child age may also moderate the relationship between parenting behaviors and child outcomes [95–97]. For example, fathers may have greater influence over child physical activity behaviors than dietary behaviors [95], but mothers appear to provide more logistic support for physical activity than fathers [52,98]. With regard to eating behaviors, there are greater correlations between same-sex parents and children [99,100], but paternal control behaviors may have a stronger effect on the child’s BMI status [64,65]. Furthermore, overweight parents may have greater concern for their child’s weight status and utilize more monitoring and controlling parenting practices to help decrease the risk of obesity in their child [101]. Overall, parents can greatly influence their child’s health and development. However, this relationship is not unidirectional, and interacts with many child, family, and environmental factors. Further research in this complex interaction is needed to develop recommendations for parents and providers as they work to decrease the risk of obesity for their child.

Specific parenting practices and behaviors can directly affect child eating and physical activity behaviors and ultimately child weight status. These practices are the most proximal parent-level factor to the outcome of interest, but are often implemented within the context of general parenting style and family functioning. These broader constructs can moderate the effect of the specific parenting practices and are therefore important to consider when examining factors affecting childhood obesity risk.

REFERENCES


INTRODUCTION

High rates of childhood obesity have been attributed to a complex system of individual, social, and environmental factors, as reviewed in other chapters. The vital role of social networks in the propagation of obesity in children and adults has been highlighted in recent studies, and is emerging as an important component of this social-ecological system to understand and intervene on. Some of this research suggests that obesity spreads within social networks as a result of interpersonal “contagion” [1–3]. However, the social contagion hypothesis is just one potential mechanism driving associations between social networks and childhood obesity. Advances in social network analysis (SNA) and applied social network research are helping to refine our understanding of the broader set of social factors and processes at play in the development and maintenance of childhood obesity. This chapter briefly introduces the key concepts in SNA, before summarizing research findings that identify mechanisms linking social networks to childhood obesity, and then discussing directions for future research and implications for childhood obesity interventions. Network interventions, which typically alter or leverage social network structures (e.g., by targeting influential individuals or naturally occurring social groups), show great promise to more effectively promote and sustain diverse health behaviors [4–6]. Interventions that leverage social networks to prevent and treat childhood obesity are in their infancy, but are likely to be bolstered by considerable interest in this approach [7–9].

SOCIAL NETWORK THEORY AND METHODS

SNA is a set of theories and methodological tools that seek to understand social systems by studying the patterns of relationships among social entities (i.e., people or organizations). These relationships (referred to as ties) between social entities (referred to as actors) can represent any affiliation of interest: close friendship, acquaintance, marriage, group comembership, monetary transactions,
online or offline communication, and so on. Social network research often focuses on understanding (1) the processes that predict network ties and generate complex social network structures, and (2) the individual and group processes/outcomes that are influenced by social networks. Social network methods provide tools for the measurement and analysis of social relations, including techniques to describe specific network structures (i.e., particular patterns or configurations of ties) that enable a more formal understanding of the key features of our social environments [10,11]. Social network theorists emphasize the role of social connections as a source of influence, support, and resources that influence actors, as well as actors’ positions in the global network, whereby individuals’ attitudes, perceptions, and behaviors are influenced by where they are situated in the larger social system [12]. For example, SNA can be used to understand whether a social network is densely or sparsely connected, and to identify actors that occupy central, potentially influential positions in a network. Additionally, social networks can be evaluated from two perspectives: personal social network measures capture information on the social actors and relationships that surround a focal individual, while complete social network measures evaluate information on all actors and relationships within a bounded social group, such as a school, a family, or a community [13].

In the context of obesity research, SNA makes it possible to assess how patterns of relationships are related to, and potentially impact, actors’ health behaviors and outcomes. Akin to traditional statistical approaches, the analysis of social network data can be descriptive or inferential. Table 16.1

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
<th>Applied Example in a Friendship Network</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-degree</td>
<td>The sum of directed ties that are received by an actor.</td>
<td>The number of friendship nominations a child receives from their peers.</td>
</tr>
<tr>
<td>Out-degree</td>
<td>The sum of directed ties that an actor sends to other people in the network.</td>
<td>The number of friends that a child nominates from a set of peers.</td>
</tr>
<tr>
<td>Geodesic</td>
<td>The shortest path (i.e., sequence of ties) that connects two actors in a network.</td>
<td>The “degrees of separation” between two children.</td>
</tr>
<tr>
<td>Centrality</td>
<td>The extent to which an actor is central to the network. This is often evaluated based on an actor’s in-degree and the extent to which they are connected to other high-degree actors.</td>
<td>The extent to which a child is popular (is nominated as a friend by many peers) and is friends with other popular children.</td>
</tr>
<tr>
<td>Size</td>
<td>The number of actors in a network.</td>
<td>The number of children in a school friendship network.</td>
</tr>
<tr>
<td>Density</td>
<td>A measure of the actual number of ties as a proportion of total possible ties in the network.</td>
<td>The proportion of observed friendship ties among children, relative to the number of ties there would be if all children in the network were friends.</td>
</tr>
<tr>
<td>Reciprocity</td>
<td>The proportion of directed ties in the network that are reciprocated.</td>
<td>The extent to which children nominate friends who have nominated them as a friend.</td>
</tr>
<tr>
<td>Degree distribution</td>
<td>The distribution of in-degrees or out-degrees across all actors in the network.</td>
<td>The variability in the number of friendship nominations that children receive and make.</td>
</tr>
<tr>
<td>Transitivity</td>
<td>The proportion of two-path relations (where ties exist between i and j, and j and k) that form triads (where ties exist between i and j, j and k, and i and k).</td>
<td>When the friends of a child’s friends become the child’s friends as well.</td>
</tr>
<tr>
<td>Cliques</td>
<td>Subgroups of densely connected nodes, identified based on degree (i.e., high density) or reachability (i.e., short geodesics).</td>
<td>When smaller groups of peers in a network share many friendships among each other, but have few friendships to peers outside of their densely connected friendship group.</td>
</tr>
<tr>
<td>Homophily</td>
<td>Tendency for actors who share a tie to have a similar actor attribute.</td>
<td>Children who are friends tend to have similar BMIs, more so than children who are not friends.</td>
</tr>
</tbody>
</table>
summarizes important descriptive measures that are often of interest to applied social network researchers. SNA also goes beyond the description of network structures and provides statistical methods to test research hypotheses—for example, to test whether actors who share a network tie are similar in weight status, or to test whether the characteristics of actors’ social connections significantly impact their weight outcomes. Because the network perspective assumes that individuals and relationships in a network are interdependent, traditional statistical models that assume data are independent are often not appropriate. Therefore, probabilistic network models have been developed that account for dependencies inherent in network data. These include dependencies between actors who share a tie, as well as more complex dependencies based on broader social structures that are important network building blocks [14]. For example, actors are often more likely to have a social connection, such as friendship, if they share a common friend (a process referred to as transitivity).

Statistical models for social networks are available for cross-sectional data (e.g., exponential random graph models) and longitudinal data (e.g., temporal exponential random graph models; stochastic actor-based [SAB] models) [15,16]. The relatively recent advancements in models for longitudinal social network data have provided a sophisticated and statistically sound approach for teasing apart micromechanisms of social selection, social influence, and confounding processes [17]. Specifically, it allows us to isolate factors that predict friendship choices from among a set of potential friends, while simultaneously testing for network and confounding effects that predict changes in individual attributes (e.g., health beliefs, behaviors, or outcomes). As we outline in the subsequent sections, this is important to accurately test the social diffusion hypothesis for obesity.

SOCIAL NETWORKS AND CHILDHOOD OBESITY

Social networks have been found to exert influence on various health behaviors and outcomes in children and adults [6,18], including obesity [1,3]. Broadly, social networks are important milieus to consider in health because they provide models for healthy or unhealthy behaviors, are sources or barriers of support, information, and resources, and can ultimately promote or impede healthy behavior change and behavior maintenance. Access to support in one’s social network can also reduce stress and increase self-efficacy, which in turn may reduce barriers to adopting healthy behaviors and achieving better health outcomes.

The adoption of a social network framework has been a natural progression for researchers interested in social influences on obesity because of the convincing evidence that social connections, such as family [19,20] and peers [21], influence behaviors and beliefs related to childhood obesity. SNA and social network theories provide a framework that goes beyond the study of social influence from an individual or dyadic (interpersonal) perspective, enabling a broader examination of how the emergent properties of social systems and their structures relate to childhood obesity. Although social network studies of childhood obesity to date are sparse and have focused predominantly on peer social networks in late childhood and adolescence, when many children are already overweight or obese, there is compelling evidence that social networks and childhood obesity dynamically influence one another. These processes are likely to be consequential for the development and diffusion of childhood obesity in diverse settings and populations.

PEER SOCIAL NETWORKS

The prevention and treatment of childhood obesity has typically focused on the role of families. However, children’s social and physical environments expand throughout development, with peer and school contexts playing an increasingly important role. To date, the influence of these social contexts on childhood obesity has been understudied [21,22], but social network studies are providing new and valuable insights into peer effects on childhood obesity.
Studies of adolescents’ peer social networks provide evidence that obesity and related health behaviors are not distributed in networks randomly; rather, these attributes are associated with social network structures in important ways. One key finding is that friends are similar in weight status and weight-related behaviors [23], and that friends’ weight similarities increase over time [24,25]. These findings have prompted claims that excess weight is “socially contagious” among peers, causing the social diffusion of obesity in social networks, and have stimulated interest in network-based obesity interventions that leverage social diffusion [5,8,26,27].

Although friend similarities in weight status may occur due to social influence, whereby youth with overweight friends are at a greater risk of gaining excess weight [2,24], it may also be explained by one or more of the following processes: (1) the selection of friends who are similar in weight status because of weight-based stigma [25,28–30] or a preference to befriend peers who have similar attributes that are correlated with obesity (e.g., gender, ethnicity) [31]; and (2) shared environments, such as school or neighborhood settings, that impact the risk of overweight. Research providing support for these various mechanisms is outlined here.

**Social Selection**

One mechanism that can lead to body mass index (BMI) similarities among friends is social selection or homophily: specifically, the tendency for friendships to form among peers who are similar in weight status (see Figure 16.1). Overweight youth have limited opportunities to form friendships because of weight-based stigma [25,28–30]. Social network studies have found that as a result of this stigma, overweight youth are likely to befriend other marginalized, overweight peers, resulting in the clustering of overweight youth in peer networks [3,25,29,30,33]. Additionally, friend similarities in weight status are likely to arise because youths prefer to affiliate with peers who have similar attributes and behaviors that are often correlated with or predict overweight. Specifically, youth have been found to befriend peers who engage in similar physical activities and sports [34,35], and additionally show strong preferences to affiliate with peers who are similar in gender, socioeconomic status, and race/ethnicity [31], preferences that are likely to contribute to correlations in weight status among friends and the clustering of obesity in peer networks.

**Social Influence**

Among adults, the likelihood of becoming obese increases with social connections (particularly friendship) to obese individuals [1]. Related findings have been reported among adolescents:

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**FIGURE 16.1** Evolution of an adolescent friendship network and weight status. Nodes are adolescents, directed ties represent close friendship nominations, and node color is based on weight status (black = non-overweight, white = overweight or obese). In this network, increasing similarity in weight status among friends (i.e., nodes in the network that share a friendship tie) is largely explained by friendship selection, and specifically the marginalization of overweight youth by their nonoverweight peers.
adolescents’ BMIs were found to be similar to the BMIs of their close friends, and these similarities increased over time [2,3,24,36–39]. These findings may reflect direct social influence, whereby friends’ weight statuses influence changes in adolescent weight status. Importantly, a few of these studies have utilized longitudinal models for social network dynamics to test for network effects on weight status, while also controlling for the effects of weight status (and other related attributes) on social selection. Their findings provide some evidence that peer networks and obesity coevolve in a mutually dependent way. One study found evidence of weight-based friendship selection in an Australian school social network but not of peer influence on weight status over 18 months [29]. Other researchers used network data from two schools in the US-based Add Health cohort, and found evidence that both social selection and social influence predicted similarity in BMI [3,35]. Because these studies looked at only one or two schools, and because of the different study populations, it is not possible to draw firm conclusions about the different results.

Social psychology and health behavior theories point to several mechanisms that may explain social network influence on weight status [21], whereby friends’ behaviors or characteristics influence adolescents’ behaviors and/or beliefs about obesity-related behaviors. First, adolescents’ diets and activities are likely to be influenced by the diets and activities of their friends. Research based on youths’ perceptions of their peers’ behaviors, and exploring social influence among pairs or small groups, has documented diverse and pervasive peer effects on physical activity [40] and diet [41–43]. Various mechanisms have been found to underpin these peer effects, including normative influence, behavior imitation, and motivations for peer approval [21]. These peer effects are likely to be especially prominent among older children and adolescents, at a time when half of their consumption of low-nutrient, energy-dense foods occurs out of the home [44], lunches and snacks are often eaten with friends [45], and leisure time and opportunities for physical activity are increasingly based in peer and school contexts.

Social network research also provides support that interpersonal social influence on obesity-related behaviors among friends gives rise to peer network effects on obesity-related behaviors (diet, physical activity), processes that may underpin the observed social contagion of obesity. This research has found that obesity-related behaviors, such as energy-dense food intake, physical activity, and physical inactivity (i.e., screen time), tend to be similar among friends, and thus cluster in friendship groups and larger peer networks [23,46,47]. And longitudinal social network studies have found that similarities among friends in physical activity [3,34,47] and consumption of energy-dense foods [48] were also explained by social influence, evidenced by the fact that adolescents’ behaviors were predicted by their friends’ behaviors, controlling for similarities when the friendships were formed. Interestingly, the influence of friends’ behaviors on adolescent behaviors was not found to be mediated via a range of social-cognitive mechanisms proposed by many health behavior theories. Specifically, the effect of friends’ behaviors on adolescent behaviors over time was not explained by a process whereby friends’ behaviors influenced adolescent descriptive peer norms, attitudes, or intentions. These findings suggest that it may be modeling processes and implicit cues, more so than normative influences, that underpin the influence of friends on these weight-related behaviors in naturalistic social networks. Alternately, adolescents’ adoption of their friends’ behaviors may be driven by impression management and goals to fit into their peer group, rather than their own beliefs about weight, eating, or physical activity. Further research is needed to better understand the mechanisms driving these social network effects.

A second process that might underpin the social contagion of obesity is the influence of friends’ weight statuses on youths’ weight norms, which may impact their weight monitoring and indirectly affect their diet and physical activity. Youth with overweight friends are also more likely to underestimate their own weight and develop inaccurate perceptions of appropriate weight status [49]. These mechanisms could normalize obesity and reinforce obesogenic behaviors among friends, resulting in the spread of obesity [50,51]. Simulation studies with adults suggest that this is a plausible mechanism explaining the diffusion of obesity in adult populations [50].
Confounding Influence

A third mechanism of note in explaining similarities in weight status among socially connected individuals is the tendency for friends to experience shared environmental risk factors for excess weight. This could lead to parallel changes in BMI, processes called confounding influences or exogenous contextual effects [52]. Adolescent friendships play out to a large extent in school, neighborhood, and community settings: environments that are linked to obesity risk. Indeed, Cohen-Cole and Fletcher’s analysis of the Add Health data suggests that peer network effects on BMI were actually better explained by shared school environments, because these friendships clustered in schools, and school characteristics and physical environments differed in the extent to which they promoted obesity [36].

Summary

In sum, the research outlined thus far suggests that the clustering and diffusion of obesity through adolescent peer networks is likely to be driven by social selection, social influence (on weight-related behaviors and weight norms), and confounding factors. However, no study to date has tested all of these mechanisms simultaneously to adequately evaluate the social contagion hypothesis. Additional research is needed that utilizes longitudinal social network data, and that includes multiple social networks nested in different settings and environments, to accurately test for the effects of weight-based social selection and social influence while accounting for the extent to which children who share social connections are exposed to the same environmental risk factors for obesity. Additional research is also needed on younger children, to understand differences in these network dynamics over children’s developmental stages. These findings can inform effective school and health policy, and contribute to the development of multilevel interventions that successfully impede or harness social network processes for obesity prevention in youth.

Family Social Networks

The importance of family social systems in influencing and addressing childhood obesity is clear, and is covered in detail in Chapter 15. Much of this work has focused on parent–child dyads in isolation of broader family social networks, and has been limited in its focus on a narrow dimension of parent–child relationships, typically parents’ influence on their children. Family social networks extend beyond these parent–child dyads; they encompass characteristics of the relationships and interactions among family members, and emergent patterns of these interactions, and thus capture much broader features of the family social environment that are also important milieus that impact childhood obesity and related behaviors.

Children and family members are likely to influence one another’s eating behaviors, activities, and obesity risks recursively, rather like a cascading chain of actions and reactions. Evidence that these more complex dependencies within family systems are relevant to childhood obesity include findings that multiple types of family members, including children and multigenerational family members, tend to engage in similar health behaviors in the areas of food choice [53], eating behavior [54], and physical activity [55,56]. And family-level support for healthy behaviors such as healthful eating has been associated with better behavioral outcomes in children [53].

However, few studies have actually mapped the multiplexity of relationships within families to understand how the characteristics of these family social networks (rather than parent or family-group characteristics) impact childhood obesity risk. A handful of studies have found evidence that particular patterns of relationships that entail health-related communication and encouragement among family members are linked to individual engagement in healthy behaviors and coengagement in healthy behaviors among parents and children (e.g., physical activity) [57,58]. These findings suggest that additional research utilizing SNA to understand family influences on childhood obesity has the potential to identify family processes that could be harnessed to reduce childhood obesity risk.
CHILDHOOD OBESITY AND SOCIAL NETWORKS AS COMPLEX SYSTEMS

The research reviewed here indicates that childhood obesity, social networks, and broader setting and environmental factors need to be considered jointly, as they operate as a social-ecological system that may give rise to similarities in weight status among social connections and lead to the diffusion of childhood obesity [59]. Further research is needed that examines the coevolution of childhood obesity and social networks within diverse family and peer settings, and that models this social-ecological environment as a complex, evolving, and interdependent system. A systems-oriented approach is necessary to identify emergent properties that impact the risk of childhood overweight, which are not evident when testing the effects of isolated components of this system. This is critical in light of evidence that networks don’t just impact childhood obesity, but that this is a system with bidirectional influences and likely feedback loops.

For example, a well-specified systems dynamics model of childhood obesity and peer networks within school and neighborhood settings (Figure 16.2) would enable a formal integration of processes that lead to friend similarities in BMI and the clustering of obesity in social networks, such as social selection (Figure 16.2A), social influence (Figure 16.2B), and shared environments (Figure 16.2D). This multilevel, systems-focused perspective would allow us to identify processes across this system that promote obesity in youth, and assess the relative impact of individual factors, social influence and diffusion, and environments on youth overweight, which are important to designing targeted strategies to reduce obesity in youth.

CONCLUSIONS

The literature reviewed here provides compelling evidence of the effects of social networks on childhood obesity, and valuable insights into diverse and complex social network processes. As with research that has identified features of physical environments that may be obesogenic, children's

![FIGURE 16.2](image-url) A model of childhood obesity and peer network system dynamics.
social environments and social networks, and the cues, norms, values, and opportunities entrenched within these contexts, can also be obesogenic or protective.

However, despite these promising findings and the prominence of conceptual and theoretical complex-system models for obesity [59], empirical research identifying social system dynamics that propagate or protect against childhood obesity is lacking. This is in part because the models for social network dynamics that provide the most sophisticated means for addressing these questions were developed fairly recently, and because the longitudinal complete social network data (i.e., data on the patterns of relationships among all individuals in a bounded population, such as all students in a school) required to adequately model social selection and influence have not been widely available. Another important gap is the limited research on the role of peer networks among younger children, and the changing impact of different relationships (e.g., family, peers, close friends, or romantic partners) on children’s behaviors and weight status across developmental stages. Additionally, important moderators of these processes, such as race and ethnicity, may play an important role in peer network–obesity dynamics but have received little consideration. For example, because rates of overweight and obesity differ markedly by race/ethnicity, with the highest rates in the United States found among Latino and African American youth [60], and because youth show strong preferences to befriend peers of the same race/ethnic background, there is likely stronger clustering of overweight in peer groups composed predominantly of Latino and African American youth. This may impact weight norms and weight-based stigma [61], and ultimately differences in peer network and obesity dynamics.

A comprehensive understanding of the links between social networks and childhood obesity can inform future obesity prevention efforts. Social networks can be leveraged for various stages of obesity initiatives, and those that holistically target relevant and important features of children’s social contexts to harness and activate social networks that support healthy behavioral change have the potential to improve their reach, effectiveness, adoption, implementation, and maintenance [4,62,63]. Broader efforts to develop network-mediated interventions that address or activate network processes for health promotion show great promise [5,6]. For example, SNA has been used to identify and train network opinion leaders to more effectively spread healthy norms and behaviors [5] and identify strategies to activate support within networks to boost behavioral change [64]. In youth, SNA has been used successfully to understand how peer networks influence adolescent substance use, research that has informed the design of effective network-based interventions that target influential peer educators to spread healthy behaviors and norms [65]. Similar strategies that harness and activate health-promoting factors in children’s social networks should now be integrated and evaluated as part of multilevel interventions on childhood obesity.

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INTRODUCTION

The built environment refers to physical and social living conditions—the human-made space in which people live, work, and recreate on a day-to-day basis [1]. The built environment is the most important determinant of health. It underlies population-level obesity for both children and adults, because contextual factors influence people to consume more calories than they burn. This chapter will provide specific evidence as to how modern physical and social environments have driven too many children to become overweight or obese.

ENERGY BALANCE

Energy balance is the difference between energy intake and energy expenditure. In order to support increases in height and developmental maturation, growing children need energy and nutrients beyond what would be required for maintaining a steady state. When children consume and absorb nutrients beyond what is needed for growth, the extra calories are stored as fat. Energy expenditure can reduce the amount of calories that might be available for storage, but too little physical activity (PA) is never the primary cause of obesity. PA is, nevertheless, necessary for normal growth and development, particularly to enable youths to build strong bones and muscles. Today, children and adults are being set up for overconsumption because of the multiple ways in which food is promoted.
Secondarily, most people need fewer calories than in the past because of active utilitarian transport and the decreasing need for physical labor.

**ENERGY INTAKE (DIET)**

Other chapters in this book review a wide variety of factors that contribute to dietary intake in children. Among them is the likelihood that many children consume excess calories simply because they are served too much food [2,3]. Most children and adults lack the capacity to tell whether they have eaten too much simply by paying attention to their appetite or feelings of fullness [4]. Total energy intake among US children and adolescents rose considerably from 1989 to 2004, and subsequently declined through 2010. Part of the increase in caloric consumption is also explained by increases in the number of daily eating occasions [5]. Overall, eating patterns indicate that children (like adults) consume too many discretionary calories. Seven sources were consistently major contributors across all time points: sugar-sweetened beverages (SSBs), pizza, full-fat milk, grain-based desserts, breads, pasta dishes, and savory snacks. Intakes of full-fat milk, meats and processed meat products, ready-to-eat cereals, burgers, fried potatoes, fruit juice, and vegetables decreased between 1989 and 2010, whereas intakes of nonfat milk, poultry, sweet snacks and candies, and tortilla- and corn-based dishes increased linearly over the 21-year period [6]. The discretionary foods consumed are a reflection of the aggressive marketing of these products in stores and on television, as well as their low cost and convenience. Food is relatively inexpensive in the United States, with the percentage of total income spent on food decreasing from 13.9% in 1970 to 9.6% in 2012 [7] and the percentage of food dollars spent away from home increasing from 25.9% to 43% over the same time period [8]. With more dollars to spend, food has taken on a strong element of entertainment (dubbed *eatertainment*), with advertisers promoting “fun” foods for children [9].

**CHILDREN AND MARKETING**

Multiple studies have examined how exposure to food advertising is associated with greater food consumption. Harris et al. conducted a study showing that children watching a TV show with food commercials consumed 45% more of a goldfish cracker snack than children watching the same TV show with no food commercials [10]. Halford et al. also conducted multiple studies showing that children watching food advertisements consume more and obese children are more likely than non-obese children to recognize food advertising [11,12].

Other studies have examined the impact of cartoon characters on children’s requests for food. One study that examined the impact of branding on taste preferences found that among young children aged 3–5, burgers wrapped in McDonald’s-branded packaging were rated as tasting better than the same burgers wrapped in a different packaging [13]. Similar findings have been shown in multiple experiments with adults, where the brand names are intentionally mislabeled [14], indicating that food (and beverage) preferences are anything but rational.

Marketing to children often promotes the least healthy foods in the most aggressive ways, showing, for example, food with high levels of sugar to have extraordinary powers [15]. The use of mixed messages and unrealistic associations are confusing and misleading [15]. A study of the use of athletes to promote food indicated that the majority of endorsements were for energy-dense and nutrient-poor foods and for beverages with added sugar [16,17].

Efforts to persuade the food industry to voluntarily refrain from targeting children has resulted in decreases in offering toys as incentives for restaurant meals and modest expenditure declines in targeting younger children (from $2.1 billion in 2006 to $1.8 billion in 2009), but marketing dollars may have shifted to older children [18]. Although the dollars spent on television advertising declined, the number of commercials broadcast was still 12–16 per day for low-nutrient foods. Large amounts of marketing dollars are being shifted to new media, such as social media and web advertising [18].
PLACE-BASED EXPOSURES TO EXCESS CALORIES

In 2009–10, the sources of the low-nutrient foods that children consumed excessively were relatively equally divided among schools (32%), stores (33%), and fast-food restaurants (35%) [19]. The following is a discussion of factors associated with increased consumption in these settings.

FOOD IN SCHOOLS

The intent of new federal school meal guidelines is to ensure access to balanced, healthy meals and to reduce exposure to low-nutrient foods, and particularly to reduce the levels of high-fat milk and pizza consumed in schools [20]. The new federal standards for school meals are currently being evaluated. One study indicated that the consumption of fruits and vegetables in school cafeterias is increasing [21]. Another showed improvements in overweight and obesity trends in California schools after policies were implemented to limit competitive foods and beverages in public schools [22].

While lunches offered by schools have improved, the food that children bring from home is still considered suboptimal. In a study of bag lunches in Houston, researchers found lunches brought from home contained more sodium and fewer servings of fruits, vegetables, whole grains, and fluid milk, compared with the National School Lunch Program (NSLP) guidelines. About 90% of lunches from home contained desserts, snack chips, and sweetened beverages, which are not permitted in reimbursable school meals [23]. Clearly, many families are unaware of what constitutes healthy balanced meals.

FOOD IN CONVENIENCE STORES/SUPERMARKETS

Retail food outlets use multiple strategies to pressure families to buy more than they need as well as to make impulse purchases. At big-box stores, foods are sold in bulk and families take home large quantities. While the intent may be to save money with large-volume purchases, people end up eating more. The consumption of stockpiled convenience foods tend to be greater than nonstockpiled foods, especially when they are visually salient [24].

One study examining the impact of salient junk food in supermarkets showed that the “pester power” effect was extremely high. Seventy-three percent of parents reported a food request from their child during the supermarket visit. Most child-requested food items were unhealthy foods (88%), with chocolate/confectionery being the most common food category requested (40%). Most parents (70%) purchased at least one food item requested during the shopping trip [25]. The availability of low-nutrient snack foods, candies, chips, and sodas has expanded to multiple nonfood outlets such as book stores, hardware stores, and car washes, and vending sodas/candies at cash registers. This makes it difficult for people to avoid low-nutrient foods.

FOOD IN RESTAURANTS

In 2010, the Boards of Supervisors in both San Francisco and Santa Clara County adopted legislation requiring that meals that include free incentive items such as toys meet certain nutritional standards, including limits on calories and sodium [26]. The San Francisco standards additionally require a minimum number of servings of fruits and vegetables. These ordinances set a national precedent in establishing an explicit regulatory standard for meals sold in the private sector but made the achievement of these standards conditional on free incentives. The response of some chain restaurants, including Burger King and McDonald’s, has been to simply charge for the toy rather than reformulate their meals; however, other restaurants are seeking to achieve the meal standards. Requiring the achievement of nutritional standards for all marketed children’s meals, regardless of the presence of an incentive, may have been a more effective policy to achieve the public health goal.
Food at Home and Destinations Including Friends’ Houses

Many studies have also examined predictors of what and how often children eat while at home. It was found that when kids had a TV in the bedroom, they had a higher probability of viewing more television. In turn, a TV in the bedroom was linked to three times the odds of a high waist circumference, high cardiometabolic risk, and elevated triglycerides [27]. Other studies have shown that watching TV is associated with snacking [28,29]. In a study following adolescent girls who wore global positioning system (GPS) monitors and kept a diary of where they went and what they ate at various destinations, it was found that at 50% of all places that girls visited food was served. Of all the places visited, including stores and restaurants, girls were most likely to get foods high in solid oils, fats, and added sugars (SOFAS) when they visited friends’ houses [30]. Such studies indicate how deeply integrated low-nutrient foods have become in daily life.

Summary of Food Exposures

By making the availability of low-nutrient foods ubiquitous, such that youth encounter and are served these foods at multiple destinations, the environment nudges people to consume too much food. Schools are beginning to address this exposure to too much low-nutrient food through standards. Standards are beginning to play a role in restaurants, but have yet to be considered in other retail food outlets. Advertising makes these low-nutrient foods more desirable, but efforts to constrain marketing on a voluntary basis have been disappointing. Other approaches to advertising, such as counteradvertising, will need to be considered.

Energy Expenditure (Physical Activity)

Children expend energy throughout the day, but are more active outdoors than indoors, partially due to constraints on space but also because they are purposefully being asked to stay sedentary and limit their movement in indoor settings [31]. Opportunities for moderate-to-vigorous physical activity (MVPA) are thus found during (1) utilitarian transport, (2) school-based PA programs and curricula, (3) community settings such as parks and other open spaces, and (4) organized extracurricular activities in and outside of school.

Utilitarian Transport

There are declining trends in active transport to school in part due to safety concerns (increasing traffic, fear of kidnapping and other crimes), but also because schools have been sited far from local communities, particularly middle and high schools, where more children are typically served than in elementary schools. Efforts to address this trend include programs such as the Walking School Bus, and Safe Routes to Schools. One evaluation in New York City found that Safe Routes to Schools programs reduced pedestrian injuries and was cost-effective [32].
Role of the Built Environment in Childhood Obesity

Many curricula have been developed to help youth be more active in school, especially during designated physical education (PE) classes. The standard goal is for youth to engage in MVPA at least 50% of the time during a PE class. However, achieving this goal is often elusive, despite the rigorous training of instructors. Many studies of PE classes indicate that youth are active less than 50% of the time because of teaching techniques that result in many students watching and waiting. Solutions may be as simple as having more equipment (a ball for each student) or promoting exercise and sports that allow all the students to be active [33,34]. Studies have tried to promote more vigorous physical activity during PE, and the most positive effects have been among boys [35]. Supervision during recess and the presence of outdoor equipment was strongly associated with PA during recess in middle schools [36]. One study in elementary school settings found that simply painting playgrounds using multicolored paints resulted in increased minutes of PA, with the largest effects seen among children who initially were the most sedentary [37].

After-School Programs

Opportunities for increasing PA can be provided after school, yet several studies that have tried to promote these activities have had difficulty in recruiting and sustaining participation [38,39]. Barriers to participation in after-school sports and PA programs include transportation, lack of funding, and the increased emphasis on academic achievement. In addition, a study of the accessibility of schoolyards and school facilities on weekends indicates that in many localities a large proportion of schools lock their gates. An analysis of the data showed a correlation between girls’ body mass index (BMI) and weekend schoolyard accessibility, such that girls who lived in neighborhoods with more locked schoolyards had higher BMI [40].

In many school districts there are no requirements for daily PE. The reduction in time allocated to school PE has been attributed to increasing academic requirements. One way to maintain PE and meet new increased academic standards would be to lengthen the school day. Indeed, some districts are already doing this. However, whether this will translate into more PA for youth is still unknown. Some studies have suggested that there is a set point for PA among youth, and that if they exercise more in school, they will compensate by exercising less after school [41]. Other studies have not found this, and have shown that absolute PA levels can be increased among school-age youth [42].

School-Based Competitive Sports

Although many schools have competitive sports programs, they may exclude those who are not sufficiently talented to make the team. With limited funding, many schools do not offer intramural sports opportunities for those youth. The problem of insufficient opportunities is exacerbated in large schools, since more students are competing for the same number of limited slots. Descriptive studies of after-school PA programs show that large schools may offer more programs, but typically have lower rates of participation, considering the size of the student body [43]. In addition, schools that serve lower-income populations tend to have fewer after school–based opportunities for PA [44].

Community Settings for Physical Activity (Streets, Sidewalks, Parks)

In urban areas, many cities have been increasing the number of parks, so people are all within 10 minutes’ walk of one. Yet a recent national study on parks indicated that they are designed to serve children more than adults. For example, 89% of neighborhood parks have playground equipment, but fewer than one-third have facilities such as tennis courts or walking paths [45]. More than 50% of park users were children and teens, while these age groups comprise less than 27% of the population [45]. Many park systems also sponsor a wide variety of leagues and activities for children, but very few for adults or seniors. Large gender disparities also exist in park use. Among
children under 13, 60% of park users are boys, and among teens aged 13–19, 65% of park users are boys [45]. This likely reflects a greater emphasis on team sports for boys than for girls. There are also disparities between parks in socioeconomic status. While gender distribution is similar across income levels, parks in low-income neighborhoods have fewer programed activities.

Over the past few decades, investments in local parks have declined [46] and park systems often limit their oversight to maintenance rather than programing and event planning. Increasingly, it is up to private groups to manage and provide PA programing for youth and others in the community.

**STREET NETWORKS, STREET CONNECTIVITY, AND SPRAWL**

Many studies that have examined street design in relationship to PA among adults show that adults walk more in neighborhoods with more intersections and which are more densely populated [47,48]. Frank et al. developed an index of walkable neighborhoods strongly based on land use and found that a difference of one standard deviation in walkability could increase PA by more than 8% [47]. The association between street connectivity with children’s PA appears to be mixed. For example, in one study no association with street design was found [49], in another more PA was seen only with boys [50], and in another the association with PA in youth was opposite that of adults (more PA in streets with lower connectivity for children, less for adults) [51].

**CONCLUSION**

Without addressing the conditions in which people live, it will be very difficult, if not impossible, to end the epidemic of childhood obesity. Given that food is the major source of obesity, food outlets are where interventions hold the greatest promise in moderating intake. Supermarkets and restaurants need standards to guide them to offer foods in ways that will not increase the risk of obesity and chronic diseases among both youth and adults. Standards and oversight could protect consumers from being served too much and from being exposed to settings that limit their ability to make thoughtful choices in their own best interests. Investments in spaces and programing for active recreation will be necessary to counter the pull of electronic media and encourage children to spend more time outdoors, where they will be most likely to engage in PA.

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The Influence of Stress on Obesity Development in Children

Sydney G. O’Connor, Eleanor T. Shonkoff, and Genevieve Fridlund Dunton

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INTRODUCTION

This chapter explores the extent to which stress influences the development of obesity in pediatric populations. Our focus is on the types of stressors and stress, both objectively and subjectively measured, which have been associated with adverse weight outcomes in children and youth. We also discuss two broad pathways, behavioral and biological, through which stress may operate on the genesis and maintenance of obesity. This chapter concludes with an overview of the limitations of the current literature, as well as recommendations for future research in the area to address these gaps.

DEFINING STRESS

Stress can be defined as an imbalance between the demands placed on an individual and the resources that he or she has to manage [1]. Stressors are external factors (e.g., events, experiences, circumstances) that may threaten safety, security, and well-being. In contrast, psychological stress is described as a reaction that occurs when the demands of stressors outweigh one’s ability to cope with those demands, which can eventually lead to poor health [2]. Both stressors and psychological stress are difficult to measure. Stressors are often characterized by objective external events, whereas psychological stress consists of an individual’s subjective internal appraisal of, or reaction to, external stressors. Whether exposure to external stressors leads to psychological stress may vary depending on individual characteristics, resources, and coping abilities. Exposure to excessive stressors and psychological stress in early life, whether objective or perceived, can have a profound impact on many developmental processes, including increased biological reactivity to stress or altered behavioral patterns that can lead to heightened obesity risk over time [3,4].

PREVALENCE OF STRESS IN CHILDREN AND YOUTH

External Stressors

Exposure to stressful circumstances is common among US children. Poverty, low parental education, minority status, and being raised outside of a two-parent family are highly prevalent. More than 50% of all US children are estimated to experience at least one of these four stressors, and worse child health outcomes are associated with experiencing a greater number of these stressors [5]. Furthermore, as much as 50% of US youth are exposed to community violence [6], another circumstance that can be viewed as a stressor.

Psychological Stress

Despite an abundance of information on the prevalence of perceived stress among adults, stress prevalence in pediatric populations is less understood. Available data illuminate perceived stress as a salient issue in the lives of youth. In 2009, the American Psychological Association (APA) expanded their annual Stress in America survey to include 1206 youth aged 8–17. Overall, children self-reported experiencing stress to a greater extent than their parents reported for them; 14% of youth aged 8–12 and 28% of teens aged 13–17 reported worrying “a lot or a great deal,” while only 2%–5% of parents reported that their child experienced “extreme stress.” The most commonly reported sources of stress in the sample included the desire to do well in school (44%) and concern for family finances (30%) [7].
The Influence of Stress on Obesity Development in Children

CONCEPTUAL MODEL OF CHILDHOOD STRESS AND OBESITY RISK

Although there is growing evidence for the contributing role of stress in the onset and perpetuation of obesity in children [3], the underlying mechanisms are not well understood. In this chapter, we propose a conceptual model linking stress and obesity in youth to delineate and explore potential pathways leading from stressful exposures to stress responses, and obesogenic processes. This model is summarized in Figure 18.1.

Our conceptual model provides a general organizational framework to understand these potential mechanisms. The model differentiates between (1) external “over the skin” exposures to objective stressors and (2) internal “under the skin” responses to stressors, including subjective perceptions and psychophysiological indicators (e.g., cortisol and heart rate reactivity) of psychological stress. The model also proposes two major pathways, behavioral and biological, through which exposure to stressors and psychological stress may lead to obesity in children.

To illustrate, an external stressor might consist of a child experiencing physical abuse, whereas psychological stress can be illustrated as the child’s subjective evaluation of the extent to which abuse is perceived as stressful, the latter of which may vary from child to child. Stressful exposures and heightened perceptions of stress can lead to behavioral consequences, such as decreased physical activity [8], and alterations in biological response, such as the accumulation of abdominal adipose tissue [9]. Over time, it is hypothesized that repeated stress exposures and responses can contribute to the development of obesity in youth [3,10,11].

EXPOSURE TO STRESSORS AND CHILD OBESITY RISK

The following sections describe major external stressors that have been found to be related to child obesity risk. A socioecological approach [12,13] is used, distinguishing between external stressors at the community/neighborhood, family, and individual levels.

COMMUNITY/NEIGHBORHOOD-LEVEL STRESSORS

Crime and Violence

Exposure of youth to community violence is as high as 50% within some US inner-city populations, and can range from witnessing stabbing to death by gunshot [6]. A review by Midei et al. [14] of six separate studies of interpersonal violence in the community and youth obesity risk found a positive

FIGURE 18.1 Conceptual model of stress and obesity.
association in half of the studies. In those studies finding an association, residing in an unsafe neighborhood was associated with greater odds of obesity in children. This review found that studies examining younger children tended to find null results, suggesting that obesogenic processes related to stress from community violence may take longer to manifest.

**Socioeconomic Status (SES)**

One of the most consistent stressors associated with child obesity risk is community/neighborhood-level SES. A study by Shih et al. [15] examined the correlation of community-level economic hardship, a summary score of six indicators including education and income, with the rate of obesity in youth. Across 135 distinct communities in Los Angeles County, they found more than twice the prevalence of obesity in communities in the highest quartile of economic hardship, compared with those in the lowest quartile. Another study by Grow et al. [16] used spatial analyses to examine the link between neighborhood-level SES indicators and obesity in census tract data from a large US city. Child obesity risk was positively associated with lower average household income, lower home ownership rates, and a greater percentage of undereducated women at the neighborhood level. A continuing challenge in this area, however, is disentangling the stress-related effects of living in a low SES neighborhood from other features (e.g., low walkability, limited access to grocery stores) that may contribute to child obesity.

**Family-Level Stressors**

**Racial/Ethnic Minority Status**

Evidence suggests that children of racial and ethnic minorities are at an increased risk of overweight and obesity. Although the mechanism for this stress obesity outcome is not clear, increased risk could be because children of racial and ethnic minorities are exposed to racial discrimination as well as other stressors such as financial and food insecurity, and neighborhood safety threats [3]. Research also suggests that racial/ethnic minority youth may experience stress from low SES differently than white children. A review by Dixon et al. [17] found that SES and obesity were positively associated among white children, but there was no clear relationship between SES and weight within black and Mexican American youth.

**Negative Family Events**

The term family stressor is used to describe stressful circumstances that originate within the family system. A study by Garasky et al. [18] examined a large nationally representative sample to determine the impact of six distinct family-level stressors, including financial strain, mental and physical health problems, conflict and disruption, housing or health insurance struggles, and lack of cognitive and emotional support in the home, on children's obesity risk. They found that the types of family stressors associated with child obesity risk varied by child age. Children 5–11 years of age from households characterized by a dearth of cognitive stimulation and emotional support were at greater risk of overweight and obesity, whereas children 6–12 years of age living in households characterized by greater physical and mental health issues and financial difficulties were at greater risk of overweight and obesity.

**Parental Stress**

Parental perceived stress has been implicated as an independent external stressor associated with child obesity risk [3]. Using a cross-sectional design, Parks et al. [19] found that parents reporting stress from a greater number of sources (e.g., financial strain, physical health problems, poverty) in a stressor index were more likely to have obese children. This same study also collected measures of parent self-reported perceived stress (using a general stress question); although they found no relationship between the number of stressors experienced and child dietary behaviors, there was a
The Influence of Stress on Obesity Development in Children

positive association between parent perceived stress and frequency of child fast-food consumption, suggesting that parental perceived stress but not the number of stressors experienced may lead to obesogenic parenting behaviors.

**INDIVIDUAL-LEVEL STRESSORS**

**Victimization/Bullying**
Youth who are bullied may be at increased risk for overweight and obesity. Midei et al. [14] conducted a literature review examining the link between exposure to bullying and obesity risk in children, finding general agreement that victimization by bullying confers greater risk of obesity in youth both cross-sectionally and longitudinally. In a longitudinal study of 1200 youth aged 12–13 years at baseline and followed for 4 years, Adams and Bukowski [20] found that bullying at the onset of the study predicted increases in body mass index (BMI) among initially obese females. This relationship was inverted for initially obese males, such that victimization at study onset predicted a decrease in BMI over time. There was no relationship between victimization and change in BMI in nonobese youth. Additionally, a meta-analysis by van Geel et al. [21] of 16 internationally representative studies and 28 independent effect sizes found a significantly greater likelihood of obese youth to be bullied, regardless of gender.

**Maltreatment**
Physical, sexual, or emotional maltreatment has been demonstrated to impact child obesity risk. A 2013 meta-analysis of 41 studies revealed that exposure to maltreatment in childhood is associated with increased odds of becoming obese over the lifespan, as measured through a variety of populations and study designs [22]. Although this meta-analysis also included studies assessing obesity outcomes in adults, several studies focused exclusively on child and adolescent weight outcomes, supporting the link between exposure to maltreatment and increased obesity risk during youth. A review by Midei et al. [14] examining 36 unique studies of weight outcomes in individuals who experienced interpersonal violence before the age of 18 similarly reported increased odds of overweight and obesity in individuals who experienced physical or sexual abuse in their youth.

**RESPONSE TO STRESS AND CHILD OBESITY RISK**

**Psychological Stress**
Children’s psychological responses to stress, including their appraisals of the severity of stress and psychophysiological stress reactions, are thought to play a contributing role in obesity risk [3], with some variation depending on the age of the child, as summarized in the following sections.

**Preschool-Age Children (Ages 0–6 Years)**
A limited number of studies have examined how psychological responses to stress in preschool-age children are related to obesity risk. Psychological responses to chronic stress, indicated by blunted cortisol and salivary alpha-amylase responses, have been associated with higher obesity in low-income preschool-age children [23,24].

**School-Age Children (Ages 6–10 Years)**
Among school-age youth, some evidence indicates that psychological stress is higher among obese youth, but findings are mixed. Using an experimental paradigm, Roemmich et al. [25] found that youth with greater reactivity to stress, assessed by perceived stress ratings and heart rate reactivity in reaction to a laboratory stressor, had a higher-percentage body fat among adolescents of average BMI percentile.
Preadolescents (Ages 10–12 Years)
A larger body of research has investigated these relationships in preadolescents, with most cross-sectional studies finding that psychological stress is associated with higher rates of obesity. One study of 10–12-year-olds measured how participants would expect to feel in response to hypothetical stressful situations. In this group, psychological stress was positively correlated with adiposity (BMI and waist circumference), but did not predict BMI status above the effects of depression and was only marginally predictive of waist circumference, accounting for the effects of depression [26]. A large, longitudinal study following children from age 7 to 11 years, which assessed stress and BMI once each year, found that perceived stress at any time point did not predict change in obesity (measured by BMI and waist circumference) for any of the subsequent years. However, children who had consistently higher perceived stress across the 3 years had higher obesity compared with those with moderate and low stress over that time period [27].

Adolescents (Ages 13–20 Years)
Evidence is mixed for the association between psychological stress and obesity among adolescents. A small, cross-sectional study of Middle Eastern adolescents aged 14–17 years found that higher perceived stress was correlated with higher odds of overweight and obesity [28]. In a cross-sectional study by De Vrient et al. [29], a measure of how stressful certain situations, such as home life or peer pressure, are perceived to be was assessed in youth aged 12.5–17.5 years. In girls, higher perceived stress was associated with overall and central adiposity (measured by BMI z-score, six skinfold measures, and body fat analysis), adjusting for overall dietary quality and moderate-to-vigorous physical activity. Other cross-sectional studies have shown contradictory results, with levels of perceived stress not differing between overweight/obese and healthy weight teenagers [30]. Another longitudinal study of adolescents (aged 12–18 years) examined whether stress at baseline predicted obesity 6–8 years later, finding no association [31]. Some studies suggest that race and ethnicity may be moderating factors, including a large, longitudinal study of girls, which found a faster rate of increase in BMI from 10–19 years for girls who experienced high versus low chronic stress, with stronger effects for black girls [32].

Behavioral Pathways Linking Stress and Obesity Risk
Stress may promote the onset and perpetuation of obesity in youth, through its effect on children’s eating and activity behavior [18,33].

Stress and Eating
Different types of stress are related to increased food intake or decreased healthy food consumption in youth. In one study of school-age children, stressful life events were linked to lower fruit and vegetable intake. However, gender was an important moderator, and after controlling for emotional eating, the link between stress and dietary intake was significant only for girls [34]. Experimental evidence suggests that social stressors, such as social ostracism, can lead overweight youth to be more motivated to work for palatable, high-calorie snack foods and to consume more of these foods [35]. Another study found that among children who were highly reactive to stress, restrained eaters consumed more calories and ate for longer after a social stressor than when they were not exposed to the stressor [36]. In a longitudinal study of fourth-grade youth, perceived stress predicted subsequent higher intake of high-calorie snack foods, mediated by emotion-driven eating [37]. Other evidence suggests contradictory evidence, and one study found that emotional distress was not correlated with unhealthy eating in a sample of school-age children [38]. Overall, findings suggest that stress may be associated with poorer dietary patterns, but evidence for effects on dietary intake are mixed and may only occur for girls. The effects of stress on dietary intake may be greater for youth who are obese, highly reactive to stress, or highly restrained eaters.
Stress and Physical Activity
Youth may be less likely to engage in physical activity following exposure to a stressor, though results are mixed. Using an experimental paradigm, Roemmich et al. [8] found that youth who were exposed to a social stressor chose to perform less leisure physical activity than those who were not exposed. Further, youth who were highly reactive to stress, as measured by heart rate reactivity, performed less physical activity than those who were less reactive. However, results may vary depending on the age of the child. One study found that negative emotions increased physical activity in children under 8 years of age but decreased physical activity in older children [34]. Physical activity may also serve as a buffer against the negative effects of being exposed to stressors [3]. Cross-sectional research indicates that adolescents who report more frequent physical activity have lower psychological stress [39,40]. However, not all studies find that physical activity is linked to lower psychological stress among adolescents [41], and more research on youth samples is needed [3].

Interactions between Stress, Eating, Physical Activity, and Obesity
Physical activity may also moderate the effects of stress on eating behavior and obesity. Experimentally, physical activity has been shown to buffer against stress-induced compensatory eating [42]. In this study, both normal weight and overweight/obese children did not engage in compensatory eating after physical activity following a social stressor. Compared with children in the sedentary behavior condition, children who engaged in physical activity burned more calories but did not increase caloric intake, leading to a more favorable energy balance. In a cross-sectional study of older youth and young adults (aged 12–24 years), physical activity buffered the effect of stress on adiposity, such that for physically active youth there was a weaker positive relationship between stress and adiposity (measured by BMI, waist circumference, and skinfold) [43]. In a similar vein, one longitudinal study found that higher stress led to lower adiposity for children who had low sedentary behavior or high moderate-to-vigorous physical activity [44].

Biological Pathways Linking Stress and Obesity Risk
Stress may also indirectly influence obesity risk in children through biological pathways that are independent of changes in eating and physical activity behavior [18,25,45]. Prolonged chronic activation of the metabolic, cardiovascular, inflammatory, and endocrine systems in response to stress has been linked to the onset and progression of obesity [10,33,45]. The experience of stress activates the hypothalamic–pituitary–adrenal (HPA) axis, leading to the release of glucocorticoids into the bloodstream. One glucocorticoid of particular importance is cortisol, produced by the adrenal cortex, which has been implicated for its role in metabolic processes [33]. Excess cortisol may lead to visceral fat formation over time [10,33]. Although the exact mechanisms are not well understood, it is thought that cortisol and other glucocorticoids are involved in the process of adipogenesis and may increase the expression of numerous genes involved in fat deposition [46]. Emerging evidence also suggests that disrupted circadian adrenal rhythms within the stress system can lead to disrupted diurnal rhythms within the adipose deposition system, triggering obesogenesis [47]. Furthermore, stress may trigger inflammatory responses such as the release of interleukin-1 beta (IL-1β) signaling within subcutaneous adipose tissue, which may lead to the development of visceral obesity. Repeated stress-induced release of IL-1β in the subcutaneous adipose tissue may impair its ability to uptake energy substrates, which may cause them to be disproportionately deposited in visceral adipose tissue, leading to obesity progression [48]. Through these biological pathways, chronic hyperactivation of the stress system may lead to the development of adiposity and ultimately increase the risk of obesity [45]. However, the exact nature of these mechanisms in children is not well understood.

Reciprocal Effects and Bidirectionality
A small line of research suggests that there may be a reciprocal relationship between stress and obesity in children, such that being obese can serve as a stressor itself or lead to increased stress
reactivity [11,25]. For example, one experimental study found that, compared with normal weight peers, obese youth aged 12–18 years showed increased stress reactivity to a social stressor, indicated by cortisol response [49]. In another experimental study among 9-year-old youth, children with higher BMI percentile, percentage body fat, and central adiposity experienced higher levels of perceived stress, as well as greater heart rate reactivity, after a social stressor than youth with lower BMI, body fat, and abdominal girth [25]. A longitudinal study of children aged 5–12 years found that adiposity at baseline led to increased stress over time, and this association was stronger for children with elevated morning cortisol levels and who consumed the greatest amount of sweet foods [44].

**RESEARCH CHALLENGES**

**CHALLENGES IN OBESITY OUTCOME MEASUREMENT**

Research in this area typically uses BMI percentile as the primary indicator of obesity in children. However, BMI does not differentiate between fat and lean body mass in terms of how they contribute to body weight. Given the potential role of stress in the accumulation of adipose tissue, other measures such as waist circumference, skinfolds, and percentage of body fat (e.g., via duel-energy x-ray absorptiometry [DXA] or bioelectrical impedance analysis [BIA]) should be incorporated in future studies of stress and obesity risk in youth.

**CHALLENGES IN STRESS MEASUREMENT**

Most studies rely on instruments that neglect to collect information on the length or intensity of stressor experience [3]. Additionally, measures of stress experienced by children often rely on parent reports, adding yet another potential layer of inaccuracy [3]. Furthermore, few studies collect both self-reported measures of stress and biomarkers of stress psychophysiology (e.g., cortisol), which, combined, may yield a more complete picture of the experience of psychological stress in children.

**RESEARCH GAPS AND RECOMMENDATIONS FOR FUTURE RESEARCH**

**LONGITUDINAL STUDIES AND NATURAL EXPERIMENTS**

Most studies examining the association between stress and obesity risk during childhood are cross-sectional in nature. This type of study design makes it difficult to disentangle directionality—whether stress leads to obesity or obesity causes stress or both. Longitudinal studies with measures of stress and obesity across multiple time points as well as natural experiments (i.e., examining changes in stress and obesity risk before and after stressful events such as natural disasters or school shootings) are needed to establish directionality.

**RESEARCH DURING EARLY CHILDHOOD**

Research on how prenatal and early-life exposure to negative events and stressful circumstances may establish unhealthy weight trajectories during the first few years of life is lacking [50]. Prenatal and early-life stressors may play a role in the etiology of early childhood obesity through maternal and infant food consumption, basal metabolism, and adipose deposition.

**REAL-TIME DATA CAPTURE**

Studies of stress, physical activity, and eating in children typically assess these exposures and behaviors on an infrequent basis (e.g., once, semiannually, or annually). Although this measurement
approach can capture interindividual (i.e., between-person) differences or change over longer periods of time, the effects of day-to-day (i.e., intraindividual) variation in key exposures and responses are unknown. Also, studies often rely on retrospective reports of perceived stress, which may be vulnerable to recall biases. These methodological limitations can be addressed through real-time data capture, repeated measures designs that can capture daily covariation between stress exposures and experiences, and energy balance behaviors.

**Research Examining Mediating Mechanisms (Behavioral and Biological Responses)**

Due to the cross-sectional nature of work in this area, few studies examine mediating mechanisms and the behavioral and biological pathways leading from stress to obesity progression in children. Future research is needed to uncover intermediary factors to target in prevention and treatment programs to reduce and buffer the effects of stress on child obesity.

**Research on Risk and Protective Factors**

Research on moderating mechanisms and effect modifiers is needed to identify risk and protective factors to identify families whose children are at the greatest risk of obesity progression, and strategies to effectively buffer these effects. These risk and protective factors may include parenting styles, household rules, and weight-related parenting practices [12], among other factors.

**Summary and Conclusions**

Overall, a sizable body of evidence implicates the potential role of psychological stress on the etiology of childhood obesity. Exposure to external stressors such as poverty, victimization/bullying, and maltreatment may be particularly salient experiences during childhood that increase obesity risk. Variations in children’s individual perceptions of, and reactions to, stress are important factors to consider in addition to objective measures of exposures to potential stressors. Whereas growing evidence has shown that psychological stress may influence children’s eating and physical activity behaviors, fewer studies have examined how stress can directly alter biological processes (e.g., metabolism, inflammation, fat deposition) that can lead to obesity in children.

The conceptual model illustrates the mechanisms through which stress may impact child obesity outcomes. The model differentiates between (1) external “over the skin” exposures to objective stressors and (2) internal “under the skin” responses to stressors, including subjective perceptions and psychophysiological indicators (e.g., cortisol and heart rate reactivity) of psychological stress, and proposes two major pathways, behavioral and biological, through which exposure to stressors and psychological stress may lead to obesity in children.

**References**

The Influence of Stress on Obesity Development in Children


Early Toxicant Exposures and the Development of Obesity in Childhood

Yun Liu and Karen E. Peterson

INTRODUCTION

Worldwide increases in child obesity have been attributed to changes in diet, a sedentary lifestyle, and genetic predisposition, as reviewed in other chapters, but these risk factors do not fully account for the pace and pattern of recent secular trends [1,2]. The health consequences of obesity across the life course [3–6] coupled with challenges and costs of management [7,8] underscore the importance of disentangling the origins of pediatric obesity. The environment to which humans are exposed has changed, due to the exponential growth in the production and use of synthetic chemicals since the late nineteenth century [9]. In 2002, researchers offered ecologic evidence relating elevated production of endocrine-disrupting chemicals (EDCs) to US obesity trends and highlighted paradoxical weight gains at low levels of exposure to these ubiquitous compounds [2]. The mechanisms underlying the association of EDCs, collectively termed obesogens [10], with the developmental programming of obesity are described in Chapter 20.

This chapter considers evidence from human studies on the impacts of early-life exposure to persistent organic pollutants (POPs), short-lived compounds, and heavy metals on measures of offspring fat mass and distribution. While cross-sectional studies have suggested that some EDCs are associated with obesity [11,12], accumulating evidence from longitudinal studies suggests that the timing of exposure and the direction of effects varies by sex across sensitive periods of development [13]. We restricted our review to human, nonexperimental studies with a prospective longitudinal design that examined the associations of perinatal toxicant exposures (in utero, breast milk) or those measured in children under 2 years with obesity-related outcomes from birth to young adulthood. For POPs and nonpersistent compounds, we summarize evidence from epidemiologic studies published over a 5-year period from 2011 to 2015 [14], given the availability of three extensive reviews of earlier studies [15–17]. For heavy metals, we discuss all human research available to date evaluating the effect of early exposure on the development of child obesity. Different lengths of
follow-up across studies can provide insights on toxicant effects across sensitive periods for obesity development [18].

**PERSISTENT ORGANIC POLLUTANTS AND OBESITY**

POPs have been widely used as pesticides, solvents, pharmaceuticals, or industrial chemicals [19], raising global concern due to their potential for long-range transport, capacity to persist in the environment, ability to bioaccumulate in ecosystems, and their negative effects on human health [20]. Humans are exposed to these persistent substances primarily through dietary ingestion, inhalation, or dermal exposure [21]. Although POPs are presently banned or restricted by the Stockholm Convention, these toxicants can bioaccumulate within the food chain and are still detectable in human tissues around the world [16]. Polychlorinated biphenyl (PCBs), organochlorine pesticides, perfluorinated compounds (PFCs), and polybrominated diphenyl ethers (PBDEs) were found in 99%–100% of pregnant women [22], and POPs have been detected in cord blood, placenta, amniotic fluid, and breast milk [23–25]. Therefore, it is possible that perinatal POPs exposure may start in utero, passing through the placenta, and continue after delivery through breast-feeding. POPs are categorized into dioxins/dioxin-like substances or non-dioxin-like substances, as determined by their capacity to bind the aryl hydrocarbon receptor (AhR) [26]. Dioxins and dioxin-like compounds such as coplanar PCBs can promote adipogenesis by increasing peroxisome proliferator–activated receptor (PPAR) expression [27] and by disturbing initiation of estrogen receptors to encourage the progress of obesity [28]. In contrast, the underlying mechanism is not fully understood for non-dioxin-like compounds such as noncoplanar PCBs, organochlorine pesticides, hexachlorobenzene (HCB), hexachlorocyclohexane (HCH), PFCs, and PBDEs. Previous studies suggest that dichlorodiphenyltrichloroethane (DDT) and p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) can exert toxicity through antiandrogenic, estrogenic, and antiestrogenic effects [16]. HCB may lead to disrupted gluconeogenic reactions. Perfluoroalkyls (PFOAs) and tributyltin (TBT) can affect fat storage, adipocyte differentiation, and insulin sensitivity via interfering with PPAR expression [16]. Polycyclic aromatic hydrocarbons (PAHs), which are a group of persistent chemicals generated in the course of incomplete combustion processes of organic materials, are suspected to act as endocrine disruptors and were recently suggested to be obesogens [29–31]. An animal study reported that benzo[a]pyrene, a high-molecular-weight PAH, directly inhibits the release of free fatty acids by adipocytes and leads to weight gain by accumulating fat mass [32].

Prior to 2011, numerous experimental reports and a limited number of epidemiological studies in humans linked perinatal exposure to synthetic chemicals to obesity in later life. Earlier prospective human studies documented an association between elevated levels of DDT or its main metabolite DDE [33] during pregnancy and obesity in their offspring [15]. The few cohort studies that examined the obesogenic effects of other organochlorine pesticides such as HCB and HCH provided inconsistent conclusions [15]. Far fewer researchers have examined the obesogenicity of other POPs, including PFCs, PBDEs, organotins, or PAHs. We identified 19 papers published between 2011 and 2015 that examined the relationship between obesity and perinatal exposure to POPs, including PCBs, DDE, DDT, HCB, HCH, PFOAs, PFOS, PBDEs, TBT, and PAHs. Most reports considered the influence of POPs, for example, PCBs (9 studies), and DDE (12 studies), while fewer investigated the impact of other compounds.

**POLYCHLORINATED BIPHENYLS**

Most of the nine prospective studies evaluating the impact of early PCB exposures failed to support the hypothesis that these synthetic chemicals predicted infant or child obesity prior to adolescence (Table 19.1). In the Spanish Infancia y Medio Ambiente (INMA)-Sabadell birth cohort, serum PCB levels during the first trimester were not associated with rapid weight gain in the first 6 months of life or overweight at 14 months, although this study was limited by sample size (n = 518) [34].
TABLE 19.1
Prospective Studies of Associations between Early-Life Exposure to Toxicants and Childhood Obesity and Related Outcomes

<table>
<thead>
<tr>
<th>Study Setting</th>
<th>n (mother–child pairs, Child Sex)</th>
<th>Exposure</th>
<th>Child Age at Follow-Up</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCBs</strong></td>
<td></td>
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</tr>
<tr>
<td>The Netherlands (Zwolle)</td>
<td>n = 61 (♀♂)</td>
<td>Cord plasma (ng/L or ng/mL)</td>
<td>12 months</td>
<td>NS BMI</td>
<td>36</td>
</tr>
<tr>
<td>Spain (Sabadell)</td>
<td>n = 518 (♀♂)</td>
<td>1st trimester serum (ng/g lipid)</td>
<td>6, 14 months</td>
<td>NS WAZ birth to 6 months, NS BMIz 14 months</td>
<td>34</td>
</tr>
<tr>
<td>Spain (Sabadell, Valencia and Gipuzkoa)</td>
<td>n = 1285 (♀♂)</td>
<td>1st trimester serum (ng/g lipid)</td>
<td>6, 14 months</td>
<td>NS WAZ 6–14 months, NS overweight 14 months</td>
<td>35</td>
</tr>
<tr>
<td>Europe (pooled 7 birth cohorts)</td>
<td>n = 1864 (♀♂)</td>
<td>Cord blood and postnatal exposure estimated with a validated pharmacokinetic model</td>
<td>Birth and 24 months</td>
<td>Postnatal PCBs: – WAZ β = –0.10 (95% CI: –0.19, –0.01)</td>
<td>41</td>
</tr>
<tr>
<td>Spain (Island of Menorca)</td>
<td>n = 344 (♀♂)</td>
<td>Cord blood (ng/mL)</td>
<td>6.5 years</td>
<td>+ [T3 (&gt;0.9 ng/mL) vs. T1 (&lt;0.6 ng/mL)]</td>
<td>25</td>
</tr>
<tr>
<td>Denmark (Faroe Islands)</td>
<td>n = 561 (♀♂)</td>
<td>Maternal serum and breast milk (μg/g)</td>
<td>5 and 7 years</td>
<td>+ in ♀, NS in ♂; BMI (kg/m²) 7 years β = 1.13 (95% CI: 0.33, 1.93)</td>
<td>40</td>
</tr>
<tr>
<td>United States</td>
<td>n = 1915 (♀♂)</td>
<td>3rd trimester serum (μg/L)</td>
<td>7 years</td>
<td>NS overweight and obesity</td>
<td>38</td>
</tr>
<tr>
<td>Greenland, Poland (Warsaw), and Ukraine (Kharkiv); n = 1109 (♀♂)</td>
<td></td>
<td>Second- and third-trimester serum and estimated postnatal (ng/g lipid)</td>
<td>5–9 years</td>
<td>NS BMI</td>
<td>37</td>
</tr>
<tr>
<td>Belgium (Flanders); n = 114 (♀♂)</td>
<td></td>
<td>Cord blood (ng/g fat)</td>
<td>7–9 years</td>
<td>+ in ♀, NS in ♂; WC β = 0.014 (p = .033)</td>
<td>39</td>
</tr>
<tr>
<td><strong>DDE/DDT</strong></td>
<td></td>
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<tr>
<td>Mexico (Morelos); n = 253 (♀♂)</td>
<td></td>
<td>First-, second-, and third-trimester serum (ng/mL)</td>
<td>Birth to 12 months</td>
<td>DDE: NS WAZ, NS BMIz</td>
<td>44</td>
</tr>
<tr>
<td>The Netherlands (Zwolle); n = 61 (♀♂)</td>
<td></td>
<td>Cord plasma (ng/L or ng/mL)</td>
<td>12 months</td>
<td>DDE: NS BMI</td>
<td>36</td>
</tr>
<tr>
<td>Spain (Sabadell); n = 518 (♀♂)</td>
<td></td>
<td>First-trimester serum (ng/g lipid)</td>
<td>6 and 14 months</td>
<td>DDE: + WAZ birth to 6 months RR = 2.42 (95% CI: 1.25, 4.67)</td>
<td>34</td>
</tr>
<tr>
<td>Spain (Sabadell, Valencia, and Gipuzkoa)</td>
<td>n = 1285 (♀♂)</td>
<td>1st trimester serum (ng/g lipid)</td>
<td>6, 14 months</td>
<td>BMIz at 14 months RR = 2.26 (95% CI: 1.12, 4.55)</td>
<td>35</td>
</tr>
<tr>
<td>Europe (pooled 7 birth cohorts)</td>
<td>n = 1864 (♀♂)</td>
<td>Cord blood and postnatal exposure estimated with a validated pharmacokinetic model</td>
<td>Birth and 24 months</td>
<td>Prenatal DDE: + WAZ β = 0.12 (95% CI: 0.03, 0.22)</td>
<td>41</td>
</tr>
</tbody>
</table>

(Continued)
TABLE 19.1 (CONTINUED)
Prospective Studies of Associations between Early-Life Exposure to Toxicants and Childhood Obesity and Related Outcomes

<table>
<thead>
<tr>
<th>Study Setting</th>
<th>Exposure</th>
<th>Child Age at Follow-Up</th>
<th>Outcome*</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain (Island of Menorca); n = 344 (♂♀)</td>
<td>Cord blood (ng/mL)</td>
<td>6.5 years</td>
<td>DDE: + [T2 (0.7–1.5 ng/mL) vs. T1 (&lt;0.7 ng/mL)] Overweight RR = 1.67 (95% CI: 1.10, 2.55) DDT: + in ♂, NS in ♀; [T2 (0.06–0.18 ng/mL) vs. T1 (&lt;0.06 ng/mL)] Overweight RR = 1.96 (95% CI: 1.06, 3.62)</td>
<td>25</td>
</tr>
<tr>
<td>Denmark (Faroe Islands); n = 561 (♂♀)</td>
<td>Maternal serum and breast milk (µg/g)</td>
<td>5 and 7 years</td>
<td>DDE: + in ♀, NS in ♂; WC 7 years β = 0.93 (95% CI: 0.36, 1.51) BMI change 5–7 years β = 0.46 (95% CI: 0.12, 0.80) with overweight mothers</td>
<td>40</td>
</tr>
<tr>
<td>United States; n = 1915 (♂♀)</td>
<td>Third-trimester serum (µg/L)</td>
<td>7 years</td>
<td>DDE, DDT: NS overweight and obesity</td>
<td>38</td>
</tr>
<tr>
<td>United States (Salinas Valley); n = 270 (♂♀)</td>
<td>Second-trimester serum (ng/g lipid)</td>
<td>7 years</td>
<td>DDE, DDT: + obesity trend with age (2, 3.5, 5, 7 years) NS at 7 years</td>
<td>43</td>
</tr>
<tr>
<td>Greenland, Poland (Warsaw), and Ukraine (Kharkiv); n = 1109 (♂♀)</td>
<td>Second- and third-trimester serum and estimated postnatal (ng/g lipid)</td>
<td>5–9 years</td>
<td>DDE: NS BMI</td>
<td>37</td>
</tr>
<tr>
<td>Belgium (Flanders); n = 114 (♂♀)</td>
<td>Cord blood (ng/g fat)</td>
<td>7–9 years</td>
<td>HCB/HCH: NS WAZ birth to 6 months, NS BMIz</td>
<td>34</td>
</tr>
<tr>
<td>United States (Salinas Valley); n = 261 (♂♀)</td>
<td>Second-trimester serum (ng/g lipid)</td>
<td>9 years</td>
<td>HCH: NS overweight and obesity</td>
<td>38</td>
</tr>
<tr>
<td>Spain (Sabadell); n = 518 (♂♀)</td>
<td>First-trimester serum (ng/g lipid)</td>
<td>6 and 14 months</td>
<td>HCB, HCH: NS WAZ birth to 6 months, NS BMIz</td>
<td>35</td>
</tr>
<tr>
<td>Spain (Sabadell, Valencia, and Gipuzkoa); n = 1285 (♂♀)</td>
<td>First-trimester serum (ng/g lipid)</td>
<td>6 and 14 months</td>
<td>HCB: + WAZ 6–14 months RR = 1.13 (95% CI: 1.00, 1.29)</td>
<td>34</td>
</tr>
<tr>
<td>United States; n = 1915 (♂♀)</td>
<td>Third-trimester serum (µg/L)</td>
<td>7 years</td>
<td>Overweight 14 months RR = 1.19 (95% CI: 1.05, 1.34)</td>
<td>38</td>
</tr>
<tr>
<td>Belgium (Flanders); n = 114 (♂♀)</td>
<td>Cord blood (ng/g fat)</td>
<td>7–9 years</td>
<td>HCB: NS ♀♂</td>
<td>39</td>
</tr>
<tr>
<td>The Netherlands (Zwolle); n = 61 (♂♀)</td>
<td>Cord plasma (ng/L or ng/mL)</td>
<td>12 months</td>
<td>PFOS, PFOA: NS BMI</td>
<td>36</td>
</tr>
<tr>
<td>Great Britain (Avon); n = 320 (♀)</td>
<td>Pregnancy serum (10–28 weeks) (ng/mL)</td>
<td>20 months</td>
<td>PFOS; + [T3 (&gt;23.0 ng/mL) vs. T1 (&lt;16.6 ng/mL)] Weight (g) β = 579.82 (95% CI: 301.40, 858.25) PFOA: NS</td>
<td>45</td>
</tr>
<tr>
<td>Denmark; n = 811 (♂♀)</td>
<td>First- and second-trimester plasma (ng/mL)</td>
<td>7 years</td>
<td>PFOS, PFOA: NS BMI, WC, overweight</td>
<td>47</td>
</tr>
<tr>
<td>Greenland and Ukraine (Kharkiv); n = 1022 (♂♀)</td>
<td>Second-trimester serum (ng/mL)</td>
<td>5–9 years</td>
<td>PFOS, PFOA: NS overweight</td>
<td>48</td>
</tr>
</tbody>
</table>

Other POPs

- PFOS, PFOA: NS BMI
TABLE 19.1 (CONTINUED)
Prospective Studies of Associations between Early-Life Exposure to Toxicants and Childhood Obesity and Related Outcomes

<table>
<thead>
<tr>
<th>Study Setting</th>
<th>Exposure</th>
<th>Child Age at Follow-Up</th>
<th>Outcomea</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark (Aarhus); n = 665 (♀♂)</td>
<td>Third-trimester serum (µg/L)</td>
<td>20 years</td>
<td>PFOA in ♀, NS in ♂: [Q4 (4.8–19.9 µg/L) vs. Q1 (0.1–2.8 µg/L)] + BMI (kg/m²) β = 1.6 (95% CI: 0.6, 2.6) + WC (cm) β = 4.3 (95% CI: 1.4, 7.3) + Overweight RR = 3.1 (95% CI: 1.4, 6.9) + Insulin (mmol/L) β = 4.5 (95% CI: 1.8, 7.2) + Leptin (µg/L) β = 4.8 (95% CI: 0.5, 9.4) – Adiponectin (µg/L) β = –2.3 (95% CI: –4.5, –0.2)</td>
<td>46</td>
</tr>
<tr>
<td>United States (Salinas Valley); n = 224 (♀♂)</td>
<td>Second- and third-trimester serum (ng/g lipid)</td>
<td>7 years</td>
<td>Maternal PBDEs in ♀, NS in ♂: – BMIz β = –0.41 (95% CI: –0.87, –0.05)</td>
<td>49</td>
</tr>
<tr>
<td>Finland (Turku); n = 110 (♀)</td>
<td>Placenta (ng/g)</td>
<td>Birth, 3, and 18 months</td>
<td>TBT: + weight gain (kg/week) 0–3 months β = 0.024 (95% CI: 0.003, 0.044)</td>
<td>50</td>
</tr>
<tr>
<td>United States (New York); n = 324 (♀♂)</td>
<td>Third-trimester personal air (ng/m³)</td>
<td>5 and 7 years</td>
<td>PAHs: + [T3 (≥3.08 ng/m³) vs. T1 (&lt;1.73 ng/m³)] BMIz 5 years β = 0.39 (95% CI: 0.08, 0.70) Obesity 5 years RR = 1.79 (95% CI: 1.09, 2.96) BMIz 7 years β = 0.30 (95% CI: 0.01, 0.59) Percentage of body fat 7 years β = 1.93 (95% CI: 0.33, 3.54) Obesity 7 years RR = 2.26 (95% CI: 1.28, 4.00)</td>
<td>30</td>
</tr>
<tr>
<td>Nonpersistent Chemicals</td>
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<td>BPA</td>
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<tr>
<td>Spain (Sabadell); n = 402 (♀♂)</td>
<td>First- and third-trimester urine (µg/g creatinine)</td>
<td>6, 14 months, and 4 years</td>
<td>+ WCz 4 years β = 0.28 (95% CI: 0.01, 0.57) NS: change in WAZ, overweight – in ♀, NS in ♂: BMIz β = –0.47 (95% CI: –0.87, –0.07) Body fat (%) β = –4.36 (95% CI: –8.37, –0.34) Overweight and obesity OR = 0.38 (95% CI: 0.16, 0.91)</td>
<td>58</td>
</tr>
<tr>
<td>United States (Salinas Valley); n = 311 (♀♂)</td>
<td>First- and second-trimester urine (µg/L)</td>
<td>9 years</td>
<td></td>
<td>57</td>
</tr>
<tr>
<td>United States (Salinas Valley); n = 188 (♀♂)</td>
<td>First-, second-, and third-trimester urine (µg/g creatinine)</td>
<td>9 years</td>
<td>BPA during late pregnancy (first and second): + Leptin (ng/mL) in ♂ β = 0.06 (95% CI: 0.01, 0.11) BPA during early pregnancy (second and third): + Adiponectin (µg/mL) in ♀ β = 3.71 (95% CI: 0.38, 7.04)</td>
<td>33</td>
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<tr>
<td>Phthalates</td>
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<tr>
<td>The Netherlands (Zwolle); n = 61 (♀♂)</td>
<td>Cord plasma (ng/L or ng/mL)</td>
<td>12 months</td>
<td>High MEOHP: – in ♀, NS in ♂ BMI (kg/m²) p = .029</td>
<td>36</td>
</tr>
<tr>
<td>Spain (Sabadell); n = 391 (♀♂)</td>
<td>First- and third-trimester urine (µg/g creatinine)</td>
<td>Birth and 6 months; 1, 4, and 7 years</td>
<td>High-molecular-weight phthalate metabolites: – in ♀, NS in ♀ WAZ 0–6 months β = –0.41 (95% CI: –0.75, –0.06) BMI (kg/m²) 4 years β = –0.38 (95% CI: –0.76, –0.01) BMI 7 years β = –0.40 (95% CI: –0.78, –0.02)</td>
<td>60</td>
</tr>
<tr>
<td>United States (New York); n = 326 (♀♂)</td>
<td>Third-trimester urine (µg/g creatinine)</td>
<td>5 and 7 years</td>
<td>Non-DEHP: – in ♂, NS in ♀ BMIz β = –0.30 (95% CI: –0.50, –0.10) Body fat (%) β = –1.62 (95% CI: –2.91, –0.34) WC β = –2.02 (95% CI: –3.71, –0.32)</td>
<td>61</td>
</tr>
</tbody>
</table>

(Continued)
### TABLE 19.1 (CONTINUED)
Prospective Studies of Associations between Early-Life Exposure to Toxicants and Childhood Obesity and Related Outcomes

<table>
<thead>
<tr>
<th>Study Setting</th>
<th>n = mother–child pairs (Child Sex)</th>
<th>Exposure</th>
<th>Child Age at Follow-Up</th>
<th>Outcome&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heavy Metals</strong></td>
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<tr>
<td><strong>Lead</strong></td>
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<tr>
<td>Mexico (Mexico City); n = 329 (♂♀)</td>
<td>One month postpartum maternal bone (μg of lead/g of mineral bone) and infant blood (μg/dL)</td>
<td>Birth to 1 month</td>
<td>Maternal lead: – attained weight (g) 1 month ( \hat{\beta} = -3.69 ) (95% CI: –7.21, –0.16)</td>
<td>66</td>
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<tr>
<td></td>
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<td></td>
<td>Infancy lead: – weight gain (g) from birth to 1 month ( \hat{\beta} = -15.1 ) (95% CI: –28.3, –1.8)</td>
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<tr>
<td>United States (New York); n = 211 (♂♀)</td>
<td>Second-trimester and postnatal 6-month blood (μg/dL)</td>
<td>6 and 12 months</td>
<td>Second-trimester lead: Higher (≥3 μg/dL) vs. lower lead (&lt;3 μg/dL)</td>
<td>67</td>
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<td></td>
<td></td>
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<td>WAZ 6 months ( \hat{\beta} = -0.771 ) (( p = .03 ))</td>
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<td>UAZ 12 months ( \hat{\beta} = -1.063 ) (( p = .02 ))</td>
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<tr>
<td>South Korea; n = 247 (♂♀)</td>
<td>Early pregnancy (first and second trimester) and late-pregnancy (delivery) blood (μg/dL)</td>
<td>Birth, 6, 12, and 24 months</td>
<td>Late-pregnancy lead:</td>
<td>68</td>
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<tr>
<td></td>
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<td></td>
<td>WAZ 12 months ( \hat{\beta} = -0.31 ) (95% CI: –0.59, –0.04)</td>
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<td>WAZ 24 months ( \hat{\beta} = -0.41 ) (95% CI: –0.71, –0.11)</td>
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<td>Early-pregnancy lead: NS</td>
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<tr>
<td>Mexico (Mexico City); n = 171 (♂♀)</td>
<td>One month postpartum maternal bone (μg/g), average infancy (between birth and 24 months), and average early-childhood blood (30 and 48 months) (μg/dL)</td>
<td>2 years</td>
<td>NS BMI</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Mexico (Mexico City); n = 1000 (♂♀)</td>
<td>One month postpartum maternal bone (μg/g)</td>
<td>Birth to 5 years</td>
<td>– in ♀, NS in ♂: weight (g) 0 to 5 years ( \hat{\beta} = -130.9 ) (95% CI: –227.4, –34.4)</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Bangladesh (Matlab); n = 1505 (♂♀)</td>
<td>First- and third-trimester urine (μg/L)</td>
<td>Birth to 5 years</td>
<td>NS weight</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Yugoslavia (Kosovo); n = 309 (♂♀)</td>
<td>Pregnancy maternal blood (9–28 weeks) (μg/dL)</td>
<td>Birth to 10 years</td>
<td>NS BMI</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Mexico (Mexico City); n = 647 (♂♀)</td>
<td>Maternal bone (μg/g) and early-childhood blood (μg/dL)</td>
<td>7–15 years</td>
<td>Maternal bone lead in ♀. NS in ♂: – BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;) ( \hat{\beta} = -0.0368 ) (( p = .01 ))</td>
<td>71</td>
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<tr>
<td>Cadmium</td>
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<tr>
<td>Taiwan; n = 402 (♂♀)</td>
<td>Cord blood (μg/L)</td>
<td>Birth to 3 years</td>
<td>– Weight (kg) 0–3 years ( \hat{\beta} \times 100 = -1.81 ) (95% CI ([\times 100] = -3.01, -0.61))</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Bangladesh (Matlab); n = 1505 (♂♀)</td>
<td>First- and third-trimester urine (μg/L)</td>
<td>Birth to 5 years</td>
<td>NS weight</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Belgium (Flanders); n = 114 (♂♀)</td>
<td>Cord blood (μg/L)</td>
<td>7 to 8 years</td>
<td>– in ♀, NS in ♂: Weight (kg) ( \hat{\beta} ) (In-transformed) = 0.937 (95% CI: 0.900, 0.979)</td>
<td>39</td>
<td></td>
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<tr>
<td></td>
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<td>BMIz ( \hat{\beta} = -0.749 ) (95% CI: –1.261, –0.237)</td>
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<td></td>
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<td>WC (cm) ( \hat{\beta} ) (In-transformed) = 0.973 (95% CI: 0.953, 0.997)</td>
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<td></td>
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<td></td>
<td>Sum of four skin folds (mm) ( \hat{\beta} ) (In-transformed) = 0.728 (95% CI: 0.587, 0.900)</td>
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</tr>
</tbody>
</table>
Early Toxicant Exposures and the Development of Obesity in Childhood

An expansion of the original INMA-Sabadell cohort to a larger study population \( n = 1285 \) confirmed earlier findings that PCBs were unrelated to infant growth in this cohort [35]. A Dutch study among pregnant mothers from Zwolle, the Netherlands, also found no association between PCB 153 measured in cord blood and infant growth [36]. Two studies found no evidence that PCBs affect weight status in school-age children. A prospective cohort study [37] of maternal–child pairs from Greenland, Poland, and Ukraine found no clear associations between PCB exposure during pregnancy and children’s body mass index (BMI) at 5–9 years. This study was consistent with earlier findings [38] from the US Collaborative Perinatal Project (CPP) showing that high levels of total PCB exposures during the third trimester were not linked to overweight or obesity in children aged 7 years. Notably, PCB exposure levels were relatively high in the CPP population, since blood samples were collected before these toxic substances were phased out in the United States.

Counter to the preceding studies that failed to demonstrate a relationship between PCBs and obesity-related outcomes in infancy or at school entry, four prospective studies showed that prenatal PCB exposure may have different impacts on child growth by age and sex (Table 19.1). A pooled analysis of seven European birth cohorts [39], the largest study to date examining the obesogenic effects of POPs, found a negative association between postnatal exposure to PCBs and weight from birth to 24 months. In mid-childhood, however, positive associations of perinatal PCB exposures

### TABLE 19.1 (CONTINUED)

<table>
<thead>
<tr>
<th>Study Setting</th>
<th>Exposure</th>
<th>Child Age at Follow-Up</th>
<th>Outcome*</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other Metals</strong></td>
<td>First- and third-trimester and postnatal 18-month urine (μg/L)</td>
<td>Birth to 2 years</td>
<td>Postnatal arsenic: – in ♀, NS in ♂; [Q4 (46–96 μg/L) vs. Q1 (2.4–16 μg/L)] Weight (kg) 18 months ( \beta = -0.34 ) (95% CI: –0.52, –0.15)</td>
<td>73</td>
</tr>
<tr>
<td>Bangladesh (Matlab); ( n = 2087 ) (♀♂)</td>
<td></td>
<td></td>
<td>Weight (kg) 21 months ( \beta = -0.27 ) (95% CI: –0.47, –0.075)</td>
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<td></td>
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<td>Weight (kg) 24 months ( \beta = -0.22 ) (95% CI: –0.42, –0.014)</td>
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<tr>
<td></td>
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<td>Gestational arsenic: NS in ♀♂</td>
<td></td>
</tr>
<tr>
<td>South Korea; ( n = 164 ) (♀♂)</td>
<td>Early pregnancy (first and second), late pregnancy (third trimester), and cord blood (μg/L)</td>
<td>Birth to 2 years</td>
<td>Arsenic: NS weight</td>
<td>64</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Late-pregnancy mercury: – Attained weight (kg) until 2 years ( \beta = -0.186 ) ( (p = .05) )</td>
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<td>Cord blood mercury: – Attained weight (kg) until 2 years ( \beta = -0.359 ) ( (p = .01) )</td>
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<td></td>
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<td>Early-pregnancy mercury: NS</td>
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</tbody>
</table>

Abbreviations: BMI, body mass index; BMIz, BMI z-score for age and sex; WCz, waist circumference z-score; NS, nonsignificant statistical test of association; overweight defined as BMI ≥85th and <95th percentile for age and sex; obesity defined as children BMI ≥95th percentile for age and sex based on reference growth curves used by primary authors; OR, odds ratio; Q, quartile; RR, relative risk; T, tertile; WAZ, weight-for-age z-score for age and sex; WC, waist circumference in cm; WHR, waist-to-hip ratio; UAZ, upper-arm circumference-for-age z-score for age and sex; PCBs, polychlorinated biphenyls; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; TBT, tributyltin; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PBDEs, polybrominated diphenyl ethers; BPA, bisphenol A; MEQHP, mono-2-ethyl-5-oxohexyl phthalate; PAHs, polycyclic aromatic hydrocarbons.

* Change in outcome per 1-unit change in the exposure unless otherwise specified.

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with fat mass and distribution were documented in girls but not boys in three observational studies. In a Flemish cohort [40], PCB levels in cord blood were positively correlated with waist circumference (WC), an indirect measure of central fat distribution in girls aged 7–9 years, but cord blood PCB levels were unrelated to BMI in children in the sample. Maternal PCB levels in pregnancy of Faroese women similarly were related to higher WC in female children aged 7 years, but only those who had overweight mothers [41]. Additionally, these authors found a significant association between prenatal PCBs and a change of BMI in girls from 5 to 7 years of age as well as BMI at 7 years [41]. In the INMA-Sabadell cohort, the concentration of PCBs in cord blood positively predicted BMI and overweight in Spanish children aged 6.5 years, an association that appeared to be stronger in girls than in boys, in contrast to nonsignificant findings at earlier ages [25].

**Organochlorine Pesticides**

Of the 12 recent prospective studies of maternal exposure to DDE or DDT we reviewed, eight documented a statistically significant, positive association with child obesity–related outcomes across different developmental periods (Table 19.1). Among maternal–child dyads in the Spanish INMA-Sabadell cohort, in utero DDE exposure was related to rapid growth in the first 6 months of life and overweight at age 14 months [34,35]. In the same cohort, DDE concentrations in cord blood also were related to an increased risk of overweight at 6.5 years of age, but DDT was significantly associated with overweight only in boys, not girls [25]. Across seven pooled European birth cohorts, DDE levels in cord blood were associated with greater weight change from birth to 24 months of age, although this effect was not seen in infants with postnatal exposure via breast milk [39]. Studies conducted in Faroese and in Flemish children reported significant positive associations between prenatal DDE and BMI change from 5 to 7 years of age [41] and obesity-related outcomes at 7 years [40] in girls but not in boys, respectively. In contrast, reports from the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study found that prenatal DDT concentrations in second-trimester serum were related to increased WC, overweight, and obesity at 9 years of age only in boys [42]. However, these authors also documented a significant trend of increased odds of obesity across ages 2, 3.5, 5, and 7 years in boys and girls combined [43].

Despite a preponderance of evidence linking persistent organochlorine pesticides to offspring weight gain and status in US and European settings, four recent studies found no association of developmental exposure to DDE with infant or child obesity (Table 19.1). A study among 253 women in Morelos State, Mexico, suggested that maternal exposure to DDE during pregnancy may not affect infant growth [44]. Similarly, three prospective studies found no clear association between maternal exposure to DDE or DDT and growth in the first year of life among children in the Netherlands [36], or with BMI in Greenlandic, Polish, and Ukrainian children aged 5–9 years [37], or 7-year-old children in the United States. [38].

Few human studies have examined early-life exposures to HCB and HCH (Table 19.1). Of four epidemiological studies considering these perinatal exposures, three found no significant association between prenatal HCB and infant growth at 6 and 14 months [34], obesity in children aged 7 years [38], or obesity in children aged 7–9 years [40], respectively. No association with HCH was found in these three studies. Only one study reported HCB was positively associated with rapid growth and overweight in Spanish infants in the INMA-Sabadell cohort [35].

**Other POPs**

Other new POPs on the Stockholm Convention list, including PFOA, PFOS, PBDEs, TBT, and PAHs, have attracted attention because their potential to promote obesity has been suggested by several animal studies. We identified five human studies published since 2011 that evaluated the effects of PFOA and PFOS on offspring obesity (Table 19.1). British girls at 20 months of age with prenatal PFOS exposure in the upper tertile were 580 g heavier compared with those in the lower tertile,
but no differences in weight were found with PFOA [45]. In contrast, a Danish cohort study [46] of 665 pregnant women found that in utero exposure to PFOA was significantly associated with BMI, WC, and overweight among female offspring followed to early adulthood, as well as levels of insulin, adiponectin, and leptin, but no association was observed for PFOS [46]. One prospective study observed a null association of prenatal PFOA/PFOS with infant BMI at 12 months [36], and two reports found no association with overweight in school-age children [47,48]. In the single human study of developmental exposure to PBDEs and risk of obesity in the Salinas Valley, California, maternal PBDE serum levels during pregnancy were significantly related to decreased BMI in 7-year-old girls [49]. Despite the relatively extensive number of experimental studies of TBT described in Chapter 11 (Blumberg), we identified only one study exploring the possible obesogenic effect of TBT in humans. A Finnish cohort study reported that TBT levels in placental tissue were associated with the weight gain of male infants during the first 3 months of life, but no associations were observed at 3 or 18 months [50]. One study found that personal airborne PAHs during the third trimester were positively associated with BMI z-score and risk of obesity at 5 years and with BMI z-score, percentage of fat mass, and risk of obesity at 7 years of age among a sample of African American and Dominican children residing in New York City [30].

**SHORT-LIVED UBQUITOUS POLLUTANTS AND OBESITY**

In addition to persistent environmental chemicals, nonpersistent compounds such as bisphenol A (BPA) and phthalates have been related to human health. BPA has been used in a wide range of consumer products including can linings, packaging materials, and children’s toys. The major route of exposure is through the consumption of foods and beverages that have been contaminated with BPA [51]. Detectable levels of BPA in blood have been found in human fetuses [52]. BPA is considered an EDC that can regulate insulin and leptin production by exerting estrogenic activity, acting as agonist and antagonist of PPARγ [16]. Experimental data suggest that prenatal BPA promotes weight gain in offspring, but this association has not been extensively studied in humans using longitudinal studies. Similarly, phthalates [53] such as diethylhexyl phthalate (DEHP), oxidative DEHP, and metabolite mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP) are used in hundreds of consumer products, including plastics, cosmetics, and personal care products. Measurable levels of phthalate metabolites have been reported in the urine of pregnant women, in amniotic fluids, and in cord blood [53–55]. Growing experimental evidence has shown that phthalates are thyroid hormone and androgen antagonists and may affect adipogenesis, lipid accumulation, and insulin resistance by regulating activation of PPARγ [56].

Nonpersistent compounds such as phthalates and BPA have been related to pediatric obesity in experimental studies, but human data are insufficient to support such a relationship [16]. The three prospective studies published between 2011 and 2015 that examined the effects of urinary BPA levels during pregnancy on postnatal growth and obesity reported inconsistent results. In the Spanish population participating in the INMA-Sabadell study, prenatal BPA was weakly associated with increased WC in 4-year-old children but not at earlier ages [57]. In the CHAMACOS cohort, maternal urinary BPA concentrations during pregnancy were inversely associated with BMI, percentage of body fat, and obesity in 9-year-old Mexican American girls, but these effects were not yet evident at 5 years [58]. In the same population, BPA exposure during late pregnancy was related to increased leptin in boys, whereas BPA in early pregnancy was associated with increased adiponectin in girls at 9 years of age [33]. Although the mechanistic pathways for sex-specific effects seen in these studies are not fully understood, one potential explanation is that BPA may affect estrogen activity by interrupting original binding at nuclear estrogen receptors. The synthesis and function of estrogen as well as the distribution of estrogen receptors vary in males and females [59]. Previous studies of associations between prenatal phthalate exposure and obesity among children are limited to a few cross-sectional reports. A recent prospective study in a small Danish sample (n = 61) reported that higher MEOHP in cord blood was related to lower BMI in male offspring from birth to 11 months [36].
Similar results were seen in a prospective study of high-molecular-weight phthalate metabolites and postnatal growth in the Spanish INMA-Sabadell birth cohort; pregnancy urinary levels were associated with reduced weight gain in the first 6 months of life and lower BMI at 4–7 years in boys [60]. In addition, one study conducted in New York City among 326 African American and Dominican mothers revealed a significant inverse association of third-trimester phthalates with BMI z-score, percentage of body fat, and WC in boys at 5 and 7 years old [61].

**HEAVY METALS AND OBESITY**

Other than synthetic industrial substances, heavy metals have also been proposed to exert obesogenic effects [2,16]. Although the underlying mechanism remains uncertain, heavy metals such as lead, cadmium, arsenic, and mercury have been found to exhibit endocrine-disrupting features in animal studies [62]. For example, lead may disrupt endocrine functions through its impact on estrogen metabolism, which leads to altered insulin-like growth factor 1 (IGF-1) levels and subsequent body growth [63]. Since the level of estrogen varies by sex, the effects of lead on child growth may have been more pronounced in girls than in boys. Similarly, cadmium, arsenic, and mercury have also been indicated to exert endocrine-disrupting properties and affect children's growth in a sex-dependent manner [62,64]. Evidence in both animal and human studies supports the hypothesis that cadmium and mercury interrupt steroidogenesis in the placenta and affect estradiol functions [62,65]. With regard to arsenic, it has been suggested to disrupt insulin signaling and glucose uptake by tissues, resulting in impaired growth [62,64].

Most studies of early exposure to heavy metals in relation to obesity have focused on the toxic effects of endocrine-disrupting metals on birth outcomes, whereas research to determine the persistence of these effects into childhood is limited and current evidence is inconsistent. Among these four toxicants, the influence of lead on child obesity has been the most extensively studied. We identified eight longitudinal studies that evaluated the toxicity of lead exposure during early life on anthropometry in children (Table 19.1). In the Early-Life Exposure in Mexico to Environmental Toxicants (ELEMENT) birth cohort, maternal bone lead at 1 month postpartum, a measure of cumulative in utero exposure, was significantly and negatively associated with attained weight at 1 month of life, and infant blood lead with weight gain from birth to 1 month of age [66]. A longitudinal study performed in Albany, New York [67], also revealed an inverse association of higher blood lead levels (≥3 μg/dL) during pregnancy with postnatal weight-for-age z-scores at 6 months and upper-arm circumference-for-age z-scores at 12 months, whereas postnatal exposure to lead at 6 months was not significantly related to infant growth. Another investigation confirmed that blood lead level at delivery but not early pregnancy (first and second trimester) negatively predicted infant weight from 12 to 24 months among participants from the Mothers and Children's Environmental Health (MOCEH) birth cohort in South Korea, and this influence was more pronounced in pregnant women with lower levels of calcium intake (<541 mg/d) [68]. To examine the persistence of these effects into preschool years, a follow-up study of 522 boys and 477 girls in the Mexico City ELEMENT cohorts found that maternal bone lead at 1 month postpartum was related to a reduced weight trajectory among female participants from birth to 5 years of age [63]. However, these authors did not observe associations of prenatal or early postnatal lead exposure with BMI at 48 months of age using the same cohort [69]. In contrast, a prospective cohort study of 1505 mother–offspring pairs living in rural Bangladesh provided evidence that pregnancy urinary lead levels were not significantly associated with child weight at age 5 [64]. Two studies considered the effects of early lead exposure on obesity-related outcomes in school-age children. A cohort study in 309 mother–offspring pairs from Kosovo, Yugoslavia, reported that gestational lead exposure was not correlated with children's BMI up to 10 years of age [70]. However, another study using the ELEMENT cohort provided evidence that maternal patella lead but not early childhood blood lead was associated with reduced BMI in 267 Mexican girls at 7–15 years of age but not in 290 boys [71].
Three prospective studies that examined the influence of early-life cadmium on child growth and obesity-related outcomes reported equivocal results. A prospective Taiwanese study reported that cadmium cord blood concentrations were negatively associated with children's weight up to 3 years of age [72]. In the Flemish population, prenatal cadmium exposure was found to be associated with reduced weight, WC, BMI z-score, and skinfolds only in girls aged 7–8 years [40]. In contrast, a study in the Matlab cohort in rural Bangladesh indicated a null association of maternal cadmium level in urine during the first and third trimesters with body weight in 5-year-old children [64,73]. Arsenic and mercury are the least documented toxic metals in terms of obesogenic effects. In the Matlab cohort, postnatal exposure to arsenic at 18 months negatively predicted child weight from 1.5 to 2 years of age in girls but not boys, whereas this effect was not observed with in utero arsenic exposure [73]. Maternal arsenic also was unrelated to body weight in these Bangladeshi children in the first 5 years of life [64]. A study in the South Korean MOCEH birth cohort revealed an inverse relationship between maternal blood mercury concentrations during late pregnancy and cord blood with attained weight over the first 24 months of life, whereas no significant association was found for early pregnancy exposure [74].

**CONCLUSIONS**

The 35 studies discussed in this chapter reveal inconsistent conclusions about the obesogenic effects of early-life exposure to environmental toxicants that may be attributable to differences in the study population, chemical congeners, levels of exposure, time windows for outcomes, and measured and unmeasured confounders. Most longitudinal human studies on the effects of early-life exposure to synthetic chemicals on overweight or obesity in childhood have focused on the prenatal period, whereas few have examined exposure via breast-feeding or early childhood or a combination. Rapid growth, overweight, and obesity among children were primarily assessed using indirect measures of adiposity such as weight gain, BMI, and WC, whereas direct measures were less commonly employed—for example, skinfolds, bioimpedance, dual-energy x-ray absorptiometry, or adipokines. Most current epidemiological data consider the influence of these chemicals on overweight and obesity during infancy and early childhood up to 9 years of age, but few studies examine the persistence of obesity in adolescence and adulthood due to the challenges of long-term follow-up. Of the reports we reviewed, the majority focused on understanding the toxic effects of DDE, PCBs, and lead, while investigations of other environmental toxicants were scarce, particularly for PBDEs, organotin compounds, PAHs, and nonpersistent chemicals, as well as other heavy metals. Overall, we found continued support for the predominantly positive effect of maternal DDE on increased risk of child obesity and less consistent associations for other substances. Several studies were limited by relatively small-to-modest sample sizes, whereas those with large sample sizes were constrained by heterogeneity across pooled populations, which could contribute to imprecision. Some longitudinal investigations also reported a substantial loss of participants during the follow-up time, which could bias findings across different developmental periods. Many authors modeled relationships with categorical measures of exposure, which may reduce statistical power, although categorical measures could reveal nonlinear or nonmonotonic relationships that could be explored in studies with larger sample sizes [14]. Among the strengths of the 35 papers reviewed here was that they all utilized a prospective, longitudinal design that can enhance causal inference. A few studies used advanced modeling for estimating postnatal exposure and measured levels of adipokines and skinfolds to assess adiposity.

Further research in larger study populations and various settings worldwide is needed to confirm the observed associations, especially for less-studied chemicals, and to evaluate potential underlying mechanisms. Studies with longer follow-up time to ascertain the persistence of compounds’ effects into later ages and developmental periods, including the transition to young adulthood, should be considered a priority for future investigations. Research with complete information about both maternal prenatal and postnatal exposure and that utilizes direct measures of adiposity
is recommended. Considering that many studies report inconsistent results regarding differential effects on boys and girls, the systematic evaluation of interaction by sex is needed. Other factors that appear to serve as effect modifiers of chemical exposures, such as maternal weight status and intake of fat, minerals such as calcium and zinc, and other micronutrients that affect their bioavailability, also require confirmation in larger studies. In addition, birth weight deserves special attention as it shows divergent functions in different analyses as a confounder or as an intermediate variable. Lastly, studies of mixtures of chemicals should be taken into consideration, given that humans have detectable levels of various obesogenic compounds and toxicants may have opposing effects on obesity-related outcomes in male and female offspring at different ages.

In conclusion, studies on the risk of obesity in relation to environmental toxicant exposures during early life provide suggestive evidence for some but not all chemicals, and many uncertainties require further exploration. With prospective study designs, large sample sizes, improved exposure assessments, direct measures of obesity, and advanced statistical analyses, data generated from these studies can contribute to a strong evidence base for recommendations and strategies to prevent pediatric obesity and its long-term sequelae.

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Early Toxicant Exposures and the Development of Obesity in Childhood


Impact of Environmental Obesogens

Focus on Mechanisms Linking to Childhood Obesity

Bassem M. Shoucri and Bruce Blumberg

THE OBESITY EPIDEMIC: BEYOND DIET AND EXERCISE

Although the prevailing paradigm of obesity remains one of energy intake versus energy expenditure, the abrupt rise in global childhood obesity rates has led researchers to explore alternative contributors. While genetics undoubtedly bestow some obesity risk, the handful of genetic loci associated with obesity in human studies account for <2% of variance in body weight [1], as reviewed in Chapter 13. This observation is not surprising given the abrupt time line of the obesity epidemic. Beyond excess caloric intake and sedentarism, well-studied environmental risk factors for obesity include stress, smoking, sleep patterns, and the microbiome, as reviewed in other chapters in this book. In this chapter, we will discuss mounting evidence implicating developmental exposure to xenobiotic compounds as a hitherto underinvestigated contributor to the global obesity epidemic [2]. This chapter complements Chapter 19, with a focus on understanding the potential mechanisms that might link obesogens to obesity development.

ENVIRONMENTAL CHEMICALS AND OBESITY

A study setting out to examine the potential effects of the environment on obesity observed over 20,000 animals, representing 12 distinct populations and 8 different species, living in proximity to...
industrialized societies [3]. These animals included pets (cats and dogs), laboratory animals (mice, rats, and primates) that were fed controlled diets, and feral rats. Notably, nearly every one of these populations showed positive trends in both weight gain and odds of obesity over the past several decades. The chance of these populations all concomitantly exhibiting the same trend in obesity was calculated as approximately 1 in 10 million [3]. These data strongly suggest that an environmental insult, independent of diet and exercise, is responsible for the parallel trend in obesity in humans and animals.

The use of synthetic chemicals in commerce has grown exponentially since the 1940s, numbering in the tens of thousands today [4]. Of particular concern is a subset of nearly 3000 chemicals, termed endocrine disrupting chemicals (EDCs), that interfere with any aspect of hormone action [5,6]. The “endocrine” label can be misleading as EDCs can perturb the action of any chemical messenger, endocrine or otherwise (autocrine, paracrine, neurotransmitter). EDCs can alter hormone synthesis and transport, or they can interfere with the cell signaling and receptor systems that regulate hormone response in target tissues. Since hormones play critical roles in development and metabolism, investigators suspect that EDCs might interfere with hormonal systems to promote weight gain and ultimately obesity [7].

THE OBESOGEN HYPOTHESIS

In 2006, our group proposed the obesogen hypothesis, which asserts that there are EDCs in the environment that confer obesity risk on exposed individuals, principally those exposed during critical windows of development [8]. These “obesogens” promote adiposity through a variety of mechanisms that include

- Disturbing normal fat development, thereby increasing the number of fat cells
- Encouraging the storage of energy within fat cells, increasing fat cell size
- Altering metabolic set points programed during development
- Interfering with neurologic and hormonal control of hedonic reward and appetite

A number of obesogens have been identified in humans and animals and the list continues to lengthen. Obesogens identified in animal studies include estrogenic chemicals (such as diethylstilbestrol [DES] [9], genistein [10], Bisphenol A [BPA] [11], and nonylphenol [12]); organotins, such as tributyltin (TBT) [13]; organochlorine pesticides (including polychlorinated biphenyls [PCBs] [14], dichlorodiphenyltrichloroethane [DDT] [15], triflumizole [16], and tolylfluorid [17]); organophosphates (such as chlordipyrifos [18] and diaizinon [19]); brominated [20] and nonbro-minated flame retardants [21] and a number of other chemicals including nicotine [22], benzo[a]pyrene [23], phthalates [24]; and perfluorooctanoic acid (PFOA) [25]. In humans, urinary phthalates are associated with waist circumference and insulin resistance in adults [26] and in children and adolescents [27,28]. Likewise, multiple studies of US [29–31] and Chinese [32] children associate urine BPA levels with obesity prevalence. Urinary phenol pesticides are correlated with obesity in adolescents [33]. Serum levels of several persistent organic pollutants (POPs), including dichlorodiphenyltrichloroethylene (DDE, a metabolite of DDT), PCBs, hexachlorobenzene (HCB), and β-hexachlorocyclohexane (β-HCH), are associated with BMI in adults [34]. Prenatal exposure to PCBs [35], DDE [36], and HCB [37] are associated with obesity later in life. Chapter 19 provides a detailed overview of the findings from human cohort studies that have examined the effects of these obesogens on obesity development.

In addition to these environmental exposures, there is a wide range of obesogenic pharmaceuticals for which weight gain is an established side effect. These include first- and second-generation anti-psychotics [38], selective serotonin-reuptake inhibitors (SSRIs) [39], systemic glucocorticoids [40], and the antidiabetic thiazolidinediones (rosi-, pio-, and troglitazone) [41]. If clinicians have already accepted weight gain as an established side effect of these medications, then it is not unreasonable
to infer that exposure to physiologically relevant doses of nonpharmaceutical xenobiotic compounds (such as EDCs) could have the same effect.

**DEVELOPMENTAL OBESEGEN EXPOSURE**

Applying the developmental origins of health and disease (DOHaD) model to the obesogen hypothesis requires monitoring of early-life EDC exposure during sensitive developmental windows together with subsequent observation of obesity and metabolic disease throughout life. Given the relatively recent establishment of the DOHaD and EDC fields, such studies are limited in number and by low sample size and lack of long-term follow-up. The strongest epidemiological evidence of an environmental obesogen programing obesity risk in utero is maternal smoking. It is well established that the children of smoking mothers are born small-for-gestational-age; however, these children experience catch-up growth in the first year of life and eventually outpace their peers. Tens of epidemiological studies have all shown an increased overweight/obesity risk in children whose mothers smoked during pregnancy [42].

A number of studies have evaluated perinatal exposure to POPs, which have long half-lives and persist in the environment despite significant regulation and outright bans on many (reviewed in Chapter 19). Taken together, these studies indicate that POPs may affect intrauterine and postnatal growth to increase risk of obesity later in childhood [43–46]. The continued follow up of ongoing cohorts will be informative in addition to new, well-designed prospective studies of precise exposure windows that track obesity and metabolic health into adulthood. It must also be accepted that human studies will always be limited by overall numbers together with confounding and interacting variables. Therefore, these should be supplemented with cell culture and animal studies that can provide a controlled environment to carry out exposures and study them mechanistically.

**DEVELOPMENT OF FAT**

One facet of the obesogen hypothesis that has received ample attention is the notion that EDCs can promote the excessive development of fat tissue. Adipocytes appear during the second trimester of pregnancy and proliferate through childhood and adolescence before leveling off at approximately 10% renewal per year in adulthood [47]. This phenomenon is independent of BMI, as weight gain/loss in adults is predominantly attributed to changes in cell size rather than cell number [47]. Visceral fat, which is linked to insulin resistance, may be the exception to this rule. In humans, visceral depot size is determined by cell number [48], and adult mice fed a high-fat diet generate new fat cells in visceral depots [49]. Therefore, adipogenic stimuli (such as an obesogen) during gestation and early life establish the number of fat cells in an individual, while fat mass in adults is regulated both by cell number and cell size in a depot-specific manner.

Adipocytes originate from the mesodermal lineage via the mesenchymal stem cell (MSC or multipotent stromal cell), a multipotent cell capable of forming bone, muscle, cartilage, tendon, fat, and other tissues. MSCs and their lineage-restricted derivatives can be found in the perivascular niche of any vascularized organ, including adipose tissue [50]. Transformation of an MSC into a mature adipocyte requires initial commitment to the adipose lineage, followed by terminal differentiation into a functioning fat cell [51]. Adipose lineage commitment requires the concerted action of multiple signaling cascades regulated by adipogenic transcription factors that induce the expression of the peroxisome proliferator–activated receptor gamma (PPARγ), the “master regulator” of adipogenesis [52]. PPARγ, a member of the nuclear receptor family, is a ligand-activated, DNA-binding transcription factor that dimerizes with the retinoid X receptor (RXR) to bind and regulate genomic targets that promote adipose differentiation [53]. Both MSCs and mouse 3T3-L1 cells (a committed preadipocyte cell line) have become valuable in vitro tools for screening candidate obesogens and characterizing their mechanisms of action.
TRIBUTYL Tin: A Model Obesogen

We and others first showed that the TBT binds and activates both PPARγ and its heterodimeric partner, RXR, to promote adipogenesis and alter lipid homeostasis [13,54]. Human and mouse MSCs, as well as mouse 3T3–L1 preadipocytes exposed to environmentally relevant levels (nanomolar) of TBT, or the pharmaceutical PPARγ agonist rosiglitazone, were shunted toward the adipocyte lineage via a PPARγ-dependent pathway [55,56]. Mice exposed to TBT, in utero, showed lipid accumulation in adipose depots, livers, and testes, and have MSCs biased toward the adipocyte lineage and away from the bone lineage [13,56,57]. Treatment of adult mice or rats with TBT resulted in obesity and fatty liver [58,59], as well as disrupted thyroid function [60].

Beyond concerns over organotin exposure, there is an expanding group of obesogens to which humans are exposed that also activate PPARγ. These include phthalates [61]; triflumizole [16]; flavanones [62,63]; bixin [64]; diocetyl sodium sulfosuccinate (DOSS), a component of the oil dispersant COREXIT [65]; and several flame-retardants including the polybrominated diphenyl ether (PBDE) BDE-47 [66], tetrabromo- and tetrachloro-BPA (TBBPA, TCBPA) [67], and triphenyl phosphate (TPP), a component of the flame-retardant Firemaster® 550 (FM550) [68].

Phthalates are widely used as plasticizers and solubilizing agents and are commonly found in personal-care products, medications, and medical equipment. Phthalates and their metabolites can be detected in the urine of nearly all humans [69], including infants [70]. These chemicals promote adipose differentiation of 3T3-L1 cells [71] and they stimulate adipogenesis and suppress osteogenesis in mouse MSCs [72]. Several in vivo studies show that prenatal phthalate exposure promotes obesity in adult mice [24,73]. In addition to activation of PPARγ, phthalates may program obesity risk through their effects on PPARα or PPARδ, thyroid metabolism, or gestational growth [74]. Urinary phthalates are associated with obesity and insulin resistance in children, adolescents, and adults [26–28,75]. Studies of prenatal phthalate exposure that examine obesity as a primary outcome are sparse, though one study of African American and Dominican mothers in New York showed a negative correlation between third trimester urine phthalates and BMI of the offspring at 5 and 7 years [76].

For a half century, brominated chemicals, such as PBDEs and hexabromocyclododecane (HBCD), have been used as flame-retardants in a variety of products [77]. Due to safety concerns, several PBDEs were phased out of U.S. production in 2005, though these chemicals linger in products and migrate into house dust, a major source of human exposure [77]. BDE-47 induces adipogenesis in 3T3-L1 cells [78], in part due to a weak activation of PPARγ [66]. A recent screen of flame-retardants and their metabolites revealed that 3-hydroxy-BDE-47 activates PPARγ with the same potency as the pharmaceutical rosiglitazone [79]. TBBPA and TCBPA have not been phased out and are still widely used. Recently, these halogenated bisphenols were identified as PPARγ agonists that stimulate differentiation of 3T3-L1 preadipocytes [67,79]. The phase out of PBDEs increased demand for alternative flame-retardants such as the organophosphate-based FM550. Perinatal FM550 exposure results in varied phenotypes in rat offspring including obesity, advanced puberty, cardiac hypertrophy, and anxiety [21]. In a subsequent study, FM550 was shown to be a PPARγ activator along with TPP, a triaryl phosphate that comprises 10%–20% of FM550 [68]. FM550 and TPP were further shown to increase adipogenesis and inhibit osteogenic differentiation of mouse MSCs [80].

PFOA is a persistent fluorochemical with hundreds of industrial applications that is found in the serum of most humans living in the United States [81]. PFOA purportedly activates PPARγ [82], though this assertion is controversial [83], and PFOA does not induce adipogenesis in 3T3-L1 preadipocytes [78]. However, in utero exposure to low-dose PFOA results in increased body weight and elevated serum insulin and leptin in postpubertal female mice [25]. These animal data were mirrored in a prospective study of 665 Danish pregnant mothers whose gestational PFOA exposure was associated with the BMI of female, but not male, offspring at 20 years of age [84]. Another Danish cohort showed no such associations [85].
Taken together, these results indicate a continued need to screen for industrial chemicals that can activate PPARγ, since there is sufficient evidence in cells, animals, and humans to believe these compounds will act as obesogens, in vivo.

ESTROGENIC OBESOGENS

Estrogens are protective against obesity and cardiovascular disease in adults, as is well demonstrated by the onset of abdominal obesity and dyslipidemia following the loss of estrogen at menopause. Emerging research, however, implicates early-life exposure to low-dose estrogens to be obesogenic. Prenatal exposure to the estrogenic EDCs, DES, genistein, and BPA results in obese adult animals [86], and urine BPA is associated with obesity prevalence in children [29,30,32]. DDT and its metabolite DDE are estrogenic and antiandrogenic, respectively, and have been implicated as obesogens in humans and animals [15,36].

DES is a synthetic estrogen that was widely prescribed to pregnant women in the mid-twentieth century to prevent miscarriage. Though mothers were unaffected, among the millions of children born to DES-treated mothers, there was a well-documented increase in several rare pathologies of the reproductive tract. Data from the National Cancer Institute’s DES Follow-Up Study showed a modest increase in obesity risk among females prenatally exposed to DES, and this risk was higher in those exposed to lower doses [87]. Mice exposed to low doses of DES prenatally become obese later in life, while high-dose exposure resulted in decreased birth weight followed by catch-up growth and subsequent obesity [88]. Similar results were observed in mice exposed postnatally, during the first 5 days of life [86,89]. Importantly, these results were recapitulated with other estrogens (2- and 4-hydroxyestradiol), suggesting an estrogen-dependent mechanism [9].

Of all the data on estrogenic EDCs, data implicating BPA as a potent obesogen are most concerning. BPA, used in polycarbonate plastics and epoxy resins, is produced in millions of tons annually and can be detected in most humans [11,69]. BPA is a potent activator of the estrogen receptor (ER) in the nucleus and also at the cell membrane where it induces rapid cell signaling events [90]. BPA promotes differentiation of 3T3-L1 preadipocytes [91] and human preadipocytes via an ER-dependent mechanism [92]. Low-dose prenatal BPA exposure in animals results in increased body weight in adult life [93]. Perinatal BPA exposure results in increased visceral fat depot size in females at weaning, as well as adipocyte hypertrophy and increased expression of adipogenic and lipogenic genes [94]. Both Trasande et al. and Bhandari et al. have shown a correlation between urinary BPA and obesity prevalence in US children from the National Health and Nutrition Examination Survey (NHANES) [27,29], results echoed in a Chinese cohort [32]. Despite these extensive data (and data implicating BPA in numerous other pathologies), regulatory agencies do not believe levels of BPA exposure are sufficient to result in adverse outcomes, and production of the high-volume chemical continues.

OTHER OBESOGENS AND THEIR MECHANISMS OF ACTION

Much attention has been paid to the ability of obesogens to act as hormone mimics that can bind nuclear receptors. Numerous EDCs have been shown to bind PPARγ and ER, though other nuclear receptors are known to be obesogen targets. BPA, whose obesogenic effects are largely attributed to its ability to bind and activate ER, is also an activator of the steroid and xenobiotic receptor (SXR) [95], the glucocorticoid receptor (GR) [96], and an antagonist of the androgen receptor (AR) [97]. Likewise, phthalates activate all three PPAR receptors (α, δ, γ) [71,98] as well as SXR [98]. The obesogenic effects of PCB 77 were shown to be dependent on the activation of the aryl hydrocarbon receptor (AhR) both in vitro and in vivo [14]. Tolyfluanid, a fungicide commonly used in Europe, promotes adipose differentiation of 3T3-L1 cells through activation of the GR [99], and mice fed a diet supplemented with tolyfluanid gain more weight and fat mass than
controls [17]. Hence, obesogens can act through several members of the nuclear receptor family, at times simultaneously, to promote obesity.

Not all obesogens are nuclear receptor ligands, and obesogens that do activate nuclear receptors may also act through alternative pathways. For example, TBT, BPA, and phthalates, all of which activate nuclear receptors, also inhibit the enzyme 11β-hydroxysteroid dehydrogenase, a critical regulator of active/inactive intracellular glucocorticoid levels [100]. TBT is further known to inhibit aromatase [101] and isocitrate dehydrogenase [102]. Prenatal exposure to nicotine results in obesity and metabolic complications [22,103], presumably through its action on nicotinic acetylcholine receptors (nAChRs), plasma membrane–associated ion channels present in the brain, hypothalamus, adrenal medulla, and other organs [104]. The pharmaceutical obesogen lithium, which has diverse mechanisms of action, promotes weight gain through increased appetite, hypothyroidism, and even a combination of thirst and improved mood that leads to the consumption of high-calorie beverages [105]. Therefore, obesogens can act through varied nuclear receptor–independent mechanisms to promote weight gain.

EPIGENETICS AND THE ENVIRONMENT

A central tenet of the DOHaD hypothesis is the notion of “developmental plasticity,” whereby the developing fetus adapts to environmental stimuli, permanently altering phenotypic expression [106]. While these adaptations may benefit the fetus in the short term, they may confer disease risk later in life within a different environmental context [107]. The definitive example of this concept is the “thrifty phenotype” seen in the offspring of malnourished mothers. These children are programmed to survive in a food-scarce environment, but when faced with caloric excess in adult life these adaptations increase the risk for cardiometabolic diseases [108]. Crucially, the genotype of these individuals remains unchanged, though environmental inputs during development have permanently altered their phenotype. That is, there are changes in gene expression during development without any alteration of DNA sequence. Of the mechanisms thought to be responsible for such a phenomenon, epigenetics is the most widely accepted, and its role in childhood obesity is discussed in detail in Chapter 14.

Epigenetics is the study of heritable changes in phenotype that are not the result of altered DNA sequence, but rather environmentally influenced modifications of the genome. These modifications include methylation and/or hydroxymethylation of DNA at cytosine residues of 5’ to guanine (CpG sites), chemical modifications of the histone proteins that package DNA into chromatin, and expression of noncoding RNAs. Epigenetic marks can alter chromatin accessibility by encouraging or disrupting transcription factor/cofactor binding to regulatory elements and recruiting silenced complexes to the genome. In mammalian development there are two major epigenetic reprogramming events during which there is a genome-wide erasure of DNA methylation marks and subsequent remethylation [109]. The first reprogramming occurs in the preimplantation embryo and the second in the developing primordial germ cells. This process plays a critical role in regulating the potency of developing cell populations from pluripotency through lineage commitment and eventual terminal differentiation [110].

There is ample evidence that environmental inputs during development can alter the epigenetic landscape to alter gene expression, development, and phenotype [111,112]. A classic model of this phenomenon is the viable yellow agouti (A⁺⁺) mouse described in Chapter 14. Studies in wild-type animals have explored the effects of maternal and paternal nutrition on the epigenetic landscape and phenotype of the offspring [113]. The progeny of rat dams fed a low-protein diet had livers with promoter hypomethylation and increased expression of PPARα (Ppara) and the GR (NR3C1) [114], later attributed to a reduction in DNA methyltransferase 1 (DNMT1) expression [115]. Maternal protein restriction in mice resulted in fetal livers with promoter hypermethylation and underexpression of the liver X receptor alpha gene (LXR-alpha) in addition to several of its target genes [116]. Maternal high-fat diet altered the feeding behavior of the
offspring via altered methylation and expression of genes in the dopamine and opioid pathways within areas of the brain associated with reward [117]. Interestingly, a paternal high-fat diet resulted in glucose intolerance and pancreatic \( \beta \)-cell dysfunction in female offspring, as well as hypomethylation and upregulation of a member of the JAK-STAT signaling pathway in pancreatic islets [118]. This study suggests that the phenotype seen in female offspring is due to high fat diet–induced epigenetic modifications of the paternal germ line. Recent work furthered this notion using a fly model, where as little as 2 days of paternal dietary intervention prior to mating resulted in obese progeny [119]. The authors went on to show this phenotype was passed through the male germ line via modifications of histone marks passed on from sperm to developing embryos [119].

Humans exposed to famine early, but not late, in gestation have a slight hypomethylation of the maternally imprinted insulin-like growth factor 2 gene (IGF2), as compared with their unexposed, same-gender siblings at 60 years of age [120]. Strikingly, the degree of methylation of a single CpG residue associated with the RXA alpha (RXRA) gene in an umbilical cord at birth predicts adiposity of the offspring at 9 years of age [121]. An ensuing study showed that hypermethylation of 4 CpGs in a differentially methylated region (DMR) upstream of RXRA was inversely associated with bone mineral density of offspring at 4 years [122]. Finally, recent data show that obesity is associated with altered small noncoding RNA expression and DNA methylation of sperm, though further studies are needed to assess whether and how these alterations of the germ line are manifested in offspring [123].

### EPIGENETICS AND EDCS

Substantial research shows that developmental exposure to EDCs alters the epigenome. Maternal exposure of agouti (A\(^{vy}\)) mice to BPA [124] or the phytoestrogen genistein [125] results in hypo- or hyperretrotransposon methylation, respectively, and a corresponding obese or lean phenotype in the offspring. Wild-type mice exposed to DES [126] or BPA [127] \textit{in utero} have increased uterine expression and altered methylation of the Homeobox A10 gene (HOXA10), which plays critical roles in uterine development and the maintenance of mature endometrium. Rats treated postnatally with PCBs have diminished global liver DNA methylation and decreased hepatic expression of DNA methyltransferases (DNMTs) [128]. Prenatal PCB exposure in rats induces liver expression of histone-modifying enzymes that subsequently reduce the transcriptional activating histone marks H3K4me3 and H4K16ac [129]. Perinatal BPA exposure results in hepatocellular damage in adult male rats and decreased hepatic expression of the \( \beta \)-oxidative gene carnitine palmitoyltransferase 1a (CPT1a) at birth, attributed to altered DNA methylation, transcription factor binding, and histone modification of CPT1a [130]. Hence, perinatal exposure to EDCs can permanently alter the development and function of varied tissues at least in part through stable alterations of the epigenome.

Adipogenesis is also regulated by epigenetic mechanisms that respond to environmental influences [131,132]. 3T3-L1 preadipocytes treated with a panel of EDCs, including TBT and BPA, experienced global changes in DNA methylation during adipose differentiation [78]. Bone marrow MSCs from mice treated with dexamethasone favor an adipose fate over bone due to reduced promoter methylation of the proadipogenic gene CCAAT/enhancer binding protein alpha (CEBPA) [133]. Mice prenatally exposed to TBT have MSCs biased toward the adipose lineage and a hypomethylated promoter region of the PPAR\(\gamma\) target gene, fatty acid binding protein 4 (FABP4) [56]. Postnatal genistein exposure resulted in increased fat mass in female rats and diminished adipose expression and hypermethylation of wingless-type MMTV integration site 10B (WNT-10B), a regulator of adipose lineage commitment [134]. Finally, prenatal exposure to polycyclic aromatic hydrocarbon (PAH) increased weight and fat mass of the offspring and adipose expression of PPAR\(\gamma\), which correlated with promoter methylation of a single CpG site [135]. The ability of EDCs to epigenetically reprogram the MSC compartment to favor the fat lineage is an emerging and exciting area of research.
ENVIRONMENTAL EXPOSURES CAN HAVE TRANSGENERATIONAL CONSEQUENCES

Of great concern is accumulating evidence linking developmental EDC exposure to disease risk not only in offspring, but also in multiple generations of unexposed descendants. Skinner and colleagues showed that high-dose exposure of pregnant F0 rats to the fungicide vinclozolin caused reproductive abnormalities in male rats through four generations (F1–F4) [136]. While the F1 fetus and F2 primordial germ cells were exposed to vinclozolin in utero, the F3 and F4 generations received no direct exposure and hence their phenotype is considered transgenerational. This study went on to show that the F3 and F4 phenotype was due to heritable epigenetic alterations of the male germ line [136]. Similar adverse effects on male reproductive health were demonstrated in F1–F3 male descendants of rodents exposed to BPA [137] and phthalates [138]. Our group first showed that developmental EDC exposure could result in a transgenerational obesity phenotype [57]. The F1, F2, and F3 progeny of F0 mothers exposed to environmentally relevant doses of TBT display increased adipose depot weights, hepatic steatosis, and MSCs reprogramed to favor the adipocyte lineage [57]. There is a small, but growing list of environmental chemicals that induce a heritable, transgenerational obesity phenotype, including a mixture of plastics-derived EDCs (BPA and phthalates) [139], a hydrocarbon mixture (jet fuel, JP-8) [140], and DDT [141].

How exactly these developmental exposures propagate disease phenotypes to unexposed generations remains an open question. Some assert that an altered intrauterine environment is sufficient to propagate a phenotype through multiple generations, independent of epigenetic changes to the germ line [142]. This assertion is contradicted by evidence of transgenerational phenotypes following paternal exposures and studies showing phenotypes beyond the F2 generation [143]. DNA methylation marks are stable through mitosis and meiosis; hence, altered epigenetic reprograming of the germ line is a key mechanism through which EDCs are proposed to cause transgenerational phenotypes [112]. DNA methylation remains the most studied epigenetic factor responsible for EDC-induced transgenerational phenomena. However, DNA hydroxymethylation, histone modifications, and a variety of noncoding RNAs have all been implicated in epigenetic inheritance [144]. That developmental EDC exposure may contribute to the vast and abrupt rise in global obesity through several generations raises the stakes of identifying obesogens, studying their mechanisms of action, and ultimately reducing human exposure.

ECONOMIC BURDEN OF EDCS

A series of studies set out to estimate the economic burden of EDC exposure in the European Union [44,145]. The total cost of EDC exposure in health-care expenditures and lost productivity were conservatively estimated to be $209 billion annually, with the true cost likely being many times higher [145]. The cost of obesity and diabetes due to EDC exposure was in the range of $20–30 billion annually [44]. It should be noted that this analysis only assessed three EDCs (DDE, phthalates, and BPA) that were backed by the strongest animal studies and longitudinal epidemiological studies in humans with measurements of prenatal exposure. EDCs, for which animal data are strong but human studies are sparse, cross-sectional and/or inconclusive (e.g., PFOA and TBT) were not included. Moreover, this study did not take into account the harrowing possibility that EDCs are programing transgenerational disease susceptibility into multiple generations of humans. Hence, the actual societal burden of EDC exposure is likely to be many fold higher than the conservative estimate.

CONCLUSIONS

The tremendous cost of obesity warrants full consideration of all risk factors that may contribute to the disease. While physicians continue to prescribe diet and exercise as a panacea for obesity, the collective
weight of the US population continues to rise, even at the bottom of the BMI distribution [146]. Current clinical management of obesity and its comorbidities remains fixated on disease prevention in adults whose health is already deteriorating. Lifestyle interventions are rarely successful, yet physicians continue to attribute these failures to genetics or even to a lack of will and determination. We have presented strong evidence that environmental exposures (EDCs, in particular) in the womb and during early development can program our obesity risk for the rest of our adult lives and possibly the lives of future generations. With this in mind, it would be appropriate to shift our focus away from adults that are already in poor health and toward young adults that are planning to have children, pregnant mothers, infants, and children. On the side of industry, there are some efforts to design chemicals that lack bioactivity [147]. However, these efforts cannot counter the vast production of EDCs worldwide and governments must take action to regulate these chemicals or incentivize industry to screen for bioactivity prior to their introduction into the manufacturing process.

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INTRODUCTION

The human body is covered with trillions of bacteria collectively known as the human microbiome, which is separated into five distinct regions; oral, nasal, skin, vaginal, and gut. Each region contains its own unique abundance and diversity of microbes. The gut contains the most abundant microbiome community, consisting of approximately 100 trillion microbes, outnumbering the cells of the human body 10 to 1 and containing more than 1000 different bacterial species and 10 times the genes of the human genome. The four main phyla of bacteria that populate the human gut are Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria with the two primary phyla being Firmicutes and Bacteroidetes. The human gut microbiome is established during infancy and contains a diverse and dynamic community of microbes that serves numerous important functions. These include the metabolism of otherwise indigestible polysaccharides that impact energy harvest and storage, the modulation of the host immune system, and protection from pathogens through gut barrier defense. Given the critical functions of the gut microbiota in the human body, any deviation in microbial composition that leads to impairments of these functions can drastically compromise host health. Alteration of the early infant gut microbiome has been correlated with the development of childhood obesity and autoimmune conditions, including asthma, allergies, and, more recently, type 1 diabetes. This is likely due to complex interactions between the mode of delivery, antibiotic use, maternal diet, components of breast-feeding, and a network of regulatory events involving both the innate and adaptive immune systems within the infant host. The main approach to studying changes in the composition of the intestinal microbiota in relation to obesity has relied primarily on the phylogenetic characterization of the microbiota of diseased individuals in comparison with apparently healthy individuals. More recently, strong evidence supporting a role for commensal bacteria on mammalian host metabolism has accumulated based on the biochemical and physiological characteristics of germ-free (GF) mice following their colonization with human microbes from obese adults. However, there are substantial interindividual and intraindividual variations in the composition of the intestinal microbiota that occur during the first 2–3 years of life, making it
difficult to establish precise cause–effect relationships between human health and the presence and relative abundance of specific microbial communities [1].

POSSIBLE MECHANISMS BY WHICH THE GUT MICROBIOME CONTRIBUTES TO OBESITY

As a result of studies in GF mice, the gut microbiome has been implicated as a contributing factor to the development of obesity. This concept was first described by Hooper et al. [3], who noticed that GF mice (mice free of all microorganisms) had 40% less total body fat than mice with a normal gut microbiota, even though they consumed 30% more calories than the normal mice [2]. They also showed that when GF mice were conventionalized with gut microbiota harvested from a normal mouse, it resulted in a 60% increase in body fat within 2 weeks, despite a significantly lower food intake. These early studies suggested a role for the gut microbiome in energy harvest and metabolism. This was perhaps not surprising given that the distal human intestine harbors trillions of microbes that allow us to extract calories from otherwise indigestible dietary polysaccharides. For example, Hooper et al. [3] showed that the colonization of GF mice with *Bacteroides thetaiotaomicron*, a common anaerobic human commensal bacteria, induced the expression of sodium/glucose transporter-1 (SGLT1) in the small intestine, resulting in a doubling of glucose absorption from the intestine.

Studies in both humans and animals investigating the role of the microbiome in the development of obesity have found that an obesity-associated microbiome has an increased capacity to harvest energy from the diet [4,5]. The obesity-associated microbiome has been shown to be enriched with genes coding for enzymes that use otherwise indigestible carbohydrates to produce the short-chain fatty acids (SCFA): acetate, propionate, and butyrate [5]. In humans, 95% of synthesized SCFA are absorbed by the colon and used by the host for energy, or serve as signaling molecules. Butyrate is the preferred source of energy for colonic epithelial cells. Acetate and propionate are transported in the portal circulation to the liver where they contribute to lipogenesis and gluconeogenesis, respectively. Furthermore, acetate is the principal SCFA found in the blood, where it can be used as an important energy source for peripheral tissues.

In addition to its role in extracting energy from the diet, the gut microbiome has been shown to contribute to the regulation of energy metabolism and storage. SCFAs have been found to not only be important energy substrates, but also effective signaling molecules, influencing energy intake and metabolism [6]. SCFAs, primarily acetate and propionate, are ligands for the G protein–coupled receptors, GPR41 and GPR43, which are broadly expressed in the gut and adipose tissue, where they have been shown to promote adipogenesis through the uptake of fatty acids and glucose, and the inhibition of lipolysis [7,8]. Furthermore, the colonization of GF mice has been shown to impact enzymes involved in fatty acid metabolism. Backhed et al. [2] found that inoculation of GF mice led to the suppression of fasting-induced adipocyte factor (FIAF), also known as angiopoietin-like 4, a circulating inhibitor of lipoprotein lipase (LPL), resulting in increased cellular uptake of fatty acids and adipocyte triglyceride accumulation. It was also observed by Backhed et al. [9] that adenosine monophosphate (AMP)-activated protein kinase (AMPK), an enzyme that functions as a fuel gauge and monitors cellular energy status, is significantly lower in conventionalized mice compared with GF mice, resulting in reduced fatty acid oxidation. While it is clear from these studies that just having a gut microbiome can increase energy harvest and storage capacity, it is unknown whether these factors contribute to the development of obesity. The microbiome may be linked to behaviors in humans, such as appetite, inflammation, or adipocyte metabolism, which can be revealed when transplanted into GF mice. However, more work needs to be done in children before they become obese, by examining the molecular biomarkers when transplanted into GF mice, including an exploration of their functional influence on adiposity and behavioral traits.

Obesity is associated with an increase in gut permeability, which allows for an increase in bacteria and bacterial components to enter the circulation and lead systemic inflammation. Alterations
Potential Role of the Microbiome in the Development of Childhood Obesity in microbial composition may lead to alterations in gut barrier function resulting in translocation of endotoxic compounds such as lipopolysaccharides (LPS), a component of gram-negative intestinal bacteria and a natural ligand for toll-like receptors (TLRs). Binding of LPS to TLRs triggers the release of cytokines and an associated inflammatory response. Cani et al. [10] found that infusion of LPS for 4 weeks in mice led to an increase in weight gain, similar to that seen in mice following diet-induced obesity (DIO) as a result of a high-fat diet (HFD), providing a causative role for gut microbiota and inflammation in the development of obesity.

Over the years, investigations of the microbial composition of lean and overweight/obese adults [11], children [12], and infants have resulted in the discovery of associations of particular bacteria with obesity. Ley et al. [13] analyzed the microbial composition of the gut in leptin-deficient ob/ob mice, an established model of obesity, and their lean counterpart, to determine if distinct variations existed. They reported that ob/ob mice had a reduced abundance of Bacteroidetes and concomitantly higher proportions of Firmicutes relative to their lean counterparts. This particular shift was confirmed in a mouse model of DIO by Turnbaugh et al. [14] and was also reported in obese humans by Ley et al. [11]. Whether these particular bacterial compositions are causative or correlative of weight gain continues to be investigated. Previous investigations in both mice and humans by Turnbaugh et al. [4] and Ridaura et al. [5], respectively, transplanted the microbiome from obese and lean donors to GF mice and found that colonization of an obese donor microbiome led to a greater increase in fat mass compared with their lean counterpart. The increase in fat mass was found to be as a result of an increased energy harvest from the diet suggesting a causative role of the microbiome in the development of obesity. Furthermore, evidence from a study by Hildebrandt et al. [15] found that shifts in microbiota composition occurred prior to the development of obesity. Additional data from Santacruz et al. [16] found that microbiome characteristics can influence potential weight loss outcomes.

It is clear from the aforementioned research that the microbiome is altered in obese individuals and there is evidence suggesting that those alterations may precede the development of obesity. When and how these alterations occur is still a matter of debate. While changes in the adult microbiome can occur through long-term dietary changes and antibiotic use, the adult microbiome is considered relatively stable. The most unstable period for the microbiome is in the first 2–3 years of life when the initial colonization and development is taking place. It is also during this time that the microbiome is most vulnerable to disruptions that could be maintained throughout life. Given the animal and human data suggesting a link between microbial composition and obesity, a disruption in normal acquisition of the microbiome may be an early contributing factor to the development of obesity. Understanding how early-life events impact the development of the microbiome may help establish points of intervention to reduce the risk of developing obesity.

EVENTS THAT IMPACT EARLY DEVELOPMENT OF THE MICROBIOME

The initial colonization of the human microbiome primarily occurs at birth and continues to increase in diversity and abundance in response to various environmental exposures until reaching a relatively stable, fully developed microbiome at approximately 2 years of age. Emerging evidence suggests that the development of the infant microbiome follows a distinct pattern of colonization punctuated by new environmental exposures such as breast-feeding and introduction to solid foods [17]. Facultative anaerobic bacteria including Staphylococcus, Streptococcus, Escherichia coli, and Enterobacteria are thought to be the initial colonizers of the gut where they consume oxygen and create an environment for obligate anaerobes [18,19]. Later, these are replaced by facultative anaerobes that dominate the gastrointestinal tract, primarily Actinobacteria and Firmicutes [20]. Deviations from this colonization pattern have been found to contribute to disease such as asthma and allergies. An emerging area of inquiry in the field of childhood obesity is determining the impact of variability in the initial and subsequent colonization of the microbiome on weight gain. Although there is a lack of direct causative evidence supporting the link between
gut bacterial composition and the development of childhood obesity, there are a few studies to date that provide indirect evidence by associating microbial composition with childhood weight gain [21–24]. Additionally, there are a number of factors that have been associated with increased risk of developing childhood obesity that also have been found to contribute to variability in initial bacterial colonization and subsequent development, including maternal health status, mode of delivery, infant diet, and antibiotic use.

Four primary factors contribute to variability in the development of the infant microbiome. The first factor influencing the infant microbiome is the mother’s microbiome. Given the vertical transmission of the microbiome from the mother to the infant, any maternal health status that confers changes to the mother’s microbiome will likely directly impact the initial colonization of the infant microbiome. Mother’s weight status, dietary intake, and antibiotic use have all been shown to impact the composition of the mother’s gut microbiome. Santacruz et al. [25] showed that overweight pregnant women had reduced numbers of Bifidobacterium and Bacteroides and increased numbers of Staphylococcus, Enterobacteriaceae, and Escherichia coli compared with normal-weight pregnant women. The contention that maternal weight status impacts infant microbiome composition was supported in a study by Collado et al. [26] They found that fecal Bacteroides and Staphylococcus concentrations were significantly higher in infants of overweight mothers during the first 6 months. Furthermore, higher maternal weights and BMIs were associated with higher concentrations of Bacteroides, Clostridium, and Staphylococcus, and lower concentrations of the Bifidobacterium group. Additionally, infants born to normal-weight mothers and mothers with normal weight gains during pregnancy had lower Akkermansia muciniphila, Staphylococcus, and Clostridium difficile [26]. In addition to maternal weight status, diabetes, and the intake of a HFD in nonhuman primates has also been shown to impact maternal and infant microbiome composition beyond weaning, even when the offspring were switched to a healthy diet, implicating early colonization may have persistent effects [27–29].

The second factor contributing to the infant’s microbiome composition is the mode of birth delivery. Infants born by vaginal delivery are colonized by microbes resident in the birth canal and the mother’s own gastrointestinal tract, whereas infants born by cesarean section (C-section) are initially colonized by skin flora [23,30,31]. The microbial composition of the vagina is substantially different from the microbial composition of the skin. Dominguez-Bello et al. [30] found, in samples taken less than 24 h after delivery, that vaginally delivered infants acquired bacterial communities resembling their own mother’s vaginal microbiota, dominated by Lactobacillus, Prevotella, or Sneathia spp., and C-section infants harbored bacterial communities similar to those found on the skin’s surface, dominated by Staphylococcus, Corynebacterium, and Propionibacterium spp., and they had a deficiency of anaerobes with lower numbers of Bacteroides and Bifidobacterium.

The third factor influencing the infant microbiome composition is the infant diet. Immediately after birth, the primary source of nutrition for the infant is maternal breast milk or infant formula, which will contribute to the next stage of bacterial colonization in the gut. Breast milk contains hundreds of species of bacteria and also contains prebiotic human milk oligosaccharides (HMOs), which are sugar polymers that bypass small intestinal degradation to serve as metabolic substrates for bacteria in the colon, particularly bifidobacteria, and help shape the infant microbiome [32]. The combination of probiotics in the form of bacteria and prebiotics in the form of HMOs provides breast milk infants with a stable and relatively uniform gut microbiome compared with formula-fed babies. Formula-fed infants are not exposed to the same nutrients that breast-fed infants are and so develop an entirely different microbiome [33]. Compared with breast-fed infants, the diversity and abundance of the genus Bifidobacterium was decreased in formula-fed infants [34]. Furthermore, Kalliomaki et al. [21] reported that bifidobacterial numbers in fecal samples during infancy were higher in children remaining normal weight compared with children becoming overweight. Finally, the introduction of solid foods during the development of the microbiome can have significant influences on bacterial colonization [35]. The introduction of solid foods requires a shift in microbiome function to meet the metabolic demand of changing nutrients. This could lead to substantial individual differences in colonization based on the type of food introduced.
A fourth factor that impacts the colonization of the microbiome is early exposure to antibiotics. Antibiotics have been shown to alter the normal assembly of the infant microbiome. Antibiotics can decrease the colonization of certain microbes while allowing others to flourish. Dardas et al. [36] found that antibiotics given within the first 30 days after birth resulted in a reduction in the dominant Firmicutes and Bacteroidetes phyla and an increase in the Proteobacteria and Actinobacteria. Multiple studies have reported that antibiotics can have long-lasting effects on gut microbiome composition. It was found in these studies that microbiome composition either took weeks to recover to preexposure levels or failed to fully recover after 6 months [37]. Antibiotics have been used for years in farm animals to accelerate weight gain. This has been shown to be the result of shifting digestion toward enhanced energy harvest [38]. Furthermore, early-life exposure to antibiotics has been shown to be associated with increased body mass and adiposity in children [39,40]. Although these studies provide evidence that antibiotics promote weight gain in humans, whether this effect is dependent on a specific antibiotic type or the amount of exposure has been insufficiently explored.

IMPACT OF EARLY COLONIZERS ON INFANT HEALTH

It is currently unclear whether early disruption in infant microbiome colonization contributes to the development of childhood obesity. It has, however, been extensively reported that early disruption in microbiome colonization can impact the development of the infant immune system. Groundbreaking studies in nonhuman primates have shown that a maternal HFD reduced the diversity of offspring intestinal microbiota in juvenile animals at 1 year of age [16], even after switching to a healthy diet at the time of weaning. This persistent effect of early-life diet suggests that maternal diet exposure during gestation and breast-feeding can pattern the composition of the microbial community, with long-lasting effects. However, studies assessing the duration of microbial disruption in these offspring are lacking.

CONCLUSION

The human gut contains a diverse and dynamic community of microbes that serve numerous important functions for the host, including metabolism of otherwise indigestible polysaccharides impacting energy harvest and storage, modulation of the host immune system, and providing protection from pathogens through gut barrier defense. Although there is substantial evidence that the microbiome itself can contribute to increased energy harvest and fat accumulation, it is still unclear whether composition shifts in the microbiome have significant impacts on these functions. The shifts in gut microbiome composition reported in obesity have been shown to increase capacity to harvest energy, but whether these changes are a cause or a consequence of obesity requires further study. A few studies have reported differences in infant microbiome composition that are associated with childhood obesity but again these differences are yet to be causatively linked to weight status. Colonization of the infant microbiome can be influenced by a wide variety of environmental exposures and has already been implicated in a number of diseases associated with its function. Ultimately, to prove causation, large, longitudinal, prospective studies are needed that serially evaluate the gut microbiome from infancy into adulthood. Future studies will hopefully shed light on which bacteria are necessary and at what abundance for proper metabolic function. The introduction of these bacteria early in development may prove to be an extremely useful tool in preventing the development of childhood obesity.

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Adipose tissue is composed of at least three different types of depot (i.e., brown, beige, and white), which can differ with the stage of development and anatomical location in individuals and between species [1]. In addition, the distribution and composition of adipose tissue changes throughout the life span of individuals (Figure 22.1). Generally, the most abundant fat is white adipose tissue, which comprises ~95% of fat mass in children and adults, with obesity being accompanied with an increased number and size of white adipocytes [2]. It not only serves as an energy reserve in the form of lipid but also act as an important endocrine organ with a number of roles, of which the best documented is appetite regulation via the release of leptin [3]. Brown adipose tissue (BAT) is only ever present in comparatively small quantities and, even in the newborn, when it is most abundant, it comprises just up to ~4% of total body weight [4]. However, as a consequence of its unique location(s), protein composition (including a substantial mitochondrial component), and high rate of blood supply, it is capable of using/dissipating exceptional amounts of energy and releasing heat when maximally stimulated [5]. This capacity is rarely, if ever, reached again in later life [6].

**INTRODUCTION**

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**BROWN ADIPOSE TISSUE AND ITS UNIQUE ROLE AT BIRTH**

The role of adipose tissue in the fetus and newborn is very different compared with childhood, adolescence, and adulthood with the largest transitions in its appearance and function occurring during late gestation and around the time of birth [7]. In large mammals, including humans, birth is characterized by the rapid initiation of nonshivering thermogenesis [1] that is recruited through the activation of the BAT-specific uncoupling protein (UCP)1, a protein present on the inner mitochondrial membrane [8]. Once activated, UCP1 allows the free flow of protons across the inner mitochondrial membrane that results in the rapid release of heat without the need to convert adenosine diphosphatase (ADP) to adenosine triphosphate (ATP) [5]. This process is dependent on the amount of UCP1, together with its capacity for unmasking guanosine diphosphate (GDP) binding sites [8]. As a consequence of the relatively high mass of BAT in the newborn and the maximal appearance of UCP1 at this age [9], BAT attains a near-maximal capacity to generate heat up to a rate of 300 W/kg compared with 1 W/kg in all other tissues [10]. BAT then gradually disappears after birth although UCP1 containing adipocytes is retained within a number of depots into adulthood [11,12]. The main depot in children and adults is believed to be within the supraclavicular region. This region
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is characterized as being hotter than most other regions of the body [13]. It does, however, also contain discrete depots that have much lower UCP1 abundance than classical BAT and is, therefore, considered to be beige fat [14]. In adults, it is clear that there is considerable variability in the characteristics of adipose tissue, both between depots and individuals, which can be observed in both preadipocytes [15] and adipocytes [16]. These differences may represent genetic determinants of adipocyte function, as recently suggested for single nucleotide polymorphism (SNP) related to fat mass and obesity-associated (FTO) obesity variant circuitry [17]. The extent to which these highly variable characteristics relate to early adipose tissue development or function remains completely unknown, which is perhaps surprising given the unprecedented rise in childhood obesity.

ADIPOSE TISSUE LINEAGE AND ITS POTENTIAL RELATIONSHIP WITH SKELETAL MUSCLE PRECURSORS

Our understanding of adipose tissue biology has been transformed over the past few years and one especially exciting discovery has been the suggestion that BAT may share a common lineage with skeletal muscle rather than white adipose tissue [18]. This new concept resulted from a series of lineage-tracing studies that can only be conducted in mice [19], so their translational relevance to larger mammals remains unknown. The first publication to suggest a new origin for BAT demonstrated that cells expressing engrailed 1 (En1; a homeobox transcription factor gene expressed in the central dermomyotome) not only gave rise to epaxial muscle, but also to interscapular BAT [20]. Furthermore, the fate of En1-expressing cells transformed from BAT alone at an early stage of embryo development, to BAT, dermis, and muscle as the embryo developed. Complementary studies then showed that newborn mice lacking both myogenic factor 5 (Myf5), which has a unique role in muscle development (and arises after the translocation of epithelial cells along the edge of the somite to the subjacent myotome), and another myoblast precursor factor, MyoD, which similarly plays a unique role in muscle development from migratory cells [21], not only have reduced muscle mass but also excessive amounts of white adipose tissue [22]. These studies ultimately led to the discovery of transcriptional regulator Prdm16 (PRD1-BF1-RIZ1 homologous domain-containing 16), which was considered to be
specific to a BAT rather than a myogenic (or skeletal muscle) lineage. Importantly, both arise from a myoblast progenitor and are distinct from the white adipogenic pathway [23].

The full extent to which BAT has a distinct lineage is now being questioned as depending on the depot. White adipocytes can have more diverse origins and be a mix of both Myf5– and Myf+ cells [24,25]. Indeed, comparable studies conducted using Pax3 tracing demonstrated a clear overlap between the origins of both brown and white adipocytes [26]. Additional populations of adipocytes have now been identified, that is, beige or brite, that are characterized as containing small groups of UCP1-expressing cells surrounded by large amounts of white adipocytes [27,28]. The thermogenic relevance of these cells remains to be established as the abundance of UCP1 is ~10% of classical BAT [29]. To date, a majority of studies investigating beige fat have been largely confined to adult rodents in which “almost everything” examined to date, brown white adipose tissue [30]. Furthermore, a diverse range of other markers for beige adipocytes have been suggested, but their applicability across species is now being questioned [31], together with the optimal conditions in which these classifications are defined [32]. White adipose tissue in humans now appears to have the capacity to undergo browning, as recently shown in children that were severely burnt [33]. This process took at least 1 month to develop but importantly was associated with an increase in energy expenditure. This raises the possibility that UCP1 can be reactivated in the postneonatal period.

FETAL ADIPOSE TISSUE DEVELOPMENT

The ontogeny of fetal BAT has been best described in sheep which, like humans, are born with a mature hypothalamic–pituitary–adrenal axis after a long gestation and with the majority of adipose tissue deposition having occurred during the final third of gestation [34]. With respect to adipose tissue distribution, the main difference between the human fetus and all other species is that fat is present around all internal organs and significant amounts of subcutaneous fat are also deposited up to term [35]. The best-studied fat depot in the fetus is the perirenal-abdominal, which constitutes at least 60% of fat in newborn sheep. It shows two distinct phases during fetal development, an early proliferative phase that commences around midgestation, followed by a second preparatory stage (i.e., for the transition at birth) [36]. This is characterized by a gradual rise in the abundance of adipocytes that show both brown and white characteristics [36]. The abundance of UCP1, therefore, gradually increases together with the main component of adipose tissue, that is, lipid [37]. The extent of the growth of perirenal adipose tissue is related to skeletal muscle development but whether other depots, such as those in the pericardial, sternal, and clavicular regions, demonstrate similar growth patterns remain to be established. The latter depots are of particular interest as in sheep they retain UCP1 into young adulthood [38] and possibly into old age.

Adipose tissue, which first appears in the sheep fetus, has a dense cellular structure but does not express UCP1 or related genes that characterize BAT [36]. Rapid cellular multiplication then occurs in conjunction with maximal gene expression of KI-67. In parallel with this process, genes normally abundant in developing cells are highly expressed, including HOXA1, HOXC9, and BMP4 and 7, that also regulate adipogenesis [39]. The growth of adipose tissue then continues up to term (~147 days gestation) when a majority of established BAT markers reach maximal abundance and the depot also contains a significant amount of white adipocytes [36]. Despite the relatively small fraction of fat (i.e., on a g/kg body-weight basis) present in most mammalian species at birth, both the amount and composition are highly sensitive to modulations in the maternal metabolic environment [38].

ADAPTATION OF ADIPOSE TISSUE AT BIRTH AND RECRUITMENT OF NONSHIVERING THERMOGENESIS

The primary role of BAT is to enable an effective thermoregulatory response following the cold exposure experienced in the transition from the uterine to extrauterine environments. Maturation of the hypothalamic–pituitary–adrenal axis largely determines the onset of nonshivering
thermogenesis [7]. A compromised BAT function, as illustrated by studies in newborn sheep, results in pronounced hypothermia, as seen with preterm delivery [40] and/or cesarean-section birth [9]. Both these conditions prevent the normal rapid increase in BAT activity and body temperature rapidly falls after birth. This is because the onset of nonshivering thermogenesis is compromised due to a markedly slower rate of the appearance of several endocrine stimulatory factors that occurs after vaginal birth at term [9]. These effects are similar to those seen in humans [38]. An injection of triiodothyronine, norepinephrine, or both, into cesarean section–delivered sheep stimulates BAT function; responses are enhanced by delivery into a cool, rather than warm, ambient temperature [41]. The extent to which this further compromises adipose tissue development is not known but is of particular interest given the increased risk these offspring exhibit with respect to being overweight or obese [42,43]. Defective BAT development in early life could potentially contribute to excess adiposity. However, as with a majority of the factors that can modulate BAT function in early life, the longer-term consequences of cesarean-section birth for adipose tissue distribution have yet to be examined longitudinally.

Previously, it has been erroneously considered that factors released from the placenta actively inhibit the onset of nonshivering thermogenesis in fetal adipose tissue [44]. This was based on measuring changes in circulating concentrations of nonesterified fatty acids (NEFA), as a marker of lipolysis, rather than direct and/or functional measurements of UCP1 [45]. Both prostaglandins and adenosine were considered to inhibit BAT function, but these have now unequivocally been shown to be stimulators of BAT function [46,47]. The fetus is of course maintained within a metabolically constrained environment, which is characterized by basal concentrations of oxygen, glucose, and NEFA [1], and its temperature is ~1°C higher than that of the mother [48]. All these factors would constrain any activation of UCP1. In a normal pregnancy, the fetus has no need to thermoregulate, although when chronically stimulated, the thermogenic potential of BAT can be enhanced [49]. Furthermore, the increase in fetal plasma cortisol and catecholamine concentrations brought about by prolonged hypoxia also enhances the abundance of UCP1, but it still remains well below that present after birth [50].

MATERNAL DIETARY EFFECTS ON FETAL ADIPOSE TISSUE DEVELOPMENT

Maternal diet can have a profound effect on fetal adipose tissue growth and development as illustrated in sheep studies, of which the timing of any maternal intervention is critical in determining the newborn outcome [51]. To date, these have primarily focused on the perirenal-abdominal depot [38], although other depots, such as the pericardial, can be as responsive [52]. The main effects are seen on UCP1; reduced maternal food consumption in late gestation reduces UCP1 in fetal fat [52], although this does not always persist after birth [53]. In contrast, enhanced maternal food intake, such as allowing the mother to eat to appetite, increases both the amount of adipose tissue [54] and UCP1 in late gestation [55,56]. The extent to which these types of adaptations are specific to brown, as opposed to white and/or beige, adipocytes remains unclear because of the diffuse nature of their distribution within different depots [36,56]. It has been suggested that epigenetics provides a primary link between changes in the early nutritional environment and later outcomes [57], but the identification of a clear pathway remains elusive especially with regard to excess adiposity [58].

EPIGENETIC MECHANISMS IMPLICATED IN ADIPOSE TISSUE DEVELOPMENT

One reason why a more precise role for epigenetic regulation of adipose tissue development is currently unavailable is the very limited amount of measurements made at this stage of life. Most longitudinal studies in humans have simply focused on changes in gene methylation in blood as an indirect measure of epigenetic adaptation without a distinct adverse phenotype (e.g., [59]). One epigenetic mechanism recruited during preadipocyte differentiation involves acetylation and
Adipose Tissue Development

decacylation [60], reversible processes controlled by competing enzymatic activities, namely, histone acetyltransferase (HAT) and histone deacetylase (HDAC) [61]. These, respectively, promote or inhibi adipocyte development [60]. There are at least 18 HDACs, subdivided into four classes [62]. When genes encoding individual HDACs are deleted, the offspring are often not viable, with the exceptions of HDAC5, 6, and 9. These types of studies have yet to show a direct role for HDAC on adipose tissue development, although it is known that HDACs are involved in development elsewhere. For example, HDAC2 is involved in heart growth and HDAC4 in bone development [62]. Class I HDACs appear to be more important in regulating adipose tissue metabolism. Inhibition of class I HDAC activity in obese mice has distinct metabolic benefits that are not seen using a class II inhibitor [63]. These differential outcomes appear to be mediated through increased BAT [63], although a complementary inhibition of adipogenesis may also occur [61]. The precise mechanisms involved have yet to be elucidated but short-chain fatty acids are inhibitors of class I HDACs and acetylation regulates the β-oxidation of NEFA [64]. Given the pronounced changes in their concentration around birth [1], they may be important epigenetic regulators of adipose tissue development.

CONCLUSION

We are now in a new and vibrant period of adipose tissue biology for which a greater understanding of the complex process in which it grows and develops could hold the key to preventing the annual rise in people who are overweight and obese. Clearly this problem starts early in life, perhaps before birth, and as such needs to be tackled at these early stages of development.

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Section IV

Behavioral and Metabolic Consequences of Childhood Obesity
Self-Esteem and Health-Related Quality of Life in Childhood Obesity

Andrew J. Hill

INTRODUCTION

Body weight affects people’s perception of themselves and others. While attitudes to obesity are shaped by age, gender, and cultural background, the prevailing climate in the developed world is antifat [1]. These negative attitudes lead to assumptions about the character and psychological state of people with obesity. However, the relationship between obesity and psychological well-being is neither linear nor uniform. Some children and adolescents with obesity have serious psychological problems. Others have mild problems, and some very few at all [2]. The purpose of this chapter is to summarize evidence on the core psychological well-being of an increasing section of children and youth. What does it mean to grow up and live as a young person seen and described as fat?

SELF-ESTEEM

Self-esteem is a long established psychological construct with a huge attendant literature. Self-esteem refers to how people perceive and value themselves. In a more elaborated form it is, “the extent to which a person believes himself to be capable, significant, successful and worthy” [3]. As Emler notes in his hugely influential review [4], the public discourse about self-esteem has moved on. In current usage, self-esteem is about psychological health and identity. It is a resource and an asset. High self-esteem is something we should have by right, as it is good for the individual and for society.
Opinion differs as to how to determine this (favorable) valuation of self. These differing perspectives offer an elaborated view of the relationship between obesity and self-esteem, and help to organize the published literature. Distinction will be made, here, between self-esteem as a generalized self-appraisal, a competence in externally (and internally) valued domains, and a metric of social acceptance (or likely rejection).

**Global Self-Esteem**

The idea that self-esteem can be assessed as an evaluative attitude to the self has been attributed to Rosenberg [5], and his scale has become the gold standard in self-esteem research [4]. The Rosenberg self-esteem scale concerns very general evaluations of oneself. The 10-item scale yields a single score, a sum of positive statements. The popularity of the scale is, in part, due to its simplicity and brevity.

Unsurprisingly, this scale is prominent in evidence reviews of the relationship between obesity and global self-esteem. In a meta-analysis of research looking at global self-esteem in all age groups, Miller and Downey [6] found an effect size of $-0.36$ (95% CI $-0.33$ to $-0.40$), a robust but small- to moderate-sized relationship. Important influences on the strength of this relationship were age and gender. The correlation between overweight and self-esteem increased up to early adulthood, from $-0.12$ to $-0.22$ to $-0.28$ in children, adolescents, and young college-age adults, respectively. In addition, the relationship was significantly stronger in females ($-0.23$) than males ($-0.09$). More recently, a systematic review of studies comparing youth with obesity and healthy-weight controls found lower self-esteem scores in those with obesity in 17 of the 21 included studies [7]. The four exceptions had a feature in common. They all reported in nonwhite ethnic groups; either samples from Asia or minority ethnic groups in the United States. The review authors urged caution, however, noting that there are other studies of youth and adults from the same countries and ethnicity/income groups that do show lower self-esteem in individuals with obesity [8].

**Perceived Self-Competence**

The global perspective of self-esteem is in fact predated by an elaborated conceptualization. The representation of self-esteem as the ratio of a person’s successes to his or her pretensions has been attributed to William James [4]. From this viewpoint, self-esteem is a personal evaluation of competence in areas that are important to a person. So there are two parts to this formulation of self-esteem: the multiple domains in which the self is evaluated and a likelihood that they are not all equal in perceived importance. Indeed, it is the discrepancy between competence and importance that defines overall self-worth. Only when a person feels low competence in an area of high importance is his or her self-worth jeopardized.

There are only a handful of commonly used multidimensional measures of self-esteem for children and adolescents [9]. Susan Harter has done most to develop the Jamesian conceptualization and assessment of perceived self-competence [10]. She argues that for children the necessary domains of competence are set by parents (scholastic competence, behavioral conduct) and peers (physical appearance, social, and athletic competence). These domains expand in number and range through adolescence into adulthood, incorporating attributes such as job competence, romantic appeal, and a sense of humor.

We conducted a systematic review of multicompetence assessments in young people with defined obesity. There were 17 studies, of which 9 were cross-sectional and 7 were weight management interventions [11]. Most had used Harter’s questionnaires. All of the studies that assessed physical appearance and athletic/physical competence found lower scores in youth with obesity. Obesity also impacted on perceived social acceptance, with lower scores reported in half of those measuring this domain. In contrast, few differences were observed in scholastic competence or behavioral conduct. Global self-worth was lower in children with obesity compared with those of healthy weight.
in six of the nine cross-sectional studies, a finding comparable with that of the global self-esteem literature discussed in the last section. There were insufficient studies to detect any effects of age or sex. Likewise, comparisons based on race or ethnicity were infrequent in this literature. But the observation that in younger (9–12 years old) minority children from low-income families, all, regardless of their weight status, had lower global self-worth than a reference white population [12] is a reminder of the inherent complexities in this area.

**Domain Importance**

Thus far, this literature says much more about successes than pretensions in children with obesity. The competencies included in Harter’s self-perception profiles may indeed be those most important to today’s youth. Harter, herself, has written about how perceived physical appearance is the number one predictor of self-esteem [13]. This is true from age 5 through to adulthood. It raises the issue of how to help children value competencies other than appearance. But given that one way of managing poor competence is to diminish the importance of that feature, it is surprising that perceived importance has not been more thoroughly investigated. An assessment of domain importance is included in the manuals for Harter’s scales but rarely used in research. Our own unpublished work suggests that for a community sample of 12-year-olds, at least, healthy-weight children and those with obesity do not differ in how important they rate appearance and athletic competencies. However, and in accord with the evidence presented earlier in this section, they do perceive themselves very differently on these features.

**Low Self-Esteem**

The response format of the Harter measures permits one further and rarely reported feature of self-esteem; the assessment of self-defined low self-esteem. One of the criticisms of the self-esteem literature generally is that too much attention is given to mean values on scales that are statistically different but of questionable functional difference. Requiring respondents to identify with either a high or low self-esteem characterization (as in Harter’s questionnaires) addresses this issue.

In a state-wide survey of 9–13-year-olds from New South Wales, Australia, we found that the perception of physical appearance was particularly affected, with 63% of girls and 33% of boys with obesity identifying with the depiction of an unattractive child [14]. In contrast, the proportion of low scorers on the global measure of self-worth was smaller. Although the relative risk of low global self-worth in girls with obesity was 4.1 times more than normal-weight peers, only 20% of the group scored in this range. Danielsen et al. [15], using the same approach to define low self-esteem, also found higher proportions of overweight/obese Norwegian 10–13-year-olds to have low physical appearance and athletic competence perception. For this population sample, the difference from healthy weight children extended to low social acceptance and scholastic competence, although the proportions were smaller than observed in the Australian children.

Complementing this, in the Australian sample, girls with obesity were more than five times less likely to have high global self-worth, something achieved by around 70% of their peers. So, while it would be unwise to assume low self-esteem in every person with obesity, the consequences of not holding oneself in high self-regard should also be recognized. In practical terms, this may flag problems with confidence and self-efficacy, issues key to behavior change and its maintenance.

**The Looking-Glass Self**

The “looking-glass self” framing of self-esteem is attributed to Charles Cooley, and again it is a long-standing and highly influential theory. Its basis is that our assessments of our own worth are based on the judgments we imagine others make of us [4]. Moreover, our predictions about these judgments depend upon the qualities we see in these other people. So, what shapes self-esteem are not our accomplishments objectively and directly appraised, but the anticipated judgments of these
accomplishments by other people. Hence, self-esteem is what we expect will be reflected by this social mirror, and the intensity of reflection depends on whom we choose as our social referents.

Mark Leary has taken this social view in a particular direction, one very relevant to obesity. Sociometer theory proposes that the self-esteem system evolved primarily as a monitor of social acceptance, the motivation being not to maintain self-esteem, \textit{per se}, but to avoid social devaluation and rejection [16]. He argues that people are particularly sensitive to changes in relational evaluation or the degree to which others regard their relationship with the individual as valuable, important, or close. Accordingly, self-esteem is lowered by failure, criticism, or rejection and raised by success, praise, and events associated with relational appreciation. Even the possibility of rejection can lower self-esteem. Two areas of research are particularly relevant to youth with obesity—interpersonal relations and victimization.

\textbf{Interpersonal Relations}

Sociometric procedures using peer-nominated friendships have shown little impact of being obese in community samples of primary school-aged children. Some 20 years ago, for example, young children with obesity were just as likely to be chosen as their lean peers as people to socialize with both inside and outside of school [17]. The situation is likely to be different now, as has been observed for teenagers. Data from the US National Longitudinal Study of Adolescent Health (Add Health) showed overweight adolescents were overrepresented in categories of no or few peer friendship nominations and underrepresented in the most popular categories [18]. Most importantly, they received fewer reciprocal nominations: that is, nominations by peers they themselves had nominated. Further analysis of this cohort indicated that overweight adolescents whose friendship attempts with nonoverweight peers were not reciprocated would turn to other overweight peers [19]. In another, smaller sample of US teenagers, friendship choices showed overweight youth were twice as likely to have overweight friends as their nonoverweight peers [20].

The relative failure to be named a friend by people you nominate suggests that the friendship ties of adolescents with obesity are less plentiful, potentially weaker, and more directed to others with obesity. In terms of self-esteem, the peer referent for self-evaluation chosen by teenagers with obesity determines their social standing: valued and held in esteem by others of similar weight but likely rejected and so of low self-esteem in the eyes of those of healthy weight (see Chapter 16 for further consideration of social networks).

\textbf{Victimization}

Peer difficulties and rejection have been observed in very young children. By age 5, parents of children with obesity are more likely to report peer relationship problems in their girls and boys than parents of healthy-weight children [21]. Five-year-olds themselves reject story characters drawn as fat as people they would choose to be friends with [22]. Rejection may be a very small step from perceived victimization.

The research evidence is unequivocal regarding the association between obesity and victimization. A meta-analysis of 16 studies and 28 effect sizes showed a significant relationship between being obese and being victimized (OR = 1.51 [1.32--1.71]; [23]). Most of these studies were of children aged 11 and upward. In an interesting development, observations of primary school teachers in the Netherlands and the children themselves revealed that children with obesity were more likely to be victimized by their peers and also more likely to bully others [24]. Indeed, there was a small group of children referred to as “bully-victims” who were both recipients and perpetrators of victimization. Children with obesity were twice as likely to be in this category as healthy-weight peers.

Restricting this to weight-related victimization, we have reported that some 42% of 9–12-year-olds with obesity identify themselves as fat victimized compared with 7% of their healthy-weight peers [25,26]. Being fat victimized was strongly associated with being victimized generally. In terms of self-esteem, those who were fat victimized scored lower in social acceptance, athletic competence, school competence, physical appearance, and global self-worth, compared with children.
Self-Esteem and Health-Related Quality of Life in Childhood Obesity

not involved in victimization (Figure 23.1). Children who bullied others for being fat had high self-competence on every domain other than behavioral conduct and global self-worth. The small group of bully-victims scored low on every measure of competence and global self-worth. Two additional points are noteworthy. First, while being fat teased was more common in children with obesity, at least half of obese children did not report these experiences. We know very little about what protects these children or what makes the other half vulnerable. Second, victimization did not impact the perceived importance of any of these domains. Once more, it would appear that these children were not managing their low self-esteem by modifying the importance of domains in which they judged themselves less competent.

QUALITY OF LIFE

Quality of life is a much younger and broader concept than self-esteem. Indeed, assessments of quality of life often include scales related to contentment with self. Health-related quality of life (HRQoL) is what is assessed in the context of obesity and, while variously defined, it describes the functional effect of a health condition on a person. HRQoL includes subjective assessments of present physical, psychological, and social state. The value of its measurement is the quantification of the impact of a health condition (and its treatment) on a person’s life in a standard and reproducible way. For health economists, HRQoL provides the basis for calculating quality-adjusted life years (QALYs) that, in turn, permit the assessment of cost-effectiveness of health interventions. For researchers and clinicians, HRQoL measures provide broad-brush characterization of subjective health impact that can be compared across health conditions, assess the burden of preventable health conditions, and guide interventions to improve people’s well-being [27].

MEASURES OF HRQoL

With HRQoL so central to evaluations of treatment outcomes and effectiveness it should be of little surprise that there is a variety of instruments to use with children [28]. There has been a surge in the number of studies on child obesity and its treatment that have included HRQoL. The
most commonly used and reported assessment of children’s HRQoL is the Pediatric Quality of Life Inventory (PedsQL). Like KIDSCREEN and the Child Health Questionnaire, this is a generic assessment that yields norm-comparable scores overall and for each of the main components. All these measures have child and parent-proxy versions.

In addition, there are condition-specific measures such as the Impact of Weight on Quality of Life-Kids (IWQOL-Kids). Here, each question starts with, “Because of my weight.” Condition-specific assessments are intended to be more sensitive to the limitations imposed by specific health conditions and therefore should be better able to detect treatment effects and clinically meaningful outcomes [29]. Lastly, there are preference-based utility measures such as the Child Health Utility (CHU-9D) and the EuroQoL-5D-Youth (EQ-5D-Y). These generic measures that underpin economic evaluation are only recently being applied to child obesity. Following close behind is the development of condition-specific preference-based measures for youth with obesity [30].

**Evidence Reviews**

The surge of interest in children’s well-being and well-being as an obesity treatment outcome is reflected in updated evidence syntheses. Tsiros et al. [29] identified 28 studies, 15 of which had used the PedsQL. Pooling these data showed strong inverse linear relationships between body mass index (BMI) and physical and social functioning. The relationship was more moderate with emotional functioning and marginal for school functioning. Parent-proxy completions scored lower (i.e., lower HRQoL) than children’s own ratings of their quality of life, although there was evidence of parents being more extreme in both low and high HRQoL. In an updated meta-analysis, children and adolescents with obesity scored lower on total, physical, and psychosocial PedsQL summary scores, with parent-proxy values again being lower than children’s [31].

Our systematic review considered only children defined as obese [11]. The great majority of studies found lower scores on physical and social functioning and on physical/general health. Six of the nine cross-sectional studies that collected data on school or work functioning reported lower scores in youth with obesity. The difference from the scholastic competence outcomes observed by Tsiros et al. in the context of self-esteem could be related to scale content. For example, two of the five scale items in PedsQL ask about absence from school, while all questions in Harter’s assessment are directed at perceived school achievement or performance.

The most recent published review at the time of writing this chapter included 34 studies and noted the use of 10 different HRQoL measures [32]. Despite this variety, there was good congruence observed. For example, only two studies failed to report a significant difference in overall scores between healthy-weight youth and those with obesity. One of these was in preschoolers but again there are other studies in this age group that do show a parentally assessed difference [33]. Clear differences were observed on each of the subdimensions of social, physical, emotional, and school functioning, with confirmation of an impact on school functioning (13 of 18 studies). As may be expected, scores in nearly all HRQoL dimensions were lower in clinical than community samples and worsened with the degree of obesity.

No information was presented on possible race/ethnicity differences. However, recent research parallels that on self-esteem in terms of apparently contradictory outcomes. For example, analysis of a multiethnic US cohort of 10–11-year-olds showed lower psychosocial PedsQL scores in children with obesity, regardless of whether they were white, black, or Hispanic [34]. In contrast, PedsQL scores of a large sample of Fijian 12–18-year-olds showed no meaningful association between obesity and HRQoL scores, although there was some variation by age [35].

**Consequences of Weight Management**

In a review of the literature on structured weight management programs for children and adolescents that included a measure of self-esteem, 18 of 21 studies were observed to report some end of intervention
improvement in self-esteem [36]. This improvement appeared to be related to the following intervention components: consistent parental involvement, group-based interventions, and actual weight loss.

The importance of the degree of weight loss is emphasized in reviews of studies that have included an assessment of HRQoL. Multidisciplinary interventions, that is those that included some sort of behavioral therapy, dietary advice, and/or physical activity, and the input of multiple health-care professionals showed no overall significant differences in HRQoL in short- or long-term follow-up [37]. Importantly, the change in both HRQoL and body weight was modest. The trend to improved HRQoL was paralleled by small reductions in BMI, mostly between $-0.06$ and $-0.15$ BMI standard deviation score (SDS) at around 6 months. Bariatric surgery, however, yields appreciable weight loss. In the 23 studies included in a meta-analysis by Black et al. [38], BMI decreased by 13.5 kg/m$^2$ at 12 months. The six studies that assessed HRQoL all showed significant improvements from baseline to postsurgery follow-up.

Returning to the self-esteem literature, we have previously noted the inconsistencies in associations between weight loss and self-esteem improvements in the intervention literature [11]. When interventions result in weight loss, most studies also observe improvements in global self-esteem and the competencies most affected, that is, physical appearance, athletic competence, and social acceptance [39]. It is surprising therefore that the degree of weight loss was correlated with self-esteem improvement in only one of the five studies that reported these associations. More recently, in an intensive, residential weight loss program for youth with obesity, attendees lost 5.5 kg ($-0.25$ BMI SDS) in just over 4 weeks [40]. Weight loss was positively associated with improvements in athletic competence and physical appearance but not global self-worth. The sample size was large ($n=303$) but the correlation coefficients small (0.13 and 0.19). Overall, this is suggestive that psychological benefit may be as dependent on some feature of the environment or supportive network as it is on weight reduction. In the context of group interventions such as residential camps, these may include the daily company of others who have obesity in common, improvements in competence or self-efficacy in newly prioritized areas (such as exercising regularly), the establishment of new friendships, or fewer experiences of weight-related victimization. And these are experienced before adolescents notice levels of weight loss that have either clinical or personal significance.

CONCLUSIONS AND IMPLICATIONS

The relationship between obesity and impaired well-being in youth is present but modest in strength. Consider the key constituents. Psychological features such as low self-esteem are likely minor contributors to the development and maintenance of obesity, albeit with the potential to interact with other risk factors. And overweight is undoubtedly only one of several influences, although an important one, on an individual’s sense of self-value. Additionally, both obesity and self-esteem are resistant to change. Longitudinally, any association will be bidirectional, in the same manner to that proposed for the relationship between obesity and depression [41]. This bidirectionality is more apparent in adults than in youth [42]. However, evidence that bidirectionality between obesity and impaired HRQoL emerges as children get older suggests that middle childhood is a key period for children in economically developed countries [43]. Changing peer relationships in the teenage years and priorities for physical attractiveness underpin this.

Mood disorders and eating disorders are other markers of impaired well-being, alongside low self-esteem and HRQoL. They are undoubtedly all interrelated. Furthermore, given that obesity persists, then the negativity associated with being fat is likely to accumulate. Unsurprisingly, therefore, those who remain obese from early childhood into adolescence have the highest levels of depressive symptoms [44] and binge eating [45]. This is a reminder that the priority for preventing obesity should never distract from addressing the needs of those already obese.

In terms of improving self-esteem and HRQoL, then, weight loss is undoubtedly important. But as reflected here, the child’s environment and supportive network is equally important. As we have previously observed, many people with obesity, adults and children, have high self-esteem,
do not suffer major depression, are in well-paid employment, and have good social relationships. This implies individual resistance or resilience. Resilience offers a different perspective to the more traditional risk-factor approach, focusing on strengths rather than deficits [46]. And it is concordant with assets-based approaches to health improvement that are extremely popular currently in public health. Assets exist within individuals (self-efficacy, drive), close community (family and friends, intergenerational), or are organizational or institutional (housing, representation/advocacy). Identifying and developing assets, many of which are external to the individual, is challenging, especially in an environment rife with antifat attitudes. But this is consistent with the view that targeting, personalization, and relationships are fundamental to improving the way that young people value themselves [4].

REFERENCES


INTRODUCTION

It is well established that overweight and obese children and adolescents are at increased risk of many physical disorders (such as type 2 diabetes, hypertension, metabolic syndrome, and fatty liver) that were once largely confined to adults [1,2]. These are not short-term problems. Rather, it appears that the comorbidities of childhood obesity often extend into adulthood, where they can decrease both the length and the quality of life [3]. Unfortunately, data are accumulating that suggest such challenges to physical health are not the only, and are arguably not even the most serious, consequences of childhood obesity. This chapter summarizes findings that indicate that obesity, and the behaviors that produce it, may also have long-term adverse consequences for the cognitive and brain health of children.

The studies that we will review rely largely on standard measures related to body weight (e.g., percentile ranking in children, body mass index [BMI] in adolescents and adults) and adiposity as indices of obesity. We will also consider the effects of consuming diets high in saturated fat and sugar (aka Western diets) on cognitive function and brain health. The Western diet is of interest because it is known to promote obesity and cognitive dysfunction [4] and because its use is widespread in Western and Westernized societies where the incidence of obesity is high [5]. Further, the possibility that obesity and excess intake may be the result of impaired cognitive functioning is considered. We acknowledge that glucoregulatory disorders, inflammation, reduced cardiovascular fitness, and insulin resistance are prominent among the factors that have been linked to cognitive dysfunction and to abnormalities in brain substrates for cognition (for reviews see [4,6,7]). However, all of these problems are comorbid with obesity and with intake of the Western diet. Sorting out
which disorders may be causes and which may be the effects of obesity and cognitive dysfunction is a long-standing challenge that remains outside the scope of this chapter.

CHILDHOOD OBESITY AND COGNITION

EXECUTIVE FUNCTION AND INHIBITORY CONTROL

Overweight and obese children exhibit deficits in a variety of cognitive capacities related to attention, inhibitory control/impulsivity, and memory. These types of deficits are often labeled as impairments in executive function (for a recent review, see [8]). Executive function includes a variety of diverse processes that are involved with cognitive and behavioral control. Tasks that require working memory, mental flexibility, task switching/multitasking, decision making, or delayed gratification are all thought to rely on executive functions [9].

Executive functions are also described as playing an inhibitory role in behavior and cognition. In this context, behavioral inhibition involves the ability to suppress prepotent responses that are incompatible with the performance of planned and situationally relevant goal-directed actions [10]. This type of inhibition also has a cognitive aspect in that it serves to suppress the ability of extraneous stimuli to attract our attention [11], or to retrieve unwanted or situationally inappropriate memories [12] that could underlie the impulsive evocation of behavior. Inhibitory control is a component of cognitive development that emerges in infancy and increases throughout childhood and adolescence [10]. Thus, there is a concern that events that impact the brain detrimentally early in life could produce impairments in behavioral and cognitive control that are exhibited throughout the lifespan.

EFFECTS OF OBESITY ON CHILDHOOD COGNITIVE FUNCTION

Overweight and obese children exhibit a number of cognitive-inhibitory problems that are associated with deficits in executive functioning. For example, a recent study conducted in 983 adolescents found that greater visceral adiposity was associated with lower performance on six measures of executive function [13]. Two of the most common measures of executive function are tasks that require mental flexibility and control over memory interference. Compared with children of lower body weight, children with higher body weights exhibit a higher number of perseverative errors on these tasks, which reflects a failure to adjust and update one’s behavior in response to changing rules or task requirements [14]. This inflexible behavioral pattern appears to be at least partly due to impaired attentional processing [15]. Because attentional difficulty in early childhood has been found to predict impaired executive functioning later in childhood [16], this finding suggests that attentional difficulties may be an early warning sign of obesity-related inhibitory impairment.

Childhood obesity is also often associated with deficits related to impulsivity and a lack of inhibitory control. For example, in delay discounting tasks that measure participants’ ability to delay a behavioral response in order to earn an incentive, obese children and adolescents appear to be less able to “wait” for the reward [17,18]. However, these deficits in behavioral control have also been observed in no-go or stop signal tasks that require participants to inhibit a prepotent behavioral response in the absence of any programmed reward [19].

REDUCED INHIBITORY CONTROL AS A CAUSE AND A CONSEQUENCE OF CHILDHOOD OBESITY

Deficits in cognitive-inhibitory processes may compromise one’s ability to resist thinking about food reward, thereby increasing one’s risk of food cue reactivity, disinhibition, and ultimately weight gain (for a detailed discussion of this idea, see [20]). Thus, there is a concern that childhood obesity may promote cognitive impairments that could increase or exacerbate one’s risk of obesity in adulthood. Consistent with this possibility, studies have shown that children who exhibit poor impulse control are also more responsive to food reward, being particularly poor at inhibiting responses to food.
versus nonfood incentives [21]. Others have found that children with a higher BMI show altered brain activation in response to food stimuli in brain areas typically associated with executive/inhibitory control (for a review, see [22]).

While these findings suggest that impulsivity is related to increased food cue reactivity, studies assessing actual food intake have yielded only equivocal evidence that impulsivity causally contributes to overeating in children. A recent cross-sectional study failed to find any significant relationships between children's impulsivity and snack intake or BMI [23]. Another study investigating eating in the absence of hunger found no relationship between executive function and intake in preschool children, but did find that lower cognitive performance, in general, was related to greater intake [24]. This is consistent with other studies showing that children with higher cognitive ability have a lower risk of becoming overweight and obese in the future [25].

Prospective studies have linked childhood inhibitory control to the development of weight gain over time. One study found that children with poorer inhibitory control had significantly higher body weights 6 and 12 months later, with the greatest weight gain occurring in the most impulsive children [26]. Indeed, a recent longitudinal study found that poor impulse control at age 4 was associated with a higher BMI 30 years later [27]. Poor inhibitory control has also been associated with resistance to weight loss for children participating in a weight intervention. Nederkoorn et al. [28] found that while obese children generally exhibited poorer inhibitory control than lean children, this was exacerbated even further in a subsample of obese children who exhibited binge-eating behavior (see also [29]). Together, these results suggest deficits in inhibitory processing may underlie aberrant eating behavior in children, and could be part of the etiology of their obesity.

**INCONSISTENCIES AND CONTROVERSIES**

Although deficits in executive-inhibitory functions have been frequently documented in overweight and obese children, the literature does not always tell a consistent story in regard to the specific underlying processes that are affected. For instance, tasks of working memory are thought to depend on the same kinds of inhibitory processes that are involved in other tasks of interference control (e.g., both require the suppression of no-longer-relevant information from memory), but obese children are not always impaired in both kinds of task (e.g., [14]). Thus, while executive function is indeed impaired in obese children, not all measures of executive function are equally sensitive to these impairments. Similarly, obese children exhibit abnormal neural activation in brain regions associated with inhibition/executive function (e.g., the prefrontal cortex [PFC]), but the direction of abnormality is inconsistent; some authors report hyperactivation of these areas [30], while others report hypoactivation [31].

Some of these discrepancies are probably due to the diverse nature of executive function that encompasses a number of potentially overlapping cognitive processes that may rely, in whole or in part, on different brain substrates. For example, while the PFC is often described as the brain site for executive function, recent reports indicate that diet and obesity are associated with impaired memory inhibitory functions that are thought to depend on the functional integrity of medial temporal lobe structures, most notably the hippocampus [32]. Moreover, reciprocal connections linking areas in the frontal cortex with the hippocampus complicate attempts to specify the neural basis for impairments in memory and executive functions [33]. Natural variations among obese children in metabolic disorder symptomology may also contribute to discrepancies in the literature, with certain biomarkers predicting neurological impairment (see [34]).

If cognitive deficits are either a cause or a consequence of childhood obesity, one might also expect that there would be a negative relationship between childhood body weight and measures of academic performance. While the data from some studies provide support for this relationship (e.g., [35]), other studies have questioned it [36]. One complication is that while academic performance relies on cognitive processes, it is also influenced by myriad factors both environmental (e.g., stress, school quality, parental support) and personal (e.g., physical health, intelligence, motivation). Thus, the relationship
between underlying cognitive capacities and obesity could be obscured to the extent that such factors either enhance or interfere with a child’s capacity to perform well in school. It also appears that physical fitness may be directly related to academic achievement. Therefore, normal-weight children in the population sample may reduce the correlation between body weight and scholastic performance to the extent that some of those children are not physically fit [37].

Obesity has also been linked to impairments in cognitive processes that are outside the normal rubric of executive function or inhibitory control. For example, recent findings indicate that in children 7–9 years old, both body adiposity [38] and self-reported saturated fat intake [39] were negatively correlated with relational memory (i.e., the ability to encode and remember relations [e.g., spatial, temporal, associative] between events). Because relational memory is also thought to rely on brain substrates that are anatomically distinct from those that appear to underlie executive function, these results suggest that obesity and diets associated with obesity may have an even broader impact on childhood cognitive and neural functioning than recognized previously.

CHILDHOOD OBESITY AND THE BRAIN

BRAIN DEVELOPMENT AND OBESITY

As indicated previously, research on the PFC has focused primarily on its role in executive function, whereas the hippocampus has largely been seen as a substrate for certain types of memory (e.g., episodic, contextual, relational, spatial). However, more recent work has identified both memory and inhibitory control functions that involve PFC and hippocampal integration [32,40]. It should not be surprising, then, that the PFC and the hippocampus have both been implicated in the cognitive/inhibitory control of food intake, and both show functional deficits in obese subjects [4,41,42].

During childhood, the brain undergoes pronounced neural proliferation, pruning, myelination, and synaptic organization [43,44]. In humans, the PFC is among the last regions to mature [45]. Interestingly, PFC development appears to be regulated at least in part by the hippocampus. Ventral hippocampal lesions during the neonatal period can induce myriad neural complications in the PFC of both rodents and primates [46,47]. These lesions are also associated with disruptions in ingestive behaviors, including increased meal duration and cumulative intake of a single food, and a distinct lack of sensory-specific satiety in the form of a rebound increase in novel food intake [48].

Perinatal lesions are rare and therefore unlikely to account for widespread increases in childhood obesity. However, there is evidence that brain pathologies may arise in response to normal events that are encountered at many stages of development. For example, prenatal stress exposure reduces hippocampal neurogenesis (which is thought to be required for adaptive memory functioning) throughout the lifespan, compromises hippocampal-dependent spatial learning [49], and increases susceptibility to diet-induced obesity [50].

DIET, OBESITY, AND BRAIN PATHOLOGY

Obesity and the Western diet have been associated with signs of structural and functional brain abnormalities that are found across the lifespan in both human and nonhuman animals. Neuroimaging studies have reported that high body adiposity in humans is accompanied by gray matter atrophy, although there is disagreement on the specific brain areas that are most affected (see [51] for a review). In adolescents, higher adiposity is predictive of reduced gray-matter volume in the PFC, which is associated with impaired cognitive function. For example, Maayan et al. [29] reported that obese adolescents scored significantly higher on measures of disinhibited eating, lower on tests of executive function, and exhibited reduced orbitofrontal cortex (a subregion of the PFC) volume compared with normal-weight controls. Another study found gray-matter volume to be reduced in the left hippocampus [52] of obese 6- to 8-year-old children.
Adult rats maintained on the Western diet develop hippocampal-dependent cognitive deficits and exhibit a cluster of symptoms consistent with neurodegenerative syndromes, including reductions in hippocampal brain-derived neurotrophic factor (BDNF; a protein involved with the growth, maturation, differentiation, and maintenance of neurons), perturbations in synaptic plasticity, nutrient transporter deficiencies, neuroinflammation, blood–brain barrier (BBB) breakdown, and impairments in hippocampal-dependent learning and memory processes [4,42,53].

Other evidence suggests that the pathology produced by the Western diet emerges early in development. Juvenile rats fed the Western diet for 2 months showed impairments in spatial reference memory in the Morris water maze and an elevated hippocampal inflammatory response [54]. In another study, 9-week-old mice were fed the Western diet until they were 24 weeks old, then returned to standard chow, which normalized their body weights [55]. At week 85, or 61 weeks following cessation of the Western diet, mice showed significant impairments in Morris water maze acquisition latency and performance, and reduced contextual fear conditioning. At week 90, these effects of the Western diet were accompanied by increased signs of inflammation and significant reductions in hippocampal gene expression for BDNF.

There are concerns that juvenile-onset diet- or obesity-induced brain pathologies may persist throughout the lifespan and lead to the development of more serious brain disease and cognitive dementias much later in life. A recent report from the Alzheimer’s Association identified obesity at midlife and its associated metabolic factors as the primary modifiable risk of developing dementia [56]. Thus, preventing childhood obesity may be critical for preventing not only adult obesity but also more serious late-life cognitive disorders.

**Western Diet and the Blood–Brain Barrier**

Normal brain function depends on the stability of the neuronal microenvironment. The BBB regulates the chemical milieu of the brain, eliminating “noise” and prohibiting the entry of potentially neurotoxic humoral substances. Composed of neurovascular endothelial cells linked by tight-junction proteins, supported by astrocytes and pericytes, and reinforced by an enzymatic barrier, the BBB precludes most molecules from entering the brain interstitial fluid [57].

The integrity of the hippocampal BBB is compromised for obese rats maintained on the Western diet or similar high-energy diets [6]. We have repeatedly observed increases in hippocampal BBB permeability to sodium fluorescein (a small molecule dye that cannot cross an intact BBB) following exposure to the Western diet [58–60]. Furthermore, reductions in the expression of tight-junction proteins in both the BBB and the choroid plexus (which comprises a brain–cerebrospinal fluid barrier) have been reported for rats maintained on the Western diet [60]. In most instances, changes in BBB permeability were observed after 90 days of maintenance on the Western diet, though one study using somewhat older rats detected increases in permeability after just 28 days of diet exposure [59].

In two studies [58,59], significantly increased hippocampal BBB permeability was observed only in rats that gained the most weight and body fat (diet-induced obese rats) on the Western diet compared with rats fed standard low-fat chow. Rats that were more resistant to the obesity-promoting effects of the Western diet (diet-resistant rats) failed to show increased BBB leakage relative to chow-fed controls. Interestingly, these studies also found that diet-induced obese, but not diet-resistant, rats showed impaired performance on behavioral tasks that depend on the functional integrity of the hippocampus, whereas neither group performed worse than chow-fed controls on hippocampal-independent learning and memory problems. The results of these studies provide evidence that the Western diet compromises the hippocampal BBB and selectively impairs hippocampal-dependent cognitive functioning.

Even subtle damage to the BBB may set the stage for neurodegeneration by permitting the influx of harmful substances into the brain interstitial fluid. Accordingly, individuals who consume the Western diet may be more vulnerable to the harmful effects of environmental contaminants (e.g., air...
pollution, pesticides, bisphenol A, lead) and therefore at increased risk of developing hippocampal and other brain pathologies that lead to cognitive impairment. Although definitive data does not yet exist, it is plausible that the BBB in children and adolescents is also vulnerable to the adverse effects of the Western diet and/or obesity. The extent to which impaired PFC and hippocampal function is based on a weakening of the BBB that occurs as a consequence of childhood obesity and exposure to the Western diet is an important open research question.

**POtential ViCIOUS CYCLE OF Obesity AND COGNITIVE DECLINE**

Based on findings such as those described previously, we have proposed that consuming the Western diet may initiate a *vicious cycle* in which cognitive processes that are involved in the inhibition of intake are impaired as a result of pathologies that develop in brain areas that serve as substrates for those processes [61]. Our current environment is rich with high-energy palatable foods and beverages, and cues that entice us to eat and drink are abundant. A reduced capacity to resist such environmental enticements would lead to increased intake, resulting in weight gain and further deterioration of brain substrates underlying the cognitive inhibition of eating and drinking, thereby resulting in progressively more intake, weight gain, and neurodegeneration (see Figure 24.1).

How might this vicious cycle begin? Reminiscent of ideas expressed previously in Schachter's 1968 externality theory [62], it seems reasonable that the capacity of environmental cues to evoke eating is countered by physiological “satiety signals” arising from one's internal milieu. One way that satiety signals promote inhibitory function is by informing animals that their energy needs have been met and that either the continuation or the initiation of intake will have nonrewarding and even aversive postingestive consequences. Recent research in our laboratory by Sample et al. [63] suggests that intake of the Western diet reduces the ability of rats to use their interoceptive satiety cues to control their appetitive behavior, while leaving control by external food-related cues relatively intact. In that study, rats maintained on standard chow were first trained to use different levels of food deprivation (internal cues corresponding to hunger and satiety) as discriminative signals for the delivery of sucrose pellets. After asymptotic discrimination performance was achieved, half of the rats were shifted to the Western diet and half remained on chow. When discrimination performance was tested 42 days later, results showed that maintenance on the Western diet weakened the rats’ ability to use their interoceptive “hunger” cues to solve the discrimination, whereas chow-fed rats were unimpaired. However, when external cues (tones, lights) were introduced along with the interoceptive cues and trained as discriminative stimuli, both diet groups showed comparable and

significant discriminative responding. In a final test, when the external stimuli were removed, rats fed the Western diet were once again unable to solve the discrimination. This outcome indicated that the Western diet did not have strong global or nonspecific effects (e.g., sensory, motivational) on performance or learning, but selectively impacted rats’ ability to utilize internal state cues to guide their food-oriented behavior.

These results indicate that intake of the Western diet reduces rats’ ability to use interoceptive cues but spares their ability to use environmental cues for control of behavior. A similar degradation of sensitivity to interoceptive cues was reported for obese human adolescents. Mata et al. [64] found that for overweight but not normal-weight adolescents, activation of the insula, a brain area thought to be important for the detection of interoceptive stimulation, was positively correlated with external eating and negatively correlated with sensitivity to interoceptive cues (in this case heart rate monitoring). This finding suggests that excess weight may be related to neurocognitive adaptations that interfere more with the utilization of interoceptive stimuli than with external cues. Considered together, the results reported by Sample et al. and Mata et al. are consistent with the hypothesis that interference with the utilization of internal satiety cues represents an early loss of inhibitory control in a vicious cycle of obesity and cognitive decline.

CONCLUSIONS

In children and adolescents, obesity and the Western diet are associated with cognitive impairments in inhibitory and executive-like processes. These deficits can increase a child’s susceptibility to memory deficits, distractions, and impulsivity, thereby interfering with normal cognitive development. Moreover, these inhibitory deficits can promote excess intake by making children more responsive to food and food cues. In addition, considerable evidence from humans and rodents link obesity and the intake of a Western diet to abnormalities (e.g., inflammation, atrophy, BBB disruption) in brain areas that are known to be important substrates for these cognitive processes (e.g., PFC, hippocampus). Beginning in childhood, a vicious cycle of diet-induced deterioration of brain function and inhibitory control could set the stage not only for adult obesity but also for serious cognitive decline much later in life.

REFERENCES

INTRODUCTION

The prevalence of childhood obesity has progressively increased in the last four decades [1]. In 2010, it was estimated that 43 million children were overweight worldwide, and this number is expected to increase up to 60 million by 2020 [1]. This increase in pediatric obesity is accompanied by an increased prevalence of type 2 diabetes (T2D) in adolescents [2]. T2D usually occurs after 10 years of age, after the onset of puberty, with an incidence estimated between 7.0 and 49.4 per 100,000 person-years in subjects between 10 and 19 years of age in the United States [2]. Recent data indicate that in the United States in 2010 about 20,000 subjects below the age of 20 showed T2D and that this number may increase up to ~84,000 by 2050 [3]. In this chapter, we will discuss the current knowledge and the future perspectives concerning the pathophysiology and therapy of pediatric T2D.

DEFINITION OF TYPE 2 DIABETES AND PREDIABETES

According to American Diabetes Association (ADA) criteria, T2D is defined as fasting plasma glucose levels higher than 125 mg/dL or plasma glucose levels higher than 200 mg/dL 2 hours after an oral glucose tolerance test (OGTT), while impaired glucose tolerance (IGT) is defined as when plasma glucose levels are higher than 140 mg/dL after an OGTT [4] (Table 25.1). Along with IGT, another prediabetic state has been defined: impaired fasting glucose (IFG). IFG is defined as serum fasting glucose levels between 100 and 125 mg/dL [4] (Table 25.1). Epidemiological studies indicate that IFG and IGT are two distinct categories of glucose tolerance that overlap only to a very limited extent in children [5]. Recently, the ADA has published recommendations to use hemoglobin A1c (HbA1c) to diagnose diabetes [4]. In particular, it has suggested a cutoff point of 6.5% to diagnose T2D. This cutoff point was chosen on the basis of cross-sectional and longitudinal studies.
conducted in adults showing that it identifies about one-third of cases of undiagnosed diabetes and that subjects with HbA1c higher than that cutoff show higher prevalence of microvascular complications in the long term [6]. Subjects with HbA1c between 5.7% and 6.4% are identified as being “at increased risk of diabetes” [4]. It has to be noted that the measure of 2-hour glucose and the measure of HbA1c are not mutually exclusive as diagnostic tools of diabetes; in fact, there is little agreement between them [7]. Thus, for a correct diagnosis and to avoid missing some patients it would be useful to measure them both.

**LINK BETWEEN OBESITY AND T2D: ECTOPIC FAT ACCUMULATION**

Obesity-related ectopic fat accumulation in key insulin-sensitive organs such as skeletal muscles and the liver causes alterations of the insulin-signaling pathway, leading to increased insulin resistance, characterized by defects in the nonoxidative pathway of glucose metabolism, higher intramyocellular lipid content, and higher visceral and hepatic fat content [8]. Fat accumulation in the liver is an important trigger of insulin resistance and its severity is associated with the presence of prediabetes in adolescents [9]. Recent studies in obese children and adolescents have elucidated the effect of hepatic steatosis on insulin sensitivity and metabolic syndrome. In a multiethnic group of 118 obese adolescents, Cali et al. observed that, independent of obesity, the severity of fatty liver was associated with the presence of prediabetes (IGT and IFG/IGT) [9] (Figure 25.1). Paralleling the severity of hepatic steatosis, there was a significant decrease in insulin sensitivity and impairment in beta cell function, as indicated by the fall in the disposition index [9]. Moreover, the authors observed that, paralleling the severity of fatty liver, there was a significant increase in the prevalence of the metabolic syndrome, suggesting that hepatic steatosis may be a predictive factor of metabolic syndrome in children [9] (Figure 25.1). Importantly, in obese adolescents the negative effect of fatty liver on insulin sensitivity is independent of the degree of visceral fat and intramyocellular lipid content [10]. A longitudinal study has shown that baseline hepatic fat content correlates with 2-hour glucose, insulin sensitivity, and insulin secretion at 2 years follow-up [11]. These data indicate that intrahepatic fat accumulation is more deleterious than ectopic fat accumulation elsewhere in the body [12].

**PUBERTY AND ETHNICITY AS MAJOR RISK FACTORS FOR T2D IN CHILDREN**

T2D usually manifests during puberty together with a peak of transient insulin resistance, probably as a consequence of the rise in growth hormone [13,14]. Previous data suggest that insulin resistance during puberty is restricted to peripheral glucose metabolism and that selective insulin resistance leading to compensatory hyperinsulinemia may serve to amplify insulin’s effect on amino acid metabolism, thereby facilitating protein anabolism during this period of rapid growth [15].

**TABLE 25.1**

<table>
<thead>
<tr>
<th>Criteria for Diagnosis of Increased Risk for Diabetes (Prediabetes)</th>
<th>Criteria for Diagnosis of Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c 5.7%–6.4%</td>
<td>HbA1c ≥6.5%</td>
</tr>
<tr>
<td>Fasting plasma glucose ≥100 mg/dL: IFG</td>
<td>Fasting plasma glucose ≥126 mg/dL.</td>
</tr>
<tr>
<td>2-hour plasma glucose ≥140 mg/dL: IGT</td>
<td>2-hour plasma glucose ≥200 mg/dL</td>
</tr>
<tr>
<td>Random plasma glucose ≥200 mg/dL in patients with symptoms</td>
<td></td>
</tr>
</tbody>
</table>


*Note:* IFG, impaired fasting glucose; IGT, impaired glucose tolerance.
Insulin Resistance and Type 2 Diabetes in Pediatric Populations

and ethnicity represent additional risk factors. In fact, African American, Hispanic, Asian/Pacific Islander, and American Indian adolescents have a much higher incidence and prevalence of T2D than non-Hispanic whites, and this is independent of any ethnic difference in overall adiposity or fat distribution [2]. Within each ethnic group, girls show a higher risk than boys, which could be because adolescent girls experience a more severe degree of insulin resistance than boys [2].

**BETA CELL IMPAIRMENT AS A KEY DETERMINANT OF TYPE 2 DIABETES DEVELOPMENT**

The relationship between insulin demand and secretion is a key factor regulating the maintenance of NGT. In fact, the beta cell response to insulin resistance results in hyperinsulinemia, which is needed to maintain normal glucose levels. In the long term, however, beta cell function tends to deteriorate and insulin secretion may not be sufficient to maintain glucose levels within the normal

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**FIGURE 25.1** (a) Prevalence of prediabetes in obese adolescents according to the degree of liver fat content (%) measured by fast magnetic resonance imaging (MRI). The prevalence rates of impaired glucose regulation (IFG, IGT, IFG/IGT) tended to rise across tertiles \( (p \text{ for trend } = .07) \). (b) Prevalence rate of each component of the metabolic syndrome (Ford’s criteria) according to the degree of liver fat content (%) measured by fast MRI. There were no differences in waist circumference (WC), fasting plasma glucose (FPG), or blood pressure (BP) across categories. The prevalence rates for triglycerides (TG) and large high-density lipoprotein (L-HDL) levels showed significant differences between low liver fat content and the remaining groups \( (p = .000) \). \( p \) values were adjusted for age, gender, and race/ethnicity. White box = low liver fat content; light gray = moderate liver fat content; dark gray = high liver fat content. (Reproduced with permission of John Wiley and Sons: license no. 3646730552564, released 06/12/2015. From Cali, A.M., et al., *Hepatology*, 49, 1896–903, 2009.)
range [16]. The deterioration of beta cells occurs faster in youth than in adults; in fact, while in adults the transition toward T2D takes about 10 years with an ~7%-per-year reduction in beta cell function, in obese adolescents beta cells deteriorate at a rate of ~20%–30% per year [17], with a mean transition time from prediabetes to overt diabetes of about 2.5 years [18].

When insulin secretion is estimated in the context of the “resistant milieu,” IGT subjects show a significantly lower degree of insulin secretion than a group with normal glucose tolerance (NGT) [19]. In particular, using hyperglycemic hyperinsulinemic clamp studies, Weiss et al. investigated the role of insulin secretion in glucose regulation in a group of 62 obese adolescents with different glucose tolerance statuses (30 with NGT, 22 with IGT, and 10 with T2D) [19]. This study showed that, compared with obese adolescents with similar insulin resistance, those with IGT have a progressive loss of glucose sensitivity of beta cell first-phase secretion and that beta cell second-phase secretion is compromised in T2D [19]. This observation recognizes that the decline of the first phase of insulin secretion is present before the overt diabetes and that it may be considered a fingerprint of prediabetes, whereas the defect in the second phase is required for the development of T2D. Differences in beta cell function have been described in various prediabetic conditions seen in obese adolescents, such as IFG or IGT, or the combined IFG/IGT states. Cali et al. documented that in obese adolescents (1) IFG is primarily linked to alterations in glucose sensitivity of first-phase insulin secretion [5], (2) IGT is characterized by a more severe degree of peripheral insulin resistance and a reduction in first-phase secretion, and (3) the co-occurrence of IFG and IGT is the result of a defect in second-phase insulin secretion and of profound insulin resistance [5].

The idea that genetic predisposition plays an important role in the development of pediatric T2D is supported by clinical studies showing that youth developing IGT or T2D show a lower insulin secretion even before the onset of IGT or T2D. The role of a preexisting beta cell dysfunction in obese adolescents with NGT has been shown in a longitudinal study [20]. In a group of obese NGT adolescents who underwent repeated OGTT over a period of 3 years, those who progressed to IGT had a lower beta cell function at baseline compared with those who did not progress. These data have recently been confirmed by Giannini et al., who, using hyperglycemic clamp studies, showed an early impairment of beta cells in subjects with NGT who subsequently went on to develop IGT or T2D [16].

**COMPLICATIONS OF PEDIATRIC TYPE 2 DIABETES**

Microalbuminuria and hypertension have been reported in cross-sectional studies in youth with T2D [21,22]. Hypertension is present in 11.6% of youth with T2D, but this number increases to 33.8% about 3.9 years after the diagnosis [23], with males showing a much higher risk than females of developing hypertension [23].

The prevalence of retinopathy in youth with T2D has been estimated at around 13.7% [24], similar to adult data from the Diabetes Prevention Program (12.6% after 3 years of T2D) [25]. A higher prevalence of retinopathy has been observed in subjects with older age, a longer duration of diabetes, and poorer glycemic control [24].

Microalbuminuria is usually seen in about 6% of youth with T2D, but this increases by about three times approximately 3.9 years after the diagnosis [23]. Moreover, an elevation of HbA1c level is strongly correlated with microalbuminuria, with every 1% increase in HbA1c level increasing the risk of microalbuminuria by 17% [23].

Along with microvascular complications, macrovascular issues are already present in youth with T2D. In fact, pediatric T2D is associated with an abnormal vascular stiffness, as measured by aortic pulse wave velocity [26]. In the SEARCH for Diabetes in Youth study, 43% of youth with poorly controlled T2D had a low-density lipoprotein cholesterol level higher than 130 mg/dL, and 40% had a triglyceride level greater than 200 mg/dL [27]. These data clearly indicate that complications of T2D are already present in the pediatric population and that their degree of severity might progress much faster than in adults.
GENETIC STUDIES IN PEDIATRIC PREDIABETES AND TYPE 2 DIABETES

So far, several genome-wide association studies (GWAS) have helped to highlight the genetic bases of T2D, and several single-nucleotide polymorphisms (SNPs) have been discovered to be associated with T2D [36]. The majority of them are intronic or nearby a gene and only a few of them are missense mutations (such as rs1801282 in PPAR-gamma, characterized by a C-to-G substitution encoding a proline-to-alanine substitution at codon 12) [37]. The majority of gene variants associated with T2D are in genes expressed in beta cells. Because of the lack of very large pediatric cohorts, the majority of GWAS have been conducted in adults and information on the genetics of T2D in youth is limited to few studies. Recently, Dabelea et al. genotyped the rs12255372 and rs7903146 variants in/or near the TCF7L2 gene in a multiethnic cohort of 1239 youths (240 cases and 999 controls) enrolled in the SEARCH study, and observed that in African Americans the rs7903146 variant was associated with an almost twofold increase in odds of showing T2D [28]. Barker et al. genotyped 16 SNPs, previously found to be associated with diabetes by GWAS, in 6000 children and adolescents and determined whether they were also associated with fasting glucose levels [29]. The authors observed that nine loci were associated with fasting glucose levels; in particular, they confirmed five previously discovered SNPs and discovered four more loci associated with fasting glucose.

More recently, it has been shown that common variants in or near genes modulating insulin secretion are associated with a higher risk of developing prediabetes and T2D in youth [30]. In particular, Giannini et al. have shown that the co-occurrence of risk alleles in or near genes expressed in beta cells is associated with a defect of insulin secretion, resulting, in conditions of extreme insulin resistance, in the development of prediabetes and T2D [30]. Similarly, Zheng et al. have observed that genetic variants in the MTNR1B gene, which is involved in modulating fasting glucose levels, are associated with the development of IFG and IGT [31]. These observations support the theory that a predisposed genetic background is associated with the onset of prediabetes and T2D at a lower age.

Despite the strength of these associations, the portion of heritability explained by the identified loci has been estimated to be around 10%. Although the sample size of GWAS continues to increase, revealing new associations, each newly associated variant has an incrementally smaller effect size and contributes only marginally to the cumulative variation of the phenotype. GWAS may be reaching the limits of their ability to reveal genetic variations underlying complex traits, and additional genetic variations, such as rare variants with large individual effects, may contribute to the heritability of complex traits such as T2D. Therefore, very recently, it has been proposed that rare variants may explain the missing heritability of T2D.

THERAPEUTIC STRATEGIES FOR YOUTH WITH TYPE 2 DIABETES

In the pediatric population, only two drugs are approved for the therapy of T2D—insulin and metformin—and the best approach to this disease in the pediatric population remains unclear. Recently, the pediatric trial Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) was completed [32]. The TODAY study was a 15-center clinical trial, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, that examined the efficacy of three approaches to the treatment of T2D in youth: metformin alone, metformin plus rosiglitazone, and metformin plus an intensive lifestyle intervention called the TODAY Lifestyle Program [32]. The authors studied 699 subjects between 10 and 17 years of age; the patients were randomized to each arm and followed up for about 3.86 years. Although the rate of failure in each arm was quite high (51.7% metformin alone, 38.6% metformin plus rosiglitazone, 46.6% metformin plus lifestyle), treatment with metformin and rosiglitazone was more effective in maintaining glycemic control than the treatment with metformin alone \((p = .006)\), and although it seemed to be better also than the metformin and lifestyle treatment, this difference was not statistically significant \((p = .16)\) [32]. Interestingly, performing subgroup analyses, the authors observed that metformin alone was less effective in non-Hispanic blacks than in non-Hispanic whites or Hispanics [32].
In general, what is really striking from the TODAY study is the high rate of failure in each arm. As it has been observed [33], this study was dealing with a highly complex population: adolescents with T2D who grew up in a very sedentary environment [32]. The data seem to suggest that any intervention in this population may be extremely challenging, thus more effort should be put into the prevention of obesity and T2D.

More recently, another multicenter effort to assess the best strategy to treat subjects with T2D has started. The Restoring Insulin Secretion (RISE) study, which involves an adult and a pediatric population, is testing interventions designed to preserve or improve beta cell function in prediabetes or early T2D [34]. Although the design has been published, the study is still ongoing and will answer a very important question: can we restore beta cell responsivity in obese kids by using insulin in the early stages of T2D or even in the prediabetic stage?

Although progress has been made over decades toward a better understanding of the pathophysiology of T2D in youth, additional research addressing how certain gene variants modulate pathogenetic mechanisms may advance the current state of knowledge and provide new insights for the prevention and the treatment of T2D in youth. There is an urgent need for novel prevention and intervention strategies to curb youth-onset T2D.

CONCLUSIONS

This overview shows that T2D can be particularly aggressive in youth. Moreover, this is the first generation in which this phenomenon is so diffuse; therefore, longitudinal data showing the long-term natural history of early onset T2D are not available yet. That is why it is important to bear in mind that childhood obesity represents a major problem for public health to be fought not only from a medical point of view but mainly from a political perspective [35,36].

REFERENCES

26 Childhood Obesity and Cardiovascular Risk

P. Babu Balagopal

INTRODUCTION

Obesity prevalence in children and adolescents has dramatically increased in the past 30 years [1]. Despite the more vigorous efforts over the last decade to prevent and control obesity, it remains at a disturbingly high state in children and adolescents. The relationship between early body mass index (BMI) and adult cardiovascular disease (CVD) risk is very complex. However, the severity of obesity, its presence for a longer period, and its tracking into adulthood are of concern because adult obesity directly portends and escalates metabolic and cardiovascular consequences. Despite the recent notion of a stabilization of obesity trends in children and adolescents [1], the issue continues to be troubling because of the concerns it raises about accelerated development of type 2 diabetes mellitus (T2DM) and CVD [2–7]. Obese children are, to a large extent, more likely than normal-weight children to become obese adults [8]. What is particularly worrisome is the fast-increasing prevalence of severe obesity in children, with an enhanced potential for the development of cardiometabolic diseases at an early age [9]. The central premise of this chapter is to briefly discuss the effect of child obesity on the development of CVD and the role of potential mediators of the relationship between childhood obesity and CVD risk (Figure 26.1). In doing so, the role of dysfunctional adipose tissue and obesity-driven biomarkers (Figure 26.2) that increase CVD risk will also be discussed.

TRACKING OF OBESITY FROM CHILDHOOD TO ADULTHOOD

An imminent risk of clinical events such as coronary heart disease (CHD) death is extremely low among youth. This notion, however, is gradually being modified because of the potential impact of obesity on early derangements in the metabolic framework of children and adolescents. Longitudinal
studies have frequently demonstrated the persistence of childhood obesity into adulthood, with increased risk of adverse consequences in terms of chronic diseases in adulthood, T2DM and CVD being the most ominous [10]. Studies including the Bogalusa Heart Study and the Coronary Artery Risk Development in Young Adults (CARDIA) study have consistently shown the adverse effects of progressive weight gain. Excess weight, once gained, is difficult to manage and tracks into adulthood. Yet, the independent contribution of early obesity to CVD risk remains inconclusive and not explicitly established. The majority of metabolic and cardiovascular complications related to obesity, however, appear to be already present at an early age in the clinical course of obesity. These include unfavorable levels of blood pressure, insulin, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein (LDL) cholesterol, and triglyceride levels [3,11,12]. More recent studies have reported alterations in various nontraditional risk factors or biomarkers of CVD [7,13]. Cardiac structure and function, including left ventricular hypertrophy (LVH) and excess left ventricular mass relative to cardiac workload, has also been reported to be adversely affected by excess fat mass in children and adolescents [11,14,15].

The risk of obesity-related comorbidities is amplified owing to various factors. The severity of obesity in childhood and its duration and persistence over many years are crucial factors that are involved in the progression of obesity to overt CVD [16]. More than two decades of obesity duration doubled the mortality risk, as reported in a recent analysis of the Framingham data [17]. An inverse association between birth weight and the development of various disorders such as CHD, hypertension, T2DM, and CVD has been suggested [5]. Although the relationship between birth weight and later obesity is less clear, it appears that a “u-shaped” curve exists [11]. While high birth weight appears to predict obesity in children and adults, low birth weight has been linked to lower lean
body mass (mainly muscle) and increased abdominal obesity and higher body fat percentage later in life [18], leading to significant health problems and adult morbidity and mortality.

Obesity is an extraordinarily complex phenotype and its silent progression to various chronic diseases is intricate. A cascade of events contribute, mostly in concert; obesity-related comorbidities can be considered the accumulated result of a range of both genetic and environmental factors (Figure 26.1). Fortunately, overt CVD is rare in children and/or young people, but many of the underlying traits and exposures that lead to CVD and related comorbidities in later life are acquired in childhood. In fact, the complex framework and the track toward CVD appear to start from the preconception period and pass through fetal development, postnatal life, childhood, adulthood, and old age [7,18]. High adolescent BMI significantly increased adult diabetes and coronary artery disease risks in Israeli military recruits who were followed from late adolescence to adulthood [19]. Some studies, however, have shown that BMI in early childhood (<9 years) is less predictive of future risk compared with BMI in the adolescent period [20]. Notwithstanding the debate on the threshold age at which obesity makes a larger contribution to future CVD risk, it is obvious that the exposures at various stages of life result in small and large insults/injuries to the system. The cumulative effects of various exposures over time lead to chronic diseases, including T2DM and CVD.

**BIOMARKERS/RISK FACTORS AND SURROGATE END POINTS IN CVD**

Because CVD is silently progressive and the atherosclerotic process takes decades to manifest into overt disease, the final disease end points are not easily detectable in children. Clinical and biological risk factors associated with CVD have been identified in children using surrogate anatomic and physiological markers and have been tracked into adulthood [21]. In this context, reliable risk
factors and biomarkers of obesity-related CVD are central to the understanding of the development of CVD in children. One focus of this chapter is on obesity-related biomarkers of CVD in children.

The major risk factors for CVD can be roughly categorized into nonmodifiable/constitutional and modifiable risk factors (Figure 26.1). These aspects have been systematically reviewed in a recent statement paper from the American Heart Association [7]. In brief, the nonmodifiable/constitutional risk factors include age, sex, and family history of atherosclerosis. The modifiable risk factors constitute a spectrum of factors categorized into two broad types: traditional and nontraditional. The major potentially modifiable traditional risk factors for CVD include behavioral/lifestyle (nutrition/diet, physical inactivity, tobacco exposure, and prenatal exposure), physiological (blood pressure, lipids, glucose, and insulin), and medical diagnostic markers (diabetes and chronic kidney disease). The nontraditional risk factors of CVD consist of various factors and biomarkers related to alterations in various organs in the body, especially adipose tissue. These include both functional markers as well as circulating markers. Obesity causes profound changes both in the vasculature and physiology of adipose tissue that lead to the altered production of numerous molecules in the tissue. They appear to engage in significant cross talk between other organs in the body, accelerating the process of atherosclerosis. Certain fundamental physiological processes such as insulin resistance (IR), coagulation and thrombosis, oxidative stress, and inflammation play crucial roles in the development and/or progression of obesity to CVD earlier than previously considered.

There are four large prospective cohort studies of CVD risk factors (from different parts of the world) that followed children into adulthood: the Cardiovascular Risk in Young Finns Study (Finland), the Childhood Determinants of Adult Health (CDAH) study (Australia), the Bogalusa Heart Study (United States), and the Muscatine Study (United States). These studies collectively demonstrated that childhood obesity, metabolic syndrome, and poorly controlled traditional risk factors contribute to the progression of coronary artery atherosclerosis and carotid artery calcification in adulthood [22]. These studies, along with the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) studies, provide support for earlier observations that atherosclerosis begins in childhood and progresses mutely through adolescence and young adulthood into middle age; a high relative risk at young age likely will be transformed into high absolute risk of advanced coronary artery lesions later in life [23].

SURROGATE MEASURES OF TARGET ORGAN DAMAGE

Since overt CVD events remain extremely rare in children and adolescents, surrogate CVD markers are used as alternative indicators of CVD events. Biomarkers of CVD are useful at multiple points as indicators of disease traits, disease state, rate of progression, or surrogate end points for monitoring treatment outcomes [11]. These surrogate biomarkers used for CVD include anatomical measures (carotid intima-media thickness [cIMT] and coronary artery calcification [CAC]), noninvasive assessment of vascular function and physiological measures (vascular structure, arterial stiffness, endothelial function, and blood pressure), and circulating biomarkers (lipids and markers of inflammation, oxidative stress, and IR). Recently, the American Heart Association published recommendations/statements regarding these surrogate markers and their use in the pediatric population [7,24].

DISLIPIDEMIA

Over the past several decades, data have accumulated linking adverse levels and patterns of lipids and lipoproteins to the initiation and progression of the atherosclerotic process in children and adolescents [2]. Atherogenic dyslipidemia is characterized by an assemblage of abnormalities that include elevated triglycerides (TG), apolipoprotein B (apoB), small LDL (sLDL) particles, and a reduced level of HDL-C [11]. No direct data from longitudinal population-based studies are available that link the absolute levels of lipids and lipoproteins in childhood to overt CVD in adulthood. However, various reports, including the Third National Health and Nutritional Examination Survey
Childhood Obesity and Cardiovascular Risk

(NHANES III), the Bogalusa Heart Study, and the Lipid Research Clinics Population Studies, have shown that, compared with children and adolescents with normal body weight, their obese counterparts have a more unfavorable profile of the preceding factors. Magnussen et al. analyzed data from the Bogalusa Heart, Young Finns, and CDAH studies and concluded that adolescent dyslipidemia combined with obesity was most strongly associated with adult cIMT [25]. The pathophysiology still remains unclear, but lifestyle, rather than genetic influences, predominate the atherogenic-type dyslipidemia phenotype [11,26]. Childhood non-HDL-C level and change in BMI over time predicted adult dyslipidemia, but was not independent of adult obesity, as shown from the Bogalusa Heart Study data [10]. Combined data from the Young Finns, Bogalusa Heart, and CDAH studies suggested that childhood BMI was the best predictor of adult HDL-C levels [25,27].

HYPERTENSION

Hypertension is one of the major cardiovascular complications associated with obesity. Contrary to the typical notion that essential or primary hypertension affects only adults, increased rates of hypertension are evident at early age in the clinical course of obesity [28]. In 2004, the NHANES data demonstrated the first hint of a shift in the epidemiology of childhood hypertension and showed that overall blood pressure levels in US children and adolescents have increased [29,30]. In autopsy studies, elevated childhood BP has been associated with atherosclerotic lesions [31]. The Bogalusa Heart Study has also demonstrated that children with elevated blood pressure are several times more likely to develop essential hypertension as a young adult [28]. The risk of hypertension in children appears to increase across the spectrum of BMI values rather than having a specific threshold effect [28]. In adults, persistent hypertension has a significant impact on health, including coronary artery disease, stroke, and kidney diseases. However, the natural history of primary hypertension in children is not available, but insights have been gleaned from data on pediatric secondary hypertension and health consequences that include aortic coarctation and chronic kidney disease [30]. Hypertension in cross-sectional studies of obese youth with T2DM has been shown to coexist with LVH as early as adolescence [11,30]. Therefore, obesity-related hypertension in the pediatric population cannot be ignored, and additional data are needed to assess the independent relationship between obesity in childhood and hypertension in adulthood.

MYOCARDIAL TISSUE REMODELING AND CHILD OBESITY

Intermediate end points between conventional risk assessment and overt disease events include left atrial enlargement, LVH, coronary calcium, increased carotid wall thickness, and abnormal endothelial function. These intermediate risk assessment points are not only related to conventional risk factors, but are also independent predictors themselves. LVH, or increased thickness of the heart’s main pumping chamber, is an essential manifestation of hypertensive damage to the organ and has been recognized as an independent contributor to increased cardiovascular morbidity and mortality. Daniels et al. showed a high prevalence of severe LVH and abnormal geometry in children and adolescents with essential hypertension [14]. This finding has been corroborated in various subsequent studies [32,33]. Gidding et al. reported coronary artery calcium and increased carotid wall thickness in adolescents with heterozygous familial hypercholesterolemia [34]. A recent study showed an association with the degree of adiposity and concentric left ventricular remodeling in midlife, whereas the cumulative effects of a longer duration of overall obesity during young adulthood contribute to eccentric remodeling, predominantly by increasing left ventricular mass [35]. Epidemiological and clinical studies have indicated that LVH in children worsened with the dual burden of obesity and elevated blood pressure than with blood pressure elevation alone. Recent data from the Bogalusa Heart Study have indicated that the process of LVH and subclinical changes in cardiac structure are influenced by excess adiposity and hypertension, both cumulatively and independently from early life [33]. These data support the presence of end organ injury in youth
Childhood Obesity: Causes, Consequences, and Intervention Approaches

(Figure 26.1). Therefore, good cardiovascular health cannot be assumed in obese children and adolescents. While there are no longitudinal data on weight trends in children with congenital heart disease, recent studies indicate a relationship between congenital heart disease and overweight/obesity [36].

**INSULIN RESISTANCE**

Although IR can be broadly characterized as an impaired biological response to insulin, it is the product of various processes. These processes are mediated at the level of cellular mitochondria that produce endoplasmic reticulum (ER) stress, oxidative stress, and adipocyte dysfunction that leads to alterations in the release of numerous adipokines. Systemic manifestation of these processes is evident mainly in fat, muscle, and liver. The direct relationship between IR and fatness is well known and it is considered the most ominous abnormality related to obesity [3,6,37]. In adults, IR is well recognized as a cardinal feature in the development of T2DM. In children and adolescents, IR is related to obesity and various metabolic and cardiovascular complications [3,6,7,13]. Obesity in children frequently persists into adulthood with increased risk of the development of IR, which is the consequence of various interrelated processes. IR is considered not only to be the key link between adiposity and T2DM, but it accelerates the progression of obesity to CVD and worsens its outcomes [11]. Despite these strong relationships, the assessment of IR in children is challenging and still lacks clarity. The hyperinsulinemic euglycemic clamp and the frequently sampled intravenous glucose tolerance test (FSIVGTT) with modeling are generally accepted as valid and reliable for the measurement of insulin sensitivity [3,38]. However, these methods pose various technical challenges for frequent use in children, such as the fact that they are time consuming, they are relatively invasive in nature, and a research setting is required to perform the studies. Despite their limitations, less invasive, surrogate estimates of IR, such as insulinemia and homeostatic model assessment (HOMA)-IR have been used in numerous studies in children. Although studies have demonstrated childhood obesity correlates with IR, assessed using various estimates of IR, obesity is not synonymous with IR [11]; studies have demonstrated that despite an equal degree of adiposity, the extent of IR is significantly higher in obese youth with impaired glucose tolerance (IGT) compared with those with normal glucose tolerance (NGT) [39]. Similarly, obese youth with T2DM are significantly more insulin resistant that those without diabetes, matched for age, sex, and BMI [40]. Further, IR in obese youth varies by ethnicity and studies have also shown the direct effects of IR on CVD outcomes, independent of BMI [3]. The association between IR and traditional risk factors such as hyperglycemia, dyslipidemia, and hypertension is well established. Recent studies have suggested strong associations between IR and various nontraditional risk factors, such as those related to inflammation, thrombosis, and oxidative stress [7,13]. Further, it appears that there is an interaction between traditional and nontraditional risk factors, and both can worsen IR, consequently leading to a vicious cycle that promotes the development of atherothrombotic disease.

**EXPANSION OF ADIPOSE TISSUE AND ADIPOCYTE DYSFUNCTION**

Insights into adipose tissue biology and metabolism in humans have rapidly evolved during the last several years. The stature of adipose tissue has been transformed from an inert organ for energy homeostasis to a biologic reservoir for nutrient storage that expands in response to overnutrition and releases lipids, various hormones, and an array of cytokines, commonly referred to as adipokines. Excess adiposity/expansion of the adipose tissue, especially its storage in specific depots of body fat, appears to be central to shifts in the metabolic and pathophysiological pathways, leading to increased risk of cardiometabolic diseases. A simplistic portrayal of this excess fat can be linked to an imbalance between energy intake and energy expenditure. Children are growing and they need to have a positive energy balance for tissue growth. How the excess energy will be partitioned and stored is crucial. It appears that, in an obesogenic environment, the surplus energy is stored as fat
cells, leading to an increase either in number (hyperplasia) or size/volume (hypertrophy), or often in both [8,41]. When the hyperplasia and hypertrophy are inadequate for the absorption of the excess circulating nutrients, the capacity of the adipocyte to store glucose and TG is also compromised, leading to dysfunctional adipose tissue (Figure 26.2). The dysfunction of the adipose tissue channels into a variety of stresses and inflammatory processes within the tissue, causing alterations in the production and regulation of numerous molecules. Some of these molecules are shown in Figure 26.2. Unfortunately, obesity-related alterations in these molecules arise quite early in life, with a profound impact on overall health, leading to cardiometabolic disease. The Bogalusa Heart Study provided the earliest evidence of the contribution of adipose tissue to increased risk of T2DM and CVD in children and adolescents [21].

The expansion of adipose tissue has profound effects not only within the adipose tissue, but on the function of most other organ systems in the body as well. The cross talk between organs is orchestrated by diverse metabolites and secretomes produced in the adipose tissue, leading to various physiological abnormalities such as ER stress and oxidative stress, and alterations in inflammatory signals, prothrombotic factors, and IR (Figure 26.2). For example, inflammatory molecules such as IL-6 stimulate the production of various acute-phase proteins such as fibrinogen, CRP, and RBP4 in the liver. Further, it appears that a vicious connection exists between weight gain, poor physical fitness, and physical inactivity; each separately or in concert reinforces the path toward CVD [7,41].

**SUBCLINICAL INFLAMMATION**

Multiple lines of evidence indicate that the presence of an obesity-related inflammatory state not only plays a crucial role in the evolution of CVD, but is central to all stages of atherosclerosis, including plaque development, disruption, and thrombosis [42]. In recent years, the pivotal role of inflammation in obesity-related CVD has become more widely appreciated in children [7]. The dysfunction of the adipose tissue results in the altered secretion of an array of molecules that are crucial in the regulation of many metabolic, hormonal, and inflammatory signals in humans (Figure 26.2). Although numerous biomarkers related to inflammation have been proposed and their predictive roles are being vigorously investigated [7,43], C-reactive protein (CRP) is probably the most studied biomarker for inflammation in children [44–47]. Studies in children have also reported a coordinated elevation in CRP, IL-6, and fibrinogen in the setting of obesity and IR [7,46]. Increases in the levels of CRP and oxidized LDL as a function of the degree of obesity has also been reported [9]. Despite the consistent finding of a raised inflammatory state in obese children [7], the relationship between childhood CRP levels and vascular function (cIMT) in adults remains uncertain [47,48]. Since a state of sustained exposure to subclinical inflammation results in cardiovascular end organ injury [42], the presence of an inflammatory state in obese children is perturbing. Although not universal, it appears that lifestyle interventions early in the clinical course of obesity reduce the elevated levels of these inflammatory factors (recently reviewed in [7,9,43]).

**OXIDATIVE STRESS**

Different pathways and mechanisms are involved in the complex link between obesity and CVD (Figure 26.1). Oxidative stress may be involved in the pathogenesis of CVD and atherosclerosis via the oxidation of LDL particles and their uptake by macrophages, as well as the production of reactive oxygen species (ROS) that cause localized damage to cells [49–52]. Oxidative stress involves an imbalance in the net concentration of ROS relative to the body’s capacity to offset their damaging effects. ER and the mitochondria play crucial roles in the production of ROS. In obesity, adipocyte dysfunction due to nutrient excess triggers the mitochondria to produce adenosine triphosphate (ATP) at a more rapid rate via the uncoupling of oxidative phosphorylation, leading to the increased production and accumulation of ROS. This could result from unfolded-protein response
(UPR)-regulated oxidative folding machinery in the ER, superoxide anion produced mainly in mitochondria, nitric oxide produced during arginine metabolism, α-ketoglutarate dehydrogenase in the tricarboxylic acid (TCA) cycle, complexes I and III of the mitochondrial respiratory chain, and several other factors [50]. With the increase in ROS production, the overall antioxidant defense mechanism is compromised, thus magnifying oxidative stress in the system, leading to mitochondrial DNA damage and IR. The direct measurement of in vivo oxidative stress is problematic. Although several markers have been suggested, whole-body oxidative stress is best reflected by systemic levels of lipid peroxidation, for example, F2-isoprostanes. Little is known about oxidative stress in the pediatric age range, but most available studies have shown concurrent elevations in inflammatory and oxidative status, paralleled by marked alterations in IR [7,43,49–51].

**Coagulation and Fibrinolysis**

Coagulation and fibrinolysis are two key components of thrombosis. The balance between these two dynamic processes is essential to maintain the fluidity of blood, and it determines the propensity for clot formation and removal [53]. The process of coagulation and the formation of a clot involve the thrombin-induced formation of insoluble fibrin strands from soluble fibrinogen. Plasminogen activator inhibitor 1 (PAI-1) is a marker of fibrinolysis, which is the basic defense mechanism of organisms for removing the clot and controlling the deposition of fibrin in the vascular system [54]. Hyperfibrinogenemia and hypofibrinolysis (enhanced levels of PAI-1) reflect a prothrombotic state en route to cardiovascular events. The manifestation of such a thrombotic state related to obesity has been reported in children and adolescents [7,55,56]. Although obesity-related derangements in coagulation and fibrinolysis systems have been consistently reported in animal and adult studies [57], the data in children are somewhat limited and mixed [7]. A recent advance in the field has been the proposed role of gamma prime (γ′) fibrinogen (an isoform of fibrinogen), which forms clots that are more resistant to fibrinolysis [58]. Elevated levels of γ′ fibrinogen have been recently reported in obese children compared with their lean counterparts [59]. Although the data on the effect of lifestyle-based interventions in obese children are consistent on the coagulation system [46,55], they are mixed with respect to its effect on the fibrinolysis system [7,55,56,59]. There is a clear gap in our understanding of the role of a hypercoagulable and hypofibrinolytic state early in the clinical course of obesity and its impact on future thrombotic events.

**CVD Risk Factors: Children Versus Adults**

While the risk factors and biomarkers are evident at early age in obese children, it is less clear whether the mechanistic regulation of these risk factors is similar in adults and children. This is important because such an understanding will help in the development of more directed therapies to prevent and/or reverse the progression of obesity into overt disease conditions. Unfortunately, studies exploring the underlying mechanisms in children are sparse. Although direct comparisons of studies in children and adults and/or the elderly are not viable, there are some glimpses of data showing potential differences in the regulation of risk factors of CVD in children and adults/the elderly [7]. For example, while hyperfibrinogenemia in children and its reduction by physical activity are mainly regulated by changes in fibrinogen fractional synthesis rates [56], elevated levels of fibrinogen in the elderly appear to be due to its deceased breakdown [60]. Elevated levels of retinol binding protein 4 (RBP4) are related to obesity-related IR in children [61] and adults [62]. An unexpected, perhaps counterintuitive, direct relationship between RBP4 and inflammation was also observed in obese children, unlike that found in disease-related inflammation [61]. These suggest that the potential regulation of biomarkers or risk factors of CVD in obese children may be different from that reported in adults and/or disease conditions other than obesity. Indeed, as far as obesity and certain CVD risk factors are concerned, children are not little adults. Thus, therapies developed in adults for reducing obesity-related CVD risk cannot be directly translated to children. Recent
Childhood obesity and cardiovascular risk studies suggest that medications approved for long-term obesity treatment, when used as an adjunct to lifestyle intervention, lead to greater mean weight loss and an increased likelihood of achieving clinically meaningful, longer-term weight loss [63]. Further studies are warranted on such adjunct therapeutic approaches that are useful in CVD risk reduction in obese children.

**CONCLUSION**

Childhood obesity tracks into adulthood and adult obesity directly impacts metabolic and cardiovascular consequences. The relationship between early obesity and adult CVD risk is complex, but many obese children and adolescents already manifest various metabolic complications, and these children are at high risk of developing cardiometabolic diseases with increased morbidity. As is obvious from the available literature, a complex interplay among biological and physiologic factors promotes the initiation and progression of obesity into metabolic and vascular diseases. Understanding the underlying mechanisms of the pathogenesis of the obese phenotype with early derangements in insulin sensitivity, oxidative stress, and subclinical inflammation is of critical importance. There is a gradation in understanding the long-term CVD risk in children, and biomarkers of CVD are important when considering the magnitude of risk and the effectiveness of interventions at different stages of the lifespan. The long-term consequences of childhood obesity are avoidable, with the available data supporting this positive message, and there remains an opportunity for intervention across the lifespan. However, better understanding of the pathophysiology and underlying mechanisms regulating the different pathways of progression from obesity to CVD is required for the development of more directed therapies in children.

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**REFERENCES**


Childhood Obesity and Cardiovascular Risk


Pediatric Nonalcoholic Fatty Liver Disease

Recent Advances in Diagnostics and Emerging Therapeutics

Elizabeth L. Yu, Kimberly P. Newton, Jonathan A. Africa, and Jeffrey B. Schwimmer

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in children and adolescents.\(^1\) NAFLD encompasses a spectrum of diseases, from isolated steatosis to steatohepatitis and fibrosis. Histological examination is required for definitive diagnosis of NAFLD. Though NAFLD is often suspected in obese children with elevated liver enzymes, it is important to recognize that obesity and NAFLD are not necessarily concomitant. In fact, NAFLD is present in only a minority of children with obesity. However, obese children with NAFLD are at a higher risk of morbidity and mortality. NAFLD also occurs in nonobese children, with average estimates of ~5% prevalence of NAFLD in normal-weight children.\(^2-4\) The pathophysiology of NAFLD, though still incompletely understood, is multifactorial. This chapter highlights pediatric NAFLD (epidemiology, diagnostic approaches, pathophysiology, the impact of NAFLD, and emerging treatments) and more closely examines the relationship between obesity and NAFLD in children.
**DIAGNOSIS OF NAFLD**

**HISTOLOGY**

**Clinical Histopathologic Diagnosis**

NAFLD is defined as 5% or greater macrovesicular steatosis in hepatocytes after exclusion of other causes of steatosis. Hepatic histology is key in the diagnosis of NAFLD. Liver histology can also determine the presence of other findings in addition to steatosis, which may lean toward diagnoses other than NAFLD.

**Components of Nonalcoholic Steatohepatitis**

The diagnosis of nonalcoholic steatohepatitis (NASH) is determined by a constellation of different components of a biopsy, not one single finding, in contrast to diseases such as cancer. In NASH, steatosis is present along with a multitude of other findings that are indicative of hepatic inflammation and cell injury. *Hepatocyte ballooning* is a manifestation of liver injury and refers to the swelling of hepatocytes. *Inflammation* refers to the presence of inflammatory cells, including polymorphonuclear leukocytes, lymphocytes, mononuclear cells, eosinophils, and microgranulomas. These hepatic changes can be either around the central vein or around the portal triad, which includes the portal vein, hepatic artery, and bile duct. *Fibrosis* is collagen deposition in the areas around the sinusoids (perisinusoidal) or around the cells (pericellular). *Advanced fibrosis* is characterized by bridging fibrosis and, at its worst, cirrhosis.

**Scoring Systems**

Pathologists have tried to tie the findings of NASH into semiquantitative scoring systems to correlate clinical findings with histology. However, none of these are used in clinical practice as of yet. The Brunt system attempts to categorize patients with NASH as mild, moderate, or severe based on histological findings and a corresponding numerical score. However, this system does not account for pediatric pathology as it was derived from adult data. The NAFLD Activity Score (NAS), developed by the NASH Clinical Research Network, is a modified version of the Brunt system and is based on three factors: steatosis grade (minimum of >5% for NAFLD) (0–3), lobular inflammation (0–3), and hepatocellular ballooning (0–2). This scoring system is exclusively used in the research setting to evaluate change, not to grade severity; higher scores are not always indicative of NASH, nor is a lower score benign.

**Fatty Liver Disease in Children versus Adults**

Pediatric NAFLD has many subphenotypes that are still beginning to be understood and which differ from adults. Hence, what is known about NAFLD in adults cannot be extrapolated to children. Histologically, there are differences in the location of fat and fibrosis along with differences in where inflammation is noted. At this point, it is unclear if the differences are part of a continuum of disease, with pediatric histology transitioning to adult histology, or if the differences are actually representative of two or more different disease processes.

**Other Diseases with Steatosis**

It is important to note that not all liver steatosis is NAFLD. Other etiologies that can have hepatic steatosis include: Wilson’s disease, hepatitis C, drugs/toxins, metabolic disorders, hepatic ischemia, and disorders of lipid metabolism. Hourigan et al. reviewed liver biopsies of 155 children with steatosis and only 37% were diagnosed with NAFLD, with other diagnoses including metabolic disease (9%), oncologic (8.4%), and viral hepatitis (6.5%). Some children who have NAFLD may have concurrent liver disease, with the most common being autoimmune hepatitis.

Overall, liver histology is an integral part of the diagnosis of NAFLD and NASH. Hepatic histology provides information on a microscopic level that has yet to be derived from noninvasive
measures. Furthermore, hepatic histology helps better define whether a patient has NAFLD or more progressive NASH and fibrosis.

**IMAGING**

To date, no imaging modality has been shown to be uniformly useful to diagnose NAFLD. This includes ultrasound. Ultrasound was found to have a positive predictive value of 47%–62%,\(^{10,11}\) and did not have a consistent correlation with findings on hepatic biopsy. In a recent systematic review\(^{12}\) evaluating the imaging of liver fat in pediatric patients, evidence did not support the use of ultrasound for the diagnosis or grading of fatty liver in a pediatric population.

An advanced MRI measure of steatosis called proton density fat fraction (PDFF) is an emerging imaging modality that has demonstrated accurate correlation with the histologic degree of steatosis. In a recent study evaluating the correlation and diagnostic accuracy of PDFF measured by MRI compared with the grade of histologic steatosis in 174 children, liver PDFF was significantly correlated with steatosis grade \((p < .01)\) and had an overall accuracy of 56% in predicting histologic steatosis grade.\(^{13}\) Though MRI is not yet sufficient to replace histologic examination for diagnosis in children, further studies are underway at this time.

**EPIDEMIOLOGY**

In the Study of Child and Adolescent Liver Epidemiology (SCALE), a 2006 study based on autopsies over a 10-year period (1993–2003) of 742 children aged 2–19 after sudden death, the overall prevalence of NAFLD was demonstrated to be 9.6% when adjusted for age, race, gender, and ethnicity.\(^1\) The prevalence of NAFLD increased to 20%–33% in obese or overweight children (Table 27.1).\(^1\) On one extreme of the spectrum, a recent study evaluating the prevalence of NAFLD among severely obese adolescents (mean body mass index [BMI] 52 kg/m\(^2\)) undergoing bariatric surgery demonstrated a 59% prevalence of NAFLD.\(^2\) Of note, patients included in this study were older adolescents who were on the maximum end of the spectrum of obesity compared with other typical study populations.

The prevalence of pediatric NASH in the general population was demonstrated to be 23% (SCALE), whereas the prevalence of NASH in adolescents undergoing bariatric surgery was similar, at 24%.\(^2,14\) In a separate study for the NASH Clinical Research Network (NASH CRN), 36% of children with NAFLD were found to have NASH.\(^{15}\)

Pediatric obesity is an emerging epidemic with ever-rising rates. As demonstrated by the National Health and Nutrition Examination Survey (NHANES), childhood obesity rates rose from 5.0% in 1960 to 15.4% in 2001 and 16.9% in 2009–2010.\(^{16}\) Though the prevalence of NAFLD is higher in children with obesity, an important distinction is that NAFLD and obesity are not interchangeable. NAFLD can also occur in normal-weight children. In SCALE, the prevalence of NAFLD in normal-weight children was 5%. In a 2012 Turkish autopsy study in 340 children aged 2–20 years with normal weight, the prevalence of NAFLD was also 5%.\(^{17}\) In a clinical study of children with NAFLD, the prevalence of normal weight ranged from 1% to 8%.\(^{3,4}\) The prevalence of overweight body habitus in children with NAFLD is 5%–21%, and the prevalence of obesity among pediatric patients with NAFLD is 72%–92% (Table 27.1).

Sex, age, race, and ethnicity are other factors affecting the prevalence of NAFLD. Male sex, older age, Hispanic ethnicity, and Asian race are factors significantly associated with a higher risk of fatty liver.\(^1\) As demonstrated in multiple studies, boys have a higher prevalence of NAFLD (11.1% in SCALE) than girls (7.9% in SCALE). NAFLD prevalence also increases with increasing age. In SCALE, the prevalence of NAFLD in children aged 2–4 was 1%, 3% in children aged 5–9, 11% in children aged 10–14, and increased to 17% of children aged 15–19.\(^1\) The prevalence of NAFLD is highest in Hispanic (12%) and Asian (11%) children and lowest in African American children (1.5%). The prevalence of NAFLD in Caucasian children is 9%.\(^1\)
TABLE 27.1
Weight Distribution in Pediatric NAFLD

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication Year</th>
<th>Sample Size</th>
<th>Population</th>
<th>Location</th>
<th>Underweight (BMI &lt; 5%)</th>
<th>Normal Weight (BMI 5% and &lt;85%)</th>
<th>Overweight (BMI 85% and &lt;95%)</th>
<th>Obese (BMI 95%)</th>
<th>Mean BMI of NAFLD Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Schwimmer et al.</em></td>
<td>2005</td>
<td>100</td>
<td>Children with NAFLD</td>
<td>San Diego</td>
<td>1%</td>
<td>1%</td>
<td>6%</td>
<td>92%</td>
<td>30.7</td>
</tr>
<tr>
<td><em>Nobili et al.</em></td>
<td>2006</td>
<td>85</td>
<td>Children with NAFLD</td>
<td>Rome</td>
<td>8%</td>
<td>51%</td>
<td>41%</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td><em>Manco et al.</em></td>
<td>2008</td>
<td>120</td>
<td>Children with NAFLD</td>
<td>Rome</td>
<td>7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mager et al.</em></td>
<td>2008</td>
<td>53</td>
<td>Suspected NAFLD (U/S)</td>
<td>Toronto</td>
<td>8%</td>
<td>21%</td>
<td>72%</td>
<td>29.7</td>
<td></td>
</tr>
<tr>
<td><em>A-Kader et al.</em></td>
<td>2008</td>
<td>106</td>
<td>Children with NAFLD</td>
<td>Arizona</td>
<td>0%</td>
<td>2%</td>
<td>10%</td>
<td>88%</td>
<td>32.8</td>
</tr>
<tr>
<td><em>Carter-Kent et al.</em></td>
<td>2009</td>
<td>130</td>
<td>Children with NAFLD</td>
<td>Cleveland, Mayo, Cincinnati, Chicago, Toronto</td>
<td>13%</td>
<td>6%</td>
<td>82%</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

**NAFLD Prevalence Study**

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication Year</th>
<th>Sample Size</th>
<th>Population</th>
<th>Location</th>
<th>Underweight (BMI &lt; 5%)</th>
<th>Normal Weight (BMI 5% and &lt;85%)</th>
<th>Overweight (BMI 85% and &lt;95%)</th>
<th>Obese (BMI 95%)</th>
<th>Mean BMI of NAFLD Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Schwimmer et al.</em></td>
<td>2006</td>
<td>742 (97 [13%] with NAFLD)</td>
<td>General population autopsy study</td>
<td>San Diego</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
<td>60%</td>
<td>30.2 (NAFLD) 33.6 (NASH)</td>
</tr>
<tr>
<td><em>Yuksel et al.</em></td>
<td>2012</td>
<td>330</td>
<td>General population autopsy study</td>
<td>Turkey</td>
<td>5%</td>
<td></td>
<td>11%</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

**NAFLD Cohorts Not Subdivided into Weight Categories**

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication Year</th>
<th>Sample Size</th>
<th>Population</th>
<th>Location</th>
<th>Mean BMI of NAFLD Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Schwimmer et al.</em></td>
<td>2008</td>
<td>150</td>
<td>Children with NAFLD</td>
<td>San Diego</td>
<td>33.8</td>
</tr>
<tr>
<td><em>Ko et al.</em></td>
<td>2009</td>
<td>80</td>
<td>Children with NAFLD</td>
<td>Seoul</td>
<td>27.6</td>
</tr>
<tr>
<td><em>Fitzpatrick et al.</em></td>
<td>2010</td>
<td>45</td>
<td>Children with NAFLD</td>
<td>London</td>
<td>25.3</td>
</tr>
<tr>
<td><em>Takahashi et al.</em></td>
<td>2011</td>
<td>34</td>
<td>Children with NAFLD</td>
<td>Japan</td>
<td>26.7</td>
</tr>
<tr>
<td><em>Schwimmer et al.</em></td>
<td>2013</td>
<td>193</td>
<td>Children with NAFLD</td>
<td>San Diego</td>
<td>31.5</td>
</tr>
<tr>
<td><em>Schwimmer et al.</em></td>
<td>2014</td>
<td>494</td>
<td>Children with NAFLD</td>
<td>NASH CRN</td>
<td>32.7</td>
</tr>
<tr>
<td><em>Alkhouri et al.</em></td>
<td>2014</td>
<td>302</td>
<td>Children with NAFLD</td>
<td>Rome</td>
<td>25.5 (NAFLD) 26.3 (NASH)</td>
</tr>
</tbody>
</table>
PATHOPHYSIOLOGY

Multiple factors interplay in the pathophysiology of NAFLD: genetics, inflammatory cytokines, insulin resistance, microbiome, and perinatal and environmental factors.

GENETICS

Genetics also play a key role in the pathophysiology of NAFLD. Prior studies have demonstrated differences in the prevalence of NAFLD between racial and ethnic groups. Although the latest NHANES data from 2011–2012 demonstrate that girls of black race or Hispanic ethnicity have the highest rates of obesity (both at 20.4%), pediatric NAFLD rates are the lowest in African Americans, at 1.5% compared with 11.8% in Hispanics. The importance of genetics in NAFLD risk has been demonstrated by studies of heritability. In a 2009 study by Schwimmer et al., obese children with and without NAFLD and their family members (parents, siblings, second- and third-degree relatives) underwent MRI to assess PDFF. Fatty liver was found in parents (78%) and siblings (59%) of obese children with NAFLD, compared with 37% of parents and 17% of siblings in obese children without NAFLD. Adjusting for age, sex, race, and BMI, heritability of liver fat fraction was .386 or 38.6%. The discovery in 2008 of rs738409, a common variant allele in the patatin-like phospholipase 3 (PNPLA3) gene that increases susceptibility to NAFLD, has led to multiple genetic studies. PNPLA3 was the first polymorphism, independent of BMI or insulin resistance, to be highly correlated with the onset and progression of NAFLD. This SNP is highly associated with hepatic fat content, as measured by magnetic resonance spectroscopy (MRS), and is independent of BMI, diabetes, or alcohol use. The highest frequency of this allele is present in Hispanics (0.49), followed by European Americans (0.23) and African Americans (0.17). In a study of 153 obese Hispanic children and adolescents, HFF, as measured by MRI, was positively related to total sugar and carbohydrate intake in patients with the GG PNPLA3 genotype. Furthermore, in a study composed of 475 obese children and adolescents, higher levels of alanine aminotransferase (ALT) were seen for each mutant allele of the PNPLA3 locus present. In an Italian study, the PNPLA34 variant allele was associated with steatosis severity, the presence of fibrosis, lobular inflammation, and hepatocellular ballooning in 149 pediatric NAFLD patients. In a contrasting study in 223 children with NAFLD from the NASH CRN, no association between PNPLA3 loci and histologic severity of NAFLD was found. Thus, further studies are needed regarding the genetics of NAFLD.

INSULIN RESISTANCE

Systemic insulin resistance is hypothesized to play a key role in the pathogenesis of pediatric NAFLD via increased free fatty-acid circulation and increased de novo lipogenesis. Insulin resistance affects hepatocyte lipid accumulation and the resultant oxidative stress, which in turn incites an inflammatory response.

INFLUENCE OF MATERNAL FACTORS AND BREAST-FEEDING ON NAFLD

Recently, it has been proposed that NAFLD may have in utero origins. Patel et al. demonstrated that fetal hepatic steatosis was significantly higher in infants born to mothers with gestational diabetes mellitus (GDM) (79%) compared with women without GDM (17%). Brumbaugh et al. demonstrated that infants born to obese mothers with GDM had 68% greater liver hepatic fat fraction (HFF) compared with those born to normal-weight mothers.

After birth, neonatal feeding practices, especially overfeeding, may have long-term consequences on de novo lipogenesis. Breast-feeding, on the other hand, may be protective in the prevention of hepatic steatosis. Nobili et al. demonstrated that in children with NAFLD, steatosis distribution,
inflammation, ballooning of hepatocytes, and fibrosis were all more severe in children who were not breast-fed compared with their breast-fed counterparts. Thus, the origins of NAFLD are affected by maternal factors; GDM, maternal obesity, and neonatal feeding habits may all play a role in the development of NAFLD.

SCREENING FOR NAFLD

The prevailing recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity were published in 2007 by an expert committee. These guidelines recommend screening for NAFLD by evaluating serum ALT and aspartate aminotransferase (AST) levels. The expert committee suggests biannual screening starting at age 10 years in obese children and overweight children with additional risk factors. The guidelines further suggest referral to a pediatric hepatologist if AST or ALT levels are twice the upper limit of normal.

The ideal age at which initial screening takes place is debated. In a recent study, Beacher et al. demonstrated that ALT elevation was found in 25% of children aged 2–5 years referred to a tertiary care clinic, and concluded that, instead of starting to screen for NAFLD via AST/ALT at age 10 years and above, as currently recommended in obese children, screening severely obese children (BMI ≥99%) should begin at age 2. ALT elevation can be common even at very young ages. Whether this is due to NAFLD is unknown.

As screening is based on laboratory results, it is important to define what is normal. The Screening ALT for Elevation in Today’s Youth (SAFETY) study demonstrated that conventional ALT cutoff values of normal used in children’s hospitals varies widely and is too high for reliable detection of chronic liver disease. The median upper limit of normal ALT used by children's hospitals in the United States was found to be 53 U/L, with a range of 30–90 U/L. In a large, nationally representative sample, the 95th percentiles for ALT levels for healthy-weight, metabolically normal children without liver disease were 25.8 U/L in boys and 22.1 U/L in girls. According to these data, the median normal ALT used in many laboratories today would actually fall into the category of twice the upper limit of normal for biologically based ALT. Thus, interpretation of aminotransferases with biologically based values in mind will assist in detecting patients who may have liver disease with higher sensitivity and specificity (sensitivity of 72% in boys and 82% in girls, and specificity of 79% in boys and 85% in girls). Sensitivity in the detection of NAFLD was lower using current children’s hospitals ALT levels (32%–48%).

In order to evaluate the prevailing guidelines, a study prospectively evaluated 347 children ≥10 years of age who were overweight or obese and who were screened for NAFLD via aminotransferases by their primary care provider and referred to pediatric gastroenterology for suspected NAFLD. In this cohort of patients referred to tertiary care, only 55% had NAFLD and the remainder were almost equally divided between not having any liver disease or having liver disease attributed to another reason besides NAFLD. Thus, we cannot conclude that elevated transaminases in obese children are automatically indicative of NAFLD.

IMPACT OF NONALCOHOLIC FATTY LIVER DISEASE

Advanced fibrosis is demonstrated in 5%–15% of children with NAFLD at the time of diagnosis. In a recent study in overweight and obese children referred from primary care to pediatric gastroenterology for suspected NAFLD, 33 out of 193 patients (17%) had advanced fibrosis on initial diagnostic liver biopsy. Advanced fibrosis and cirrhosis increase the risk of hepatocellular carcinoma (HCC) and the need for liver transplant. NASH-associated cirrhosis is now the second-most common cause of liver transplantation in adults and is anticipated to overtake the hepatitis C virus (HCV) and alcohol-induced cirrhosis as the leading cause of hepatic transplantation within the next decade. The risk of HCC can be present even in childhood, based on a recent report of a 7-year-old
child developing HCC in association with NAFLD. It is anticipated that NAFLD-associated HCC will increase as the prevalence of obesity and NAFLD continue to rise.

Although mortality data in pediatric NAFLD are limited, a 2009 natural history study following pediatric NAFLD (mean follow-up time of 6.4 years) found children with NAFLD to be at higher risk of mortality in comparison with the general population. The standardized mortality ratio in NAFLD patients was 13.6%, with significantly shorter observed survival free of liver transplantation in the NAFLD cohort, compared with the expected survival of the general US population with similar age and sex.

Children with NAFLD are at greater risk of cardiopulmonary, endocrinologic, and psychologic comorbidities compared with children with obesity alone and children without NAFLD (Table 27.2). Obstructive sleep apnea (OSA) is a condition whereby recurrent partial or complete upper airway obstruction occurs during sleep, leading to hypoxic events, oxidative stress, and ischemic and reperfusion tissue injury. Obesity is a risk factor for OSA. Symptoms of OSA manifest as snoring, daytime sleepiness, and poor school performance. Two recent studies have demonstrated an OSA prevalence of 60% in mainly obese children with NAFLD, which is much higher than the prevalence of OSA in the general population of 1.2%–5.7%. Moreover, in children with NAFLD, the presence of OSA may impact disease severity. For instance, in a study with 65 NAFLD patients, Nobili et al. demonstrated that the presence of NASH (compared with NAFLD) and fibrosis was associated with more severe OSA. Hypoxemia, defined as oxygen saturation <90%, was correlated with increased activation of intrahepatic inflammatory cells and increased circulating markers of hepatocyte fibrosis and fibrogenesis. Similarly, Sundaram et al. demonstrated that NAFLD in association with OSA had more severe hepatic fibrosis. Thus, OSA is an important comorbidity in NAFLD and screening questions should include the presence of snoring and/or daytime sleepiness.

NAFLD is associated with type 2 diabetes; however, the prevalence of type 2 diabetes among children with NAFLD is not yet certain. In a case series of pediatric NAFLD, the frequency of type 2 diabetes has ranged from 2% to 14%. Larger studies to allow a more stable estimate are still needed. Insulin resistance is a major common factor between NAFLD and type 2 diabetes, as it plays a role in the pathogenesis of both.

Dyslipidemia is also commonly associated with NAFLD. In a study of 120 children with NAFLD from Italy, over 60% had elevated serum triglycerides and 45% had low high-density lipoprotein (HDL). Furthermore, fibrosis was associated with higher total serum cholesterol and triglycerides. The dyslipidemia that occurs in children with NAFLD in conjunction with obesity appears to be more severe than in children with obesity alone. This was shown in a study by Schwimmer et al. that compared 150 children with NAFLD with 150 overweight and obese children without NAFLD. Children with NAFLD had significantly higher total cholesterol, low-density lipoprotein (LDL), and triglycerides.

Hypertension is another comorbidity in patients with NAFLD, independent of BMI and obesity. In a study comparing 150 children with overweight or obese body habitus without NAFLD with 150 children with NAFLD, children with NAFLD had higher rates of elevated systolic blood pressure (SBP) than similarly overweight children. In a 2014 study from the NASH CRN evaluating 382 children with NAFLD, higher rates of high blood pressure were demonstrated both cross-sectionally and longitudinally in NAFLD patients compared with patients with obesity alone. In this study, 36% of the patients had elevated blood pressure at baseline, and 21% had persistent high blood pressure over the 48-week follow-up period. Furthermore, children with high blood pressure were more likely to have more severe steatosis (mild 19.8%, moderate 35%, severe 45.2%) than children without high blood pressure (mild 34.2%, moderate 30.7%, severe 35.1%).

In addition to physical impacts, NAFLD also has a substantial psychological burden. A study from the NASH CRN demonstrated impaired quality of life (QOL) in children with NAFLD compared with healthy children. More than one-third of children with NAFLD were found to have impaired QOL. Not surprisingly, children with NAFLD had worse total physical and psychosocial health scores compared with healthy children. Difficulty sleeping, sadness, and fatigue constituted
### TABLE 27.2
Co-Morbidities in Pediatric NAFLD

#### Diabetes

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication Year</th>
<th>Location</th>
<th>Sample Size</th>
<th>Age</th>
<th>Children with NASH (%)</th>
<th>NAFLD Criteria</th>
<th>Children with Diabetes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwimmer et al.</td>
<td>2003</td>
<td>San Diego</td>
<td>43</td>
<td>2–17 years</td>
<td>Nonstated</td>
<td>Biopsy</td>
<td>14%</td>
</tr>
<tr>
<td>Nobili et al.</td>
<td>2006</td>
<td>Italy</td>
<td>84</td>
<td>3–18 years</td>
<td>26%, 5% advanced fibrosis</td>
<td>Biopsy</td>
<td>2%</td>
</tr>
<tr>
<td>Carter-Kent et al.</td>
<td>2009</td>
<td>5 centers in US/Canada</td>
<td>130</td>
<td>3–18 years</td>
<td>82% NASH, 20% advanced fibrosis</td>
<td>Biopsy</td>
<td>7%</td>
</tr>
<tr>
<td>Patton et al.</td>
<td>2010</td>
<td>NASH CRN</td>
<td>254</td>
<td>6–17 years</td>
<td>35% NASH, 14% advanced fibrosis</td>
<td>Biopsy</td>
<td>3%</td>
</tr>
<tr>
<td>Kistler et al.</td>
<td>2010</td>
<td>NASH CRN</td>
<td>239</td>
<td>5–17 years</td>
<td>39% NASH, 14% advanced fibrosis</td>
<td>Biopsy</td>
<td>4%</td>
</tr>
</tbody>
</table>

#### Dyslipidemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>Location</th>
<th>Sample Size</th>
<th>Age</th>
<th>Population</th>
<th>NAFLD Criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cali et al.</td>
<td>2007</td>
<td>New Haven</td>
<td>49</td>
<td>Mean 15 years</td>
<td>BMI &gt;95%</td>
<td>Fast MRI</td>
<td>If HFF &gt;5.5%, higher TG and very low density lipoprotein (VLDL), lower HDL</td>
</tr>
<tr>
<td>Manco et al.</td>
<td>2008</td>
<td>Italy</td>
<td>120</td>
<td>3–18 years</td>
<td>NAFLD</td>
<td>Biopsy</td>
<td>63% with high TG, 45% with low HDL, fibrosis assoc. with higher TC and TG</td>
</tr>
<tr>
<td>Schwimmer et al.</td>
<td>2008</td>
<td>San Diego</td>
<td>300</td>
<td>5–17 years</td>
<td>NAFLD vs. BMI &gt;85%</td>
<td>Biopsy</td>
<td>Higher TC, LDL, TG in NAFLD patients</td>
</tr>
<tr>
<td>Pacifico et al.</td>
<td>2014</td>
<td>Italy</td>
<td>136</td>
<td>Mean 12 years</td>
<td>Lean, obese, obese + NAFLD</td>
<td>Biopsy</td>
<td>NAFLD/obese group with higher TG, lower HDL</td>
</tr>
<tr>
<td>Study</td>
<td>Publication Year</td>
<td>Location</td>
<td>Sample Size</td>
<td>Age</td>
<td>Population</td>
<td>NAFLD Criteria</td>
<td>Results</td>
</tr>
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<td>-----------------------</td>
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</tr>
<tr>
<td>Schwimmer et al.</td>
<td>2008</td>
<td>San Diego</td>
<td>300</td>
<td>5–17 years</td>
<td>NAFLD vs. BMI &gt;85%</td>
<td>Biopsy</td>
<td>Higher SBP, TC, LDL, TG in NAFLD patients</td>
</tr>
<tr>
<td>Manco et al.</td>
<td>2010</td>
<td>Italy</td>
<td>80</td>
<td>9–16 years</td>
<td>Obese vs. obese + NAFLD</td>
<td>Biopsy</td>
<td>No relation to liver disease; carotid intima-media thickness (CIMT) elevated in obese and obese plus NAFLD</td>
</tr>
<tr>
<td>Singh et al.</td>
<td>2013</td>
<td>St Louis</td>
<td>44</td>
<td>Mean 15 years</td>
<td>Lean, obese, obese + NAFLD</td>
<td>MRS</td>
<td>NAFLD/obese group with higher SBP, DBP, and LV strain compared with obese/no NAFLD</td>
</tr>
<tr>
<td>Pacifico et al.</td>
<td>2014</td>
<td>Italy</td>
<td>136</td>
<td>Mean 12 years</td>
<td>Lean, obese, obese + NAFLD</td>
<td>Biopsy</td>
<td>NAFLD/obese group with higher SBP, TB, lower HDL, more LV dysfunction, higher LV mass</td>
</tr>
<tr>
<td>Schwimmer et al.</td>
<td>2014</td>
<td>NASH CRN</td>
<td>382</td>
<td>2–17 years</td>
<td>NAFLD</td>
<td>Biopsy</td>
<td>Prevalence of HTN = 36% at baseline, persistent HTN = 21%, patients with HTN more likely to have steatosis</td>
</tr>
</tbody>
</table>
almost half of the variances in QOL scores. In another study comparing children with NAFLD with obese children, children with NAFLD were found to have higher levels of depression and lower self-esteem compared with their obese control counterparts. Furthermore, this study demonstrated that postdiagnosis standard-care counseling on lifestyle and dietary changes had no impact on QOL or other psychosocial measures longitudinally.

**APPROACH TO CARE**

Weight loss, through lifestyle modifications in the form of increased activity and healthier dietary choices, is the most commonly recommended first-line treatment of NAFLD. Other emerging treatment modalities that require additional study are pharmacologic therapies, with targets ranging from the intestinal microbiome to insulin resistance, and bariatric surgery.

Weight loss improves insulin sensitivity, decreases reactive oxygen species and delivery of free fatty acids to the liver, and thus should counteract predominant mechanisms involved in the pathogenesis of NAFLD. It is hypothesized that a 3%–5% reduction in total body weight decreases hepatic steatosis, but a 10% or more reduction in total body weight may be required to prevent progression and result in improvement in steatohepatitis. In a recent study of 293 adults with NAFLD, the highest rates of NASH resolution and fibrosis regression occurred in patients with a loss of 10% or more of their total body weight. Of the patients who lost 10% or more of their total body weight, 90% had complete resolution of NASH, compared with 58% NASH resolution in patients who lost 5%–10% of their total body weight. In a recent pediatric study, for those children who were adherent to a 2-year lifestyle intervention, there was improvement in weight, aminotransferases, and liver histology. An earlier study also demonstrated that an uncontrolled, 12-month lifestyle modification program (a balanced, low-calorie diet tailored to individual preferences and moderate physical activity of 30–45 minutes a day, three times a week) was associated with significant decreases in BMI (average BMI decreasing from 25.9 to 23.8) and ALT (average ALT decreasing from 62 to 33 IU/L).

Notably, there is a lack of randomized controlled trials with evidence to show that lifestyle interventions are effective for the treatment of NAFLD in children. Thus, there is a need for large randomized controlled trials that investigate specific dietary interventions and exercise regimens in children with carefully staged NAFLD, in order to have specific evidence-based recommendations for the treatment of NAFLD.

Bariatric surgery is increasingly performed on adolescents for weight reduction. The impact of bariatric surgery on children with NAFLD, however, is not entirely clear. Moreover, it is not known whether bariatric surgery improves histologically severe NASH. A recent study evaluating pre- and postsurgery NAFLD scores among adolescents with preexisting NAFLD undergoing laparoscopic adjustable gastric banding demonstrated significant improvements in NAFLD scores, which decreased by an average of 0.68 (p < .01) 2 years postoperatively. In 2015, the hepatology committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published a position paper regarding bariatric intervention in severely obese children and adolescents. A BMI >97% with major comorbidities (including NASH with significant fibrosis) was recommended as a criteria for bariatric surgery. Though multiple studies have demonstrated improvement in liver histology in adults following bariatric surgery, outcome data in adolescents are currently lacking.

Though pharmacologic therapy is not uniformly recommended in pediatric NAFLD, avid interest and evaluation of multiple medications as potential therapeutic targets is underway. Metformin, an insulin-sensitizing agent, was proposed as a therapeutic target for NAFLD, as insulin resistance is believed to play a major role in the pathogenesis of NAFLD. Additionally, metformin has previously been demonstrated to reduce body weight, improve insulin resistance, and have chemoprotective benefits in decreasing HCC. Initial pilot studies were promising. After 24 weeks of therapy, 40% of subjects with NAFLD had normalization of ALT. Additionally, 90% of subjects had a significant reduction in hepatic signal fat fraction via MRS signal fat fraction imaging.
separate study in 30 children with NAFLD, 24 months of therapy with metformin as well as lifestyle interventions was compared with lifestyle interventions alone. Metformin was not more effective than lifestyle intervention in improving transaminase levels and hepatic steatosis. Treatment of NAFLD in Children (TONIC), a large, multicenter, double-blind, placebo-controlled trial by the NASH CRN, evaluated the efficacy of metformin and vitamin E over 96 weeks of therapy in patients with NAFLD. Metformin was associated with significant improvement in hepatocellular ballooning compared with placebo, but did not improve ALT, steatosis, inflammation, or fibrosis.

The TONIC trial also evaluated the efficacy of vitamin E, an antioxidant, as a potential therapeutic, given oxidative stress is believed to be a contributor to the pathogenesis of NAFLD. After 96 weeks of vitamin E treatment, pediatric patients with NAFLD did not have any significant decrease in ALT compared with placebo. Similar to metformin, vitamin E was associated with significant improvement in hepatocellular ballooning but not steatosis, inflammation, or fibrosis.

Cysteamine, another antioxidant, is also a potential therapy for NAFLD as it readily enters into hepatocytes and can replete glutathione, which may be therapeutic as glutathione depletion contributes to hepatocellular injury and fibrosis. In a small pilot study, 11 children with NAFLD received cysteamine therapy for 24 weeks. Significant reductions were demonstrated in serum transaminases (ALT decreased from 120.2 IU/L at baseline to 55 IU/L at week 24), serum adiponectin, and CK-18 levels. Currently, the NASH CRN is in the process of completing a multicenter, placebo-controlled clinical trial in children aged 8–17 with NAFLD to evaluate whether 52 weeks of cysteamine treatment will result in an improvement in the severity of liver disease.

Dietary docosahexaenoic acid (DHA), a major dietary long-chain polyunsaturated fatty acid, lowers serum triglycerides and has both insulin-sensitizing and anti-inflammatory properties. Thus, dietary DHA supplementation is of interest as a possible therapeutic target for NAFLD. In a clinical trial by Nobili et al., children aged 6–16 years with NAFLD received DHA 250 mg/day, DHA 500 mg/day, or placebo (n = 20/group). No effect was noted on BMI or ALT after DHA treatment. In a continuation study of 20 children with NAFLD, treatment with DHA for 18 months was associated with the modulation of hepatic progenitor cells and prolonged hepatocyte survival.

Recent studies have suggested a role for microbiome gut dysbiosis in the development of NAFLD in children. In animal models, the composition of gut microbiota can influence intrahepatic fat accumulation via mechanisms such as increased monosaccharide absorption from the intestinal lumen and the production of hepatotoxic products. Though multiple studies in humans have been performed, outcomes in regard to whether modification of the gut microbiome can impact obesity and NAFLD are currently mixed. In a recent randomized clinical trial, the effects of VSL#3 in obese children with NAFLD were evaluated. A total of 44 children were enrolled, with 22 receiving VSL#3 and 22 receiving a placebo for 4 months. There was an 8% decrease in BMI noted with probiotic treatment, with no change in the placebo group. There was no improvement in ALT or insulin sensitivity in either group.

A separate study of 21 obese children with persistently elevated hepatic transaminases and increased echogenicity on ultrasound evaluated the effect of Lactobacillus rhamnosus. After 8 weeks of therapy with L. rhamnosus, ALT was noted to decrease significantly (70 to 40 U/L on average) in the treatment group. In the control group, ALT was unchanged. These preliminary studies provide a rationale for further studies of the impact of dysbiosis and the microbiome on NAFLD in children.

SUMMARY

NAFLD is a frequent cause of chronic liver disease in children. Although the prevalence of NAFLD and NASH is higher in obese children, NAFLD occurs in both obese and nonobese children. Multiple factors play a role in the pathophysiology of NAFLD, including maternal and neonatal factors, insulin resistance, and genetics. Multiple studies are currently underway to gain additional insight into the complex relationships between these multiple factors and NAFLD.
NAFLD can be associated with many negative health consequences, from increased risk of cirrhosis and HCC to multiple extrahepatic comorbidities such as OSA, diabetes, dyslipidemia, and hypertension. Effective treatment modalities for NAFLD are more important than ever. Lifestyle modifications, such as improved diet and increased physical activity, are the recommended first line of treatment. Multiple pharmacologic and surgical options are being evaluated. Pediatric NAFLD is likely to play an increasingly important role in the care and management of obese children.

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Sleep Outcomes and Childhood Obesity

Kristie R. Ross and Susan Redline

INTRODUCTION

As the prevalence of childhood obesity has increased, so has our understanding of the relationship between adiposity and sleep disorders in children and adolescents. Obesity is associated with sleep-disordered breathing (SDB), daytime sleepiness, short sleep duration, and hypersomnolence disorders. These associations are complex, with evidence of bidirectional relationships between obesity and sleep disorders that are modified by age and other comorbidities. The focus of this chapter is to review the sleep-related consequences of childhood obesity, with a focus on SDB.

EPIDEMIOLOGY OF SDB

Sleep-disordered breathing (SDB) is a term that is used broadly to describe abnormal breathing and/or gas exchange during sleep. SDB includes a spectrum of severity from primary snoring to upper-airway resistance syndrome (UARS) to obstructive sleep apnea syndrome (OSAS). Untreated SDB is associated with behavioral and neurocognitive effects across its spectrum, and metabolic and cardiovascular effects in its more severe form. Methodologic challenges in describing the epidemiology of SDB are reviewed in detail elsewhere [1].

Primary snoring refers to the presence of snoring—a cardinal symptom of turbulent nasopharyngeal airflow—occurring without gas exchange abnormalities or significant sleep fragmentation. The prevalence of snoring, as reported by caregivers, is highly variable depending on the definition used, but a meta-analysis of studies that included over 95,000 children worldwide found the prevalence to be 7.45% (95% CI 5.75–9.61) [1].

In OSAS and UARS, there is recurrent intermittent partial or complete collapse of the upper airway during sleep, which results in arousals (UARS and OSAS) or impaired gas exchange (OSAS). The severity, frequency, and consequences of the airway collapse separate OSAS from UARS. While the American Academy of Pediatrics clinical practice guideline recommends that polysomnography (PSG) be performed to diagnose OSAS in children [2], the definition of OSAS using...
PSG-measured variables is not consistent across studies. In addition, for practical reasons (including cost and the limited availability of pediatric sleep laboratories), many children are diagnosed with and referred for treatment of OSAS without undergoing PSG. Most studies suggest an OSAS prevalence of 4%–11% using questionnaires and 1%–4% using PSG in otherwise healthy children [1].

**ROLE OF OBESITY IN CHILDHOOD SDB**

Obesity has long been recognized as an important risk factor for SDB in adults [3]. More than 50% of the attributable risk of SDB in individuals less than 50 years of age has been attributed to obesity [4], and the growing obesity epidemic has been identified as a contributor to a 14%–55% relative increase in SDB prevalence over the last 10 years [5]. In children, while there are case reports of hypoventilation during sleep associated with morbid obesity going back 50 years, early reports of pediatric OSAS did not describe obesity as a common feature [6,7]. Instead, the children in these series had high rates of adenotonsillar hypertrophy (66%–72%) and failure to thrive (27%). As the prevalence of childhood obesity rose, researchers began reporting an association between obesity and SDB. In 1989, Mallory et al. reported a series of 41 children and adolescents with greater than 150% ideal body weight, of whom 37% had an abnormal PSG, most indicating mild-to-moderate SDB [8]. Silvestri and others studied 32 obese children, and found high rates of symptoms of SDB as well as polysomnographic evidence of OSAS (59%) [9]. In this series, children with an ideal body weight of 200% or more and adenotonsillar hypertrophy were at particularly high risk of OSAS [9].

The first large study to suggest an association between obesity and SDB in children was the Cleveland Family Study, in which 399 children aged 2–18 years were studied with in-home PSG [10]. SDB was characterized using a relatively high apnea–hypopnea index (AHI) of 10 or higher. Obesity (body mass index [BMI] >28) was associated with 4.69 (95% CI 1.59–14.15) increased odds of moderate-to-severe SDB after adjusting for race. In a case control study conducted in Asia published in 2003, 46 obese otherwise healthy children (>120% ideal body weight) and 44 age- and sex-matched controls were studied using fiber-optic upper-airway examinations and PSG [11]. Sleep architecture was similar in both normal-weight and obese children. However, SDB was much more common in the obese children. Consistent with other studies of snoring in healthy children, 15.9% of the normal-weight children in this series had habitual snoring and 2.3% had evidence for OSAS (obstructive apnea index ≥1). Obese children had a higher prevalence of snoring and OSAS, at 34.8% and 26.1%, respectively. Adenoidal enlargement and a narrow velopharyngeal space were also more common in the obese participants. Verhulst and colleagues subsequently published a series of studies further establishing a relationship between obesity and SDB in children and adolescents, including evidence that, as in adults, SDB is associated with several inflammatory and metabolic abnormalities [12,13]. This relationship, confirmed by others, is explored further in another section of this chapter. In a large population-based cohort study in the United Kingdom of children aged 6 months to 6 years, those with early evidence of SDB had higher standardized BMI scores than nonsnorers or children with later onset of snoring [14].

Obesity and SDB likely share many risk factors, including race, socioeconomic status, genetic markers, prematurity, and chronic respiratory conditions [15–17]. Many of these processes share proinflammatory and oxidative signaling pathways, potentially resulting in additive or synergistic effects, or the modification of risk or outcomes. Thus, discerning the causal relationships between obesity and SDB can be challenging. The Cleveland Children’s Sleep and Health Study was a population-based cohort of 907 children with stratified sampling to achieve a study population composed of approximately 50% children who had been born preterm and with overrepresentation of minority children [18]. Investigators used questionnaires and in-home overnight cardiorespiratory studies to estimate the prevalence of SDB and to understand how risk factors including race, sex, prematurity, and obesity affected the risk of SDB. SDB was measured longitudinally over three examinations: when children were aged 8–11 years, 13–16 years, and 16–19 years. Obesity was not associated with SDB at ages 8–11 years. In contrast, among adolescents aged 16–19 years,
BMI z-score was associated with a significant 2.7-fold increased odds of SDB (per unit change in z-score) [19]. Similar to the latter finding, a study of 234 Caucasian children aged 2–18 years studied with overnight PSG found a relationship between OSAS and obesity only in adolescents 12 years of age and older who had a 3.5-fold increased risk of OSAS with each standard deviation increase in BMI z-score [20]. In another study that included Caucasian and Hispanic children, obesity was more common in children with SDB that persisted during a 5-year study period from mid-childhood to very early adolescence [21]. The evidence for relatively stronger associations between obesity and SDB in older children and adolescents compared with younger children may be based on several factors, including differences in the magnitude and distribution of adiposity and underlying differences in anatomic susceptibility as airway structures develop and lymphoid hyperplasia changes.

The importance of distinguishing between classic pediatric OSAS and obesity-related OSAS was proposed in 2007, with the suggestion that this distinction may help understand the long-term impact of the disorder and suggest treatment strategies [17]. Further delineation of subgroups defined by anatomic risk factors, neuromuscular activation of the airway, central components of ventilatory control, and arousal thresholds, may help with strategies for “personalizing” treatment strategies. Additionally, elucidating how these risk factors relate to obesity may be important, given that obesity may influence allergic/lymphatic tissues and airway inflammation (see Figure 28.1).

While rigorously designed clinical trials to test the hypothesis that treatment responses vary based on phenotype have not been done, there are data supporting this concept. In particular, there is some evidence that daytime sleepiness may be greater in children with SDB who are obese, compared with their nonobese peers. Furthermore, the level of objectively measured sleepiness was significantly correlated with the level of BMI ($r = 0.44, p = 0.001$) [22]. Excessive daytime sleepiness has been linked to inflammation, and the authors postulate that the inflammatory dysregulation that occurs in both obesity and SDB interact to result in augmented sleepiness. Similarly, it has been suggested that obese children with SDB may also have poorer cognitive outcomes than nonobese children with SDB. In a study that compared nonobese children with OSAS, obese children with OSAS, and age- and sex-matched healthy control children, those with both obesity and OSAS had lower scores on the Weschler Intelligence Scale for Children compared with nonobese children with SDB. Both groups were lower than healthy controls [23].

The presence of obesity may impact not only the presentation but also the severity of OSAS. In the Childhood Adenotonsillectomy Trial (CHAT)—a randomized, controlled trial of children aged 5–9 years in which early adenotonsillectomy was compared with watchful waiting in the treatment

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**FIGURE 28.1** Theoretical scheme showing complex and bidirectional relationships between sleep-disordered breathing, obesity, and comorbidities. Dotted lines represent relationships that are less well established.
of mild-to-moderate OSAS—obesity, along with race and the score of a validated SDB screening questionnaire, were the only significant predictors of OSAS severity in children. In this study population, children with a BMI z-score of 2 or higher had a 1.22 (95% CI 1.02–1.45) increased likelihood of more severe OSAS (defined by an oxygen desaturation index >10) [24].

Characterizing the distribution of fat may be important in understanding SDB risk and outcomes. In adults, measures of central adiposity are more closely related to OSAS than BMI. There is early evidence that there are similar patterns in children. In the CHAT study, an elevated waist circumference, but not BMI, was associated with the persistence of SDB in the watchful waiting group [25]. A pilot study of 20 otherwise healthy obese adolescents showed that the AHI was not correlated with BMI but was strongly correlated with visceral fat volume measured by computed tomography (CT) of the abdomen ($r = .73, p < .001$) [26].

The presence of asthma and allergic upper-airway disease may also provide insight into SDB and obesity phenotypes, and shed light on genetic susceptibility and proinflammatory and oxidative signaling derangements that occur in the airway and systemically [27]. In the Cleveland Family Study, multiple upper- and lower-airway symptoms were independently associated with moderate SDB after adjusting for obesity and race [10]. Analysis of the relationship between obesity, wheezing, and SDB in participants in the Cleveland Children’s Sleep and Health Study showed that while SDB and obesity were each independently associated with asthma and wheezing, the relationship between obesity and lower-airway symptoms was partly mediated by SDB [28]. Similarly, in a longitudinal cohort study in which SDB was strongly associated with severe asthma, BMI z-score modified the relationship between SDB and asthma severity [29]. Others have shown that markers of airway inflammation (exhaled nitric oxide) and airway obstruction (pulmonary function testing) are more consistently abnormal in children with both SDB and obesity than in either process alone [30,31].

**METABOLIC AND CARDIOVASCULAR CONSEQUENCES OF SDB**

Untreated SDB is associated with neurocognitive and behavioral problems, endothelial dysfunction, systemic inflammation, cardiac dysfunction, and metabolic abnormalities, prompting recommendations that all children be screened during routine well-child care [32]. However, a major challenge is the lack of data that identify which threshold levels of SDB confer increased risk of these chronic health conditions. This is particularly relevant given that SDB may remit or change in severity during development [19]. Cardiovascular and metabolic diseases, including hypertension, insulin resistance and type 2 diabetes, and coronary artery disease and its precursors, are classically problems of adulthood. The epidemic of obesity has made it imperative that pediatricians recognize and address risk factors earlier in life. The role of early-life obesity in these disorders in childhood is reviewed in detail elsewhere in this book (Chapters 25 through 27). Our focus will be on reviewing the evidence that SDB either interacts with obesity or independently influences cardiovascular, inflammatory, and metabolic processes.

**BLOOD PRESSURE AND ENDOTHELIAL DYSFUNCTION**

While frank hypertension is rare in children, the association between SDB and elevated blood pressure (BP) measurements in children has been the subject of several studies [33–36]. In a study of 39 children with OSAS and 21 children with primary snoring, investigators showed that after adjusting for obesity, obstructive apneas, repetitive oxygen desaturations, and arousals were associated with 24-h BP dysregulation [34]. While a meta-analysis published in 2007 did not find sufficient evidence to support a relationship between SDB and elevated BP [37], several studies have shown an association between childhood SDB and elevated BP, with literature published after the meta-analysis suggesting that there is a relationship between BP and primary snoring and mild OSAS [35,36,38]. In a study of 105 children with SDB (ranging in severity from primary snoring to moderate-to-severe OSAS) and 35 nonsnoring controls, BP during waking and during overnight
monitoring was 10–15 mm higher across the SDB groups compared with healthy controls [35]. In another study in which children in Hong Kong were followed prospectively for 4 years after initial diagnosis of OSAS, the baseline AHI was associated with BP during wake and sleep after 4 years [36]. Treatment rates of OSAS were low in this community-based sample of predominantly mild OSAS, and the findings were independent of obesity.

Endothelial dysfunction may occur prior to the onset of hypertension, is a marker of cardiovascular risk, is associated with OSAS in adults, can be measured noninvasively, and can provide information on preclinical risk of cardiovascular outcomes. In a case control study of 108 obese and nonobese prepubertal children without hypertension or other chronic cardiovascular or metabolic diseases (54 with OSAS and 54 without OSAS, matched based on age, sex, and race), endothelial function was measured using a modified hyperemic test [39]. OSAS and obesity were both associated with endothelial dysfunction, in a severity-dependent manner. Children with both OSAS and obesity had substantially higher rates of endothelial dysfunction (62.5%) than those with only OSAS (AHI >5, 20%) or obesity (38.7%) alone. In a study of 59 children with habitual snoring, this group also found that, similar to adults with OSAS, endothelial function deteriorates during the night in an OSAS severity-dependent manner [40]. Others have shown that endothelial dysfunction is more prevalent and that markers of oxidative stress are higher in children with primary snoring and OSAS, compared with healthy controls [41]. Furthermore, both improved following adenotonsillectomy.

Metabolic syndrome, characterized by visceral adiposity and a cluster of abnormalities in glucose and lipid regulation, is a risk factor for future cardiovascular morbidity in both adults and children. OSAS is associated with insulin resistance and metabolic syndrome in adults [42]. In the Cleveland Children’s Sleep and Health Study there was a close association between SDB and metabolic syndrome. After adjusting for age, race, sex, and prematurity, adolescent children with SDB (AHI ≥5) had a 6.49 (95% CI 2.52–16.7) increased odds of having metabolic syndrome [33]. The intermittent hypoxemia seen in OSAS may be the strongest driver of this relationship [12]. Gozal et al. demonstrated an improvement in lipid homeostasis and inflammatory profiles in children with OSAS following adenotonsillectomy [43]. These findings were seen only in obese children, and an improvement in glycemic control was seen primarily in obese children in whom adenotonsillectomy resulted in the resolution of OSAS. Visceral adiposity is more closely correlated with insulin resistance and OSAS in adults than total body fat. Further research is needed to tease apart the influences of visceral adiposity and SDB on metabolism in children.

**Nonalcoholic Fatty Liver Disease**

As reviewed in the previous chapter, nonalcoholic fatty liver disease (NAFLD) is an obesity-associated condition characterized by a spectrum of histological changes ranging from steatosis to nonalcoholic steatohepatitis (NASH) that can progress to cirrhosis and end stage liver disease. In adults with NAFLD, the presence of OSAS predicts more advanced disease (fibrosis) independently of obesity and metabolic syndrome [44]. The first study to report an association in children was published in 2008, in which 518 children evaluated for SDB underwent liver enzyme measurement [45]. Of the 376 nonobese children enrolled, <1% had elevated liver enzymes. In contrast, among the 142 overweight or obese children, 32% had elevated liver enzymes, and 91% of those children had OSAS, compared with 72% in the obese children without elevated liver enzymes. Verhulst and colleagues also reported an association between SDB and fatty liver disease (elevated transaminases and/or abnormal abdominal ultrasound) in a clinical sample of overweight children and adolescents [46]. More recent work has shown relationships between biopsy-proven NAFLD and OSAS in children [47,48]. In a series of 25 children (mean age 12.8 ± 1.9 years) with NAFLD who underwent PSG, while there was no relationship between OSAS/hypoxemia and the presence of NASH on biopsy, there was an association between OSAS/hypoxemia and more advanced liver fibrosis stages. Consistent with the hypothesis that oxidative stress due to intermittent hypoxemia may drive the progression of NAFLD, there was a correlation between oxygen nadir and the
NAFLD fibrosis stage [47]. Among 65 children with biopsy-proven NAFLD, the presence and severity of OSAS was associated with 4.8-fold increased odds of NASH on biopsy as well as nearly 6-fold increased odds of significant fibrosis, independent of measures of adiposity and metabolic abnormalities [48].

**IMPACT OF OBESITY ON TREATMENT FOR CHILDHOOD SDB**

Adenotonsillectomy is a first-line treatment for children with OSAS and adenotonsillar hypertrophy, irrespective of the presence of obesity. Obesity has long been recognized as a condition that may confer elevated risk of perioperative complications and as a risk factor for the failure for OSAS to resolve completely after surgery.

**Perioperative Complications**

In 1994, obesity was identified as a potential risk factor for perioperative respiratory complications following adenotonsillectomy based on a small series that included one morbidly obese child [49]. Subsequent larger studies have been mixed, with some confirming evidence of increased perioperative risk in obese children compared with their normal-weight peers, and others failing to find a difference. In a retrospective review of 2170 children undergoing PSG at a single center, overweight and obese children were more likely than normal-weight children to have oxygen desaturation below 90% during surgery (40.4% vs. 30.9%, \( p = .004 \)) as well as experience upper-airway obstruction intraoperatively (5.9% vs. 0.2%, \( p = .001 \)) and during recovery (3.7% vs. 0.3%, \( p = .001 \)). BMI independently predicted the need for admission \( (p < .001) \) [50].

**Obesity and Response to Adenotonsillectomy**

In 2004, Mitchell and Kelly published an uncontrolled series of 30 obese children with OSAS aged 3–17 years. Adenotonsillectomy resulted in an improvement in the respiratory disturbance index from 30.0 to 11.6 \( (p < .001) \), with corresponding improvements in quality of life, but 53% of participants had evidence of persistent OSAS on postoperative PSG [51]. In another uncontrolled series of 18 obese children with OSAS and 22 nonobese children with OSAS, 5% of the nonobese children had an AHI of more than 3 six weeks after adenotonsillectomy, compared with 35 of obese children \( (p = .03) \). More striking was the finding that after 1 year following adenotonsillectomy, 79% of obese children had either persistence or recurrence of SDB, compared with 27% of nonobese children \( (p = .004) \). African American children and those with a more rapid gain in BMI during the follow-up period were at particularly high risk of persistence or recurrence [52]. Others have shown that quality of life measures show less improvement in obese children following surgery compared with nonobese children [53]. A meta-analysis published in 2009 that included four studies with 110 children showed a significant reduction in AHI in obese children following adenotonsillectomy (by 18.3 events per hour, 95% CI 11.2–25.5), but 51% of children had persistent evidence for OSAS on PSG \( (\text{AHI} \geq 5) \). One study showed that waist circumference was negatively correlated with response to adenotonsillectomy, independent of BMI, OSAS severity, neck circumference, and demographic factors [54], suggesting the potential importance of central obesity in influencing OSAS treatment outcomes. These data, however, are from uncontrolled studies and have potential for selection and information bias.

The CHAT study is the first randomized, controlled study to evaluate early adenotonsillectomy compared with watchful waiting in children with OSAS [55]. Children with significant comorbidities, very severe OSAS \( (\text{AHI} \geq 30) \), significant hypoxemia, very severe obesity \( (\text{BMI z-score} \geq 3) \), and who used medications for attention deficit hyperactivity disorder were excluded. PSG, neuro-psychological testing, behavior rating scores, and health outcomes were measured as outcomes. Investigators were blinded to the study group assignment. Compared with surgical treatment,
Sleep Outcomes and Childhood Obesity

Watchful waiting did not improve the primary outcome of neuropsychological testing but did improve the secondary outcomes of PSG findings, parent behavior ratings, and quality of life. The AHI improved in both the early adenotonsillectomy and watchful waiting groups during the study, but significantly more so in the surgical group. In both the surgery and control arms, obesity was associated with a lower likelihood that OSAS improved [56]. Of the nonobese children, 54% had normalization of the AHI in the watchful waiting group and 85% had normalization in the early adenotonsillectomy group. Obese children were significantly less likely to have normalization of PSG findings in either group, with 29% normalizing in the watchful waiting group and 67% in the early adenotonsillectomy group. However, the relative benefit of surgery versus watchful waiting was similar in both arms, suggesting that surgery is a reasonable option for obese children with OSAS, but follow-up evaluation is important.

Uncontrolled studies have suggested that adenotonsillectomy is associated with accelerated weight gain in children with failure to thrive where it would be considered beneficial, but also in normal-weight and obese children. Better understanding of the role of postoperative weight gain across children with different weight levels could influence the risk/benefit assessment of surgery, as well as assist with strategies for long-term postoperative monitoring. The CHAT study design allowed investigators to determine if early adenotonsillectomy was associated with weight gain compared with watchful waiting across a spectrum of baseline BMIs [57]. After adjustment for baseline weight and other relevant covariates, early surgery was associated with larger increases in multiple measures of weight compared with watchful waiting during the 7-month follow-up period, including BMI z-score. BMI z-score change was associated with early adenotonsillectomy, being overweight or obese at baseline, and baseline AHI. It was not associated with AHI at follow-up. While BMI z-score increased in normal-weight children during the study, there was no difference in the proportion who became overweight or obese at follow-up (15% in early adenotonsillectomy group vs. 17% in watchful waiting, p = .72). However, among children who were overweight at baseline, 52% became obese in the early adenotonsillectomy group vs. 21% in the watchful waiting group (p < .05). Longer follow-up periods would be needed to determine if these weight changes persist or worsen, but these findings suggest that preoperative counseling about the risk of weight gain and need for follow-up should be incorporated into practice.

Weight loss in obese adults is associated with an improvement and in some cases the resolution of OSAS [58]. There are limited data that weight loss is an effective treatment for OSAS in adolescents [59]. However, given the elevated perioperative risks and the longer-term risk of accelerated weight gain, referral to medically supervised weight management programs in obese children with mild-to-moderate OSAS may be a reasonable approach. Close follow-up with repeated testing to monitor for worsening of OSAS would be important components of this approach. Referral to a pediatric sleep medicine specialist for evaluation and treatment with positive airway pressure should be strongly considered in children with moderate to severe residual OSAS following surgical treatment or in those who are not surgical candidates.

**SUMMARY**

Screening for SDB is recommended for all children [32], with a need for particular vigilance in the growing population of overweight and obese children. The presence of additional risk factors, including asthma, prematurity, and neighborhood-level factors, may further increase the risk. When obesity and SDB coexist, the presenting symptoms and complications may be more severe due to either additive or synergistic interactions of proinflammatory and oxidative signaling pathways. Further work is needed to establish the relevance of the patterns of adiposity to SDB and its consequences in children. Risk related to treatment and response to treatment may differ in obese children, and further work is needed to understand the best long-term strategies to treat OSAS in obese children.
REFERENCES


Section V

Treatment and Prevention of Childhood Obesity
INTRODUCTION

Childhood is an opportune time to address the serious disease of obesity. Since children are still growing, slowing their rate of weight gain or encouraging modest weight losses can help children normalize their weight [1]. However, it is this very fact that children are still growing that has often resulted in obesity in childhood not being treated seriously. The assumption has been that a child who is overweight or obese will “grow out of it,” but this is not the case. Without effective intervention, an estimated 82% of children who are obese, defined as having a body mass index (BMI) at or above the 95th percentile for sex and age [2], will track obesity into adulthood [3]. As reviewed in other chapters in this book, obesity at any age is associated with major physical (e.g., type 2 diabetes, cardiovascular disease) and psychological health burdens (e.g., depression) [4,5] that are costly to the individual as well as to society. For example, current health-care costs related to obesity are estimated to be $315.8 billion annually or 27.5% of health-care spending in the United States [6]. By successfully addressing obesity in childhood, not only do we help children lead healthier, happier lives but we may also be engaging in a form of indicated or targeted prevention of obesity and its costly comorbidities in adulthood [7]. Fortunately, effective treatments for childhood obesity have been developed, and in this chapter we will (1) provide a brief review of the literature in support of treatment of childhood obesity, (2) describe the components of family-based behavioral treatments for childhood obesity, (3) summarize the factors found to impact or predict the effectiveness of these treatments, and (4) explore future directions in the management of childhood obesity.
CURRENT TREATMENT RECOMMENDATIONS FOR CHILDHOOD OBESITY

The US Preventive Services Task Force (USPSTF) recommends that clinicians start tracking BMI percentiles at 2 years of age, that they screen children aged 6 years and older for obesity, and offer them or refer them to a comprehensive, behavioral intervention to promote improvement in weight status [3]. These recommendations are based on the results of a rigorous scientific review that demonstrated the efficacy of interventions of moderate (26–75 contact hours) to high (>75 contact hours) intensity that include dietary, physical activity, and behavioral counseling components [8]. Other organizations and professional groups have issued similar recommendations or treatment guidelines (i.e., the National Institute on Care and Excellence [NICE]; the Expert Committee on Childhood Obesity) [9–11].

Underpinning these recommendations and guidelines is a significant body of research pointing to the superiority of intensive, multicomponent lifestyle interventions in inducing weight loss in children and in reducing medical and psychological comorbidities associated with obesity compared with no-treatment controls, education only, or single-component conditions. The amount or duration of treatment contact has also been found to be a consistent predictor of long-term weight outcomes in children [12,13]. Furthermore, the inclusion of parents or caregivers in the treatment of childhood obesity improves weight loss outcomes in comparison with interventions that only target the child. In fact, interventions with a family-based component result in a 6% greater mean reduction in percentage overweight compared with those without [14]. A representative sample of these reviews and meta-analyses and their main findings are summarized in Table 29.1.

When obesity is addressed at an early age, weight loss outcomes are more robust and enduring [15–17]. These findings highlight the importance of catching obesity early in childhood and responding with a treatment of sufficient scope and intensity to help prevent children from tracking obesity into adolescence. Unfortunately, treatment for older children and adolescents with extreme obesity and severe medical comorbidities is somewhat more complicated. For this population, the use of pharmacotherapy (Chapter 30) and/or weight loss surgery (Chapter 31) in combination with evidence-based behavioral weight loss treatment may be considered [10]. However, there are few studies evaluating the long-term outcomes and safety of pharmacological and surgical treatments for pediatric obesity. Also, adherence to lifestyle behavior changes is still necessary following weight loss surgery and to potentiate the success of pharmacotherapy [18]. Therefore, even youth who meet the criteria for these more invasive interventions will benefit from participation in multi-component, behavioral weight control interventions.

FAMILY-BASED BEHAVIORAL WEIGHT LOSS

Family-based behavioral weight loss treatment (FBT) is a multicomponent behavioral weight control intervention developed and refined by Leonard Epstein, Denise Wilfley, and colleagues [19,20]. FBT targets both parents and children and is considered a first-line treatment for this population [1]. Not only does FBT have a positive impact on weight, but improvements in other health parameters such as reductions in blood pressure and cholesterol levels and psychological well-being are associated with FBT [21,22]. Although the majority of the research base for FBT rests on work done with children of elementary to middle school age [19], it has also been successfully adapted for use with preschoolers [23] and adolescents [24].

To improve a child’s weight status, FBT targets the modification of energy balance behaviors (i.e., decreasing caloric intake and increasing caloric expenditure) through the use of behavioral treatment techniques and the active involvement of a parent or caregiver. In FBT, the parent or caregiver, who is often also overweight or obese, is encouraged to change his or her own energy balance behaviors as well as support the child in these endeavors. Furthermore, the parent or caregiver is charged with the task of engineering the home environment so that it is conducive to
healthy energy balance behaviors for the entire family. This focus on making changes throughout the household is an important tenet of FBT. Although significant weight change can occur within the first few months of FBT, weight losses are better maintained over the long term by extending treatment contact to allow for the focus on both the continued practice of behavioral change skills and the development of family and social networks in support of weight loss maintenance behaviors [25]. The components of FBT are described in the following sections and in Table 29.2.
There are three primary goals in FBT regarding dietary modification: (1) decrease caloric intake, (2) improve nutritional quality, and (3) shift food preferences. To facilitate a decrease in caloric intake while improving nutritional quality, FBT uses a family-friendly method of categorizing foods according to traffic light colors [26]. In this way, families learn to gradually adopt healthier eating habits through decreasing portion sizes, decreasing their intake of high-energy dense, low-nutrient dense foods (Red foods), increasing their intake of lower-calorie, more nutritious foods (Green foods), and by regularly consuming three meals a day. In FBT, families are discouraged from “swapping” high-calorie, non-nutritious foods (e.g., soft drinks, cookies) with calorie-free or low-fat substitutes to help shift taste preferences away from “junk” foods to more nutritious food
choices. Additionally, families are encouraged to eat more meals at home, since this change in eating pattern has been found to be positively associated not only with improvements in the nutritional quality of foods eaten but also with improvements in weight status [27].

**Energy Expenditure Modification**

FBT’s primary goals related to shifting energy expenditure are to increase moderate-to-vigorous physical activity and to decrease engagement in sedentary pursuits (e.g., non-school- or work-related screen time). Again, the colors of the traffic light are useful in helping families differentiate among activities to increase (Green: moderate-to-vigorous physical activity) and those to decrease (Red: sedentary pursuits). In addition to being encouraged to increase time spent in moderate-to-vigorous physical activities, families are also encouraged to increase lifestyle activities such as using stairs instead of elevators, or walking or riding a bike to school rather than taking a car. Since sedentary activities are often accompanied by eating, decreasing sedentary time helps decrease caloric intake while also creating opportunities for greater energy expenditure [28]. Increasing physical activity not only facilitates weight change in the short term, regular physical activity is predictive of percentage overweight in treated children 10 years after their participation in FBT [29].

**Behavior Modification**

FBT is first and foremost a behavioral intervention employing such techniques as self-monitoring, goal setting, shaping, modeling, reward systems, and stimulus control to effect changes in energy balance behaviors. Self-monitoring is a mainstay of behavioral change efforts [30]. In addition to its utility in helping individuals develop awareness of behavioral patterns and choices, it aids in establishing baseline rates of target behaviors to facilitate goal setting and the implementation of reward systems. The value of self-monitoring is highlighted by research that has demonstrated greater decreases in child percentage overweight with increased frequency of self-monitoring [31], and research with adults suggests that the number of behavioral change techniques an individual reports using is associated with weight loss success [32]. FBT has an advantage in that it employs a variety of behavioral change techniques, and current advances in the basic cognitive and behavioral sciences are informing the development of additional behavioral change tools for use in FBT. For example, techniques have been developed to improve episodic future-thinking skills in children and their parents to improve impulse control, and implementation intention procedures may be used to improve prospective thinking or memory, which in turn may strengthen goal-setting skills [33].

**Parental Involvement**

While parental participation during multicomponent childhood obesity treatments has been shown to be positively related to child weight loss outcomes [34], in FBT, participating parents and caregivers are also taught to systematically use behavioral principles and positive parenting approaches to help shape and support their child’s weight change efforts [1]. For example, through the use of stimulus control and positive parenting techniques, such as allowing children latitude in making choices among a variety of healthy foods, parents are able to support their children in reducing energy intake without using restrictive feeding practices, which in turn results in better weight loss outcomes [35]. Parents are also encouraged to use limit setting to help create structure and routines around eating, activity, and sleep behaviors. Since parents or caregivers participating in FBT are often overweight or obese themselves, they are also encouraged to actively work toward changing their own weight status in addition to supporting their child’s efforts. Parental weight loss is positively associated with child weight loss, perhaps through changes made to the shared environment as well as through parental use and modeling of healthy weight-regulating behaviors [36,37].
fact, children who are overweight or obese may be particularly sensitive to adult influence in terms of the transmission of healthy behaviors [38], underscoring the importance of active parental or caregiver involvement in FBT.

**Socioenvironmental Contexts**

A child's weight-related dietary and physical activity behaviors are developed and maintained in the context of the family home as well as the broader community within which children and their families live, work, study, and play [39]. When new weight control behaviors are acquired during the course of FBT, these new behaviors do not replace the old behaviors associated with weight gain but rather coexist with them [40]. Unfortunately, new behaviors are not very generalizable outside of the setting in which they were learned; however, old learning or old behaviors are easily activated across the different contexts of our obesogenic world. As a result of this contextual influence on the acquisition and practice of energy balance behaviors, FBT takes a socioenvironmental or multilevel approach to behavioral change in order to improve maintenance of weight loss over time [41]. To address these challenges to the maintenance of newly learned weight-regulating behaviors, FBT teaches families to be aware of the impact these various contexts have on them and to identify and plan for the different constraints or barriers to maintaining a healthy energy balance across these different levels of influence. In addition, they learn how to identify and capitalize on facilitators or supports for healthy living, not only within the family but also within peer networks and the community.

**Peer Level**

Peer interactions are naturally reinforcing to children and good peer relationships have a positive influence on overall quality of life. When peers are supportive of healthy energy balance behaviors, weight loss maintenance efforts are enhanced [42]. Conversely, a lack of peer support for physical activity and healthy eating are likely to contribute to weight gain [25]. Therefore, in FBT, families are encouraged to establish healthy peer networks and to disentangle socializing from unhealthy activities such as eating high-energy dense, low-nutrient dense foods and sedentary pursuits such as playing video games. Unfortunately, weight-related teasing and bullying from peers can be a source of great distress, and children with severe social problems have been less successful in weight loss maintenance [20]. In an effort to improve children's confidence in their ability to relate positively to peers, FBT includes training in pro-social techniques for dealing with teasing and cognitive-behavioral techniques to improve body image and self-esteem.

**Community Level**

The community or built environment offers many opportunities as well as challenges to families participating in FBT as they attempt to maintain healthy energy balance behaviors. For example, Epstein and colleagues [43] found that families with greater access to parks and open spaces were more likely to maintain their weight losses up to 2 years, compared with families with less access to parks and open spaces but with greater access to grocery and convenience stores. Families are often unaware of the ways in which their communities impact their behavioral choices. In FBT, families engage in a number of activities to help increase their familiarity with what their built environment has to offer and in what ways it might interfere with the establishment of healthy habits over the long term. Problem solving, goal setting, and stimulus control are techniques that families can use in FBT to better work around or with their built environments. In addition, families are encouraged to become advocates for increased access to healthy foods and activity choices in their schools, their work places, and other community settings. In FBT, families are encouraged to build a culture of health in their homes, in their relationships, and in their communities to provide support for the difficult challenge of healthy weight maintenance in our obesogenic world.
TREATMENT DURATION, MODALITY, AND SETTING

Reviews of the literature on childhood obesity interventions (e.g., [12]) support the importance of treatment duration (26–75 h of contact) to achieving successful weight loss maintenance, especially when multiple levels of influence are addressed and there are strong behavioral and family components to the intervention, such as are found in FBT [25,29]. Given its efficacy and congruence with current USPSTF and Expert Committee guidelines for the treatment of pediatric obesity, there is a desire to make FBT more broadly available to children and their families.

One way to scale up treatment and make family-based weight loss interventions more available would be to deliver treatment in a group format. However, a recent review of group-based childhood weight loss programs found that group-only treatment formats may not achieve clinically significant weight changes [44]. Decreases in BMI z-scores of greater than 0.25 have been linked to changes in cardiometabolic outcomes in children, and thus are considered to have clinical significance. In this review, the median decrease in BMI z-score for group-only interventions was 0.15. Outcomes improved when an individual family component was included in the treatment along with group sessions (mixed format). These mixed-format programs had median BMI z-score changes of 0.2, closer to clinically significant outcomes than the group-only treatments. It is possible that in group-only interventions without an individualized behavioral component, families do not have sufficient support from the interventionist to make the necessary changes in their energy balance behaviors to realize clinically significant weight losses.

Another way to improve the availability of FBT while preserving its potency would be to conduct FBT with individual families within primary care settings. Colocation is a model of coordinated health care that places a behavioral health-care provider within the same location as the primary care physician. Preliminary research suggests that FBT interventionists can be successfully collocated within pediatric primary care practices and weight losses can be achieved in both the parent and the child [45]. However, an abbreviated form of FBT in terms of both treatment content and intensity was used in this study. Although further research is needed to test the efficacy of full-dose FBT in the primary care setting, the colocation of a behavioral health interventionist within primary care would allow pediatricians to more easily utilize the algorithm created by the American Academy of Pediatrics Institute for Healthy Childhood Weight for the assessment and management of childhood obesity in children 2 years of age and older using the 2007 Expert Committee recommendations [46].

This algorithm includes three important pretreatment components for the pediatrician: assessment of healthy eating and active living behaviors, prevention counseling on healthy eating and active behaviors, and the accurate determination of weight classification. After completion of the pretreatment components, patients move through a stepped-care approach of four stages, starting at the least intensive stage and advancing through the stages as necessary, based on the response to treatment, age, BMI, health, risks, and motivation. In Stage 1, “Prevention Plus,” the primary care provider helps the family create positive behavioral change regardless of change in BMI, with an aim for weight maintenance or a decrease in BMI velocity. After 3–6 months without weight status improvement, children advance to Stage 2, “Structured Weight Management.” This builds on Stage 1 by including more intensive support and structure to help achieve healthy behavioral change. After 3–6 months without weight status improvement, children advance to Stage 3, “Comprehensive Multidisciplinary Intervention,” which involves more structured behavioral modification, including food and physical activity monitoring and goal setting. Given the constraints on primary care physicians’ time and training, Stage 3 will typically involve referral to a weight management clinic with a multidisciplinary team. After 3–6 months without weight status improvement, children advance to Stage 4, “Tertiary Care Intervention.” Stage 4 is designed for children with a BMI of ≥95% with significant comorbidities and children with a BMI of ≥99% who do not show improvement in Stage 3. Stage 4 consists of intensive diet and physical activity counseling, with the use of medication and surgery when appropriate. With a colocated behavioral health interventionist, families advancing...
to Stage 3 and beyond can continue their behavioral weight loss treatment in the familiar setting of the pediatrician’s office, which they may prefer over being referred to an outside facility [47]. Colocation also allows for easier coordination of care, which is important given obesity’s potential for medical comorbidities. It should be noted that the “wait and see” components as outlined in Stages 1 and 2 (i.e., after 3–6 months without weight status improvement children advance to the next stage or intensity of treatment) could result in an additional 12 months of weight gain for a given child. Weight gain is more difficult to address than to prevent [7] and valuable intervention time could be lost by taking this “wait and see” approach [48].

CONCLUSIONS AND FUTURE DIRECTIONS

Childhood obesity poses a significant public health concern and, left untreated, tracks into adulthood, with all its associated comorbidities placing a tremendous burden on our health-care system and causing significant emotional distress to those affected by obesity. Evidence supports early intervention for obesity during childhood, as robust and sustainable changes can be made at this time. Family-based behavioral treatment for childhood obesity, a multicomponent treatment that intervenes across several contexts, has demonstrated effectiveness in reducing weight and improving physiological and psychosocial outcomes in children and their parents. Given its reach beyond the target child, FBT may be a very cost-effective way to treat obesity across multiple generations. Since siblings of overweight/obese children are at greater risk of overweight/obesity themselves [49], the potential for FBT’s impact to generalize to other family members’ health is an important area for future research.

Although FBT is a very effective treatment for childhood obesity, transdisciplinary research is needed to facilitate our understanding of individual, modifiable factors that can affect treatment response and to contribute to the development of even more potent, personalized, and efficient forms of FBT. For example, we know that a child’s weight loss by the eighth week of FBT predicts long-term treatment success [48]. Given this knowledge, advances in educational and systems sciences [50,51] could be brought to bear to assist in the development of mastery learning models [52] or adaptive treatment algorithms [53] that would allow the intensity or direction of FBT to adjust to the needs of individual families, thus conserving resources and improving treatment outcomes. Also, appetitive traits such as high food reinforcement, binge or loss-of-control eating, and impulsivity are associated with weight gain and may inhibit treatment response [1]. Learning theory and behavioral economics can inform the development and assessment of cognitive and behavioral interventions to address these traits within FBT to improve weight loss maintenance in this subset of families [50,54].

FBT is an effective behavioral health treatment that is uniquely well suited for implementation within primary care settings using colocated behavioral health providers. As insurers and medical service delivery systems shift toward a health-care market that incentivizes prevention and the effective management of complex, multilevel diseases such as obesity, interventions such as FBT will be in demand to meet this need. In anticipation of this shift in the health-care system, and to make effective care more broadly available to children who are overweight or obese and their families, it will be necessary to determine how best to scale up FBT for broader implementation without losing its potency. Feasible and effective approaches to training interventionists to deliver FBT on a large scale with a high degree of fidelity, such as web-based learning systems and patient simulation methods, will need to be developed and tested to ensure high-quality delivery of FBT to more children and their families.

REFERENCES


INTRODUCTION

Because comprehensive lifestyle interventions may have insufficient impact on body weight and medical comorbid conditions among severely obese children and adolescents [1–4], there is abiding interest in adjuvant therapies, including pharmacotherapy, for pediatric obesity. This chapter reviews medications that are either approved by the US Food and Drug Administration (FDA) for use in pediatric patients aged <16 years, are not FDA approved but have undergone pediatric trials, or, because they are approved by the FDA to be used in adults for obesity management [5,6], are considered by the FDA to be approved for use in adolescents aged ≥16 years. Some medications in late-stage clinical trials for obesity treatment are also discussed. Pharmacotherapy for the treatment of childhood obesity is generally prescribed only after 3–6 months of lifestyle modification has not been sufficiently successful at reducing weight. Nevertheless, pharmacotherapy is always considered an adjunct, to be administered together with intensive lifestyle modification [7]. Limited data suggest that, as in adults [8], pharmacotherapy without a concurrent behavioral modification program for adolescent obesity is less successful [9]. Finally, although there are few pediatric data on this issue, it is recommended that, as in adults [5], clinicians can maximize the likelihood of
long-term positive outcomes by discontinuing obesity pharmacotherapy in those without sufficient early weight loss (4%–5% of initial body weight after 12–16 weeks’ therapy). In this chapter, both FDA-approved and candidate medications have been organized according to their major mechanism of action; when insufficient pediatric data are available, adult studies are discussed. Common side effects, contraindications, and necessary monitoring for each agent are described in Table 30.1.

**DRUGS DECREASING ENERGY INTAKE**

**CENTRALLY ACTING ANOREXIENT AGENTS**

Norepinephrine, serotonin, and dopamine are neurotransmitters implicated in reward and appetite control pathways. The classical anorexiant agents act within the central nervous system to modulate these neurotransmitters and their receptors. There are currently no long-term pediatric safety or efficacy data for any of these drugs. However, the FDA has approved several drugs that exert anorexiant effects by stimulating adrenergic tone [10,11] for short-term use in adults. Phentermine, diethylpropion, and the other amphetamine-related drugs (Table 30.1) have been studied only in small pediatric trials [12–17] lasting no more than 12 weeks. The adverse effect profiles of both of these drugs are related to their amphetamine-like structure. All three drugs are Drug Enforcement Administration (DEA) Schedule IV controlled substances with a relatively low potential for abuse [18,19]. Because of their adverse effect profile [20] and the absence of trials showing long-term weight loss efficacy, none of the amphetamine-like agents are recommended or approved for obesity management in children. Other compounds such as fenfluramine and its stereoisomer dexfenfluramine affect appetite through their serotonergic effects [21–26]. These drugs increase serotonin release and inhibit its reuptake [11,27]. Although some large trials found fenfluramine was significantly more effective than placebo in adolescents in decreasing body mass index (BMI) [24], both agents increased the risk of valvular heart disease and have been removed from use [28]. Lorcaserin is a selective serotonergic 5HT2C receptor agonist that decreases food intake [29]. Adults treated with lorcaserin lose an additional 3.2% of initial body weight versus placebo [30–32]. The FDA approved lorcaserin to treat adults with BMI ≥30 kg/m² or BMI ≥27 kg/m² accompanied with at least one comorbid condition, with the specification that patients who have not lost ≥5% of their baseline body weight by 12 weeks should discontinue therapy [33]. There are limited data suggesting that combining lorcaserin with phentermine may improve short-term weight loss in adults [34]. There are no published pediatric data using lorcaserin, although trials are underway [35]. Given its limited efficacy in adults, lorcaserin is unlikely to be highly effective as a monotherapy in pediatric samples.

**AGENTS WITH PRIMARILY DOPAMINERGIC EFFECTS**

*Methylphenidate* and *dextroamphetamine* are amphetamines that inhibit dopamine reuptake, thus increasing the dopaminergic tone [36,37]. Most medications in this class are DEA Schedule II controlled substances and are considered to have a high potential for abuse [20]. The anorectic effect of these drugs has been observed in many adult [38,39] and pediatric [40,41] samples. Apart from their abuse potential, these drugs also have a significant side-effect profile including agitation, insomnia, tachycardia, hypertension, and hyperhidrosis [42–44]. This and the absence of trials showing long-term weight loss efficacy make this class not recommended for obesity management. Lisdexamfetamine dimesylate inhibits the reuptake of dopamine (and, to a lesser extent, norepinephrine) and decreases food intake [45]. In a 12-week trial of adults with binge-eating disorder, lisdexamfetamine produced a weight loss of 4.3 kg (vs. −0.1 kg in the placebo group) [46]. Lisdexamfetamine is FDA approved for the treatment of attention deficit hyperactivity disorder (ADHD) in patients aged 6 and older and for binge-eating disorder in adults. However, it is not approved for the management of obesity.
### TABLE 30.1
Medications for Obesity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Status</th>
<th>Common Side Effects</th>
<th>Monitoring and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine, diethylpropion, and mazindol</td>
<td>FDA-approved only for short-term use in adults.</td>
<td>Insomnia, elevation in heart rate, dry mouth, taste alterations, dizziness, tremors, headache, diarrhea, constipation, vomiting, gastro-intestinal distress, anxiety, restlessness</td>
<td>Monitor HR, BP. Contraindicated in uncontrolled hypertension, hyperthyroidism, glaucoma, agitated states, history of drug abuse, MAOIs. Caution prescribing to patients with even mild hypertension.</td>
</tr>
<tr>
<td>Fenfluramine, dexfenfluramine</td>
<td>Not FDA-approved for weight loss; voluntarily removed from the US market.</td>
<td>Drowsiness, dry mouth, headache, abdominal pain, insomnia, increased activity, irritability</td>
<td>Associated with an increased incidence of primary pulmonary hypertension. Associated with valvular heart disease.</td>
</tr>
<tr>
<td>Lisdexamfetamine dimesylate</td>
<td>Not FDA-approved for weight loss; approved for binge-eating disorder in adults and for attention deficit hyperactivity disorder in patients aged 6 years and older.</td>
<td>Dry mouth, sleeplessness (insomnia), increased heart rate, jittery feelings, constipation, anxiety</td>
<td>Contraindicated with MAOIs. Risk of sudden death in people who have heart problems or heart defects, and stroke and heart attack in adults. Monitor blood pressure and heart rate. Psychotic or manic symptoms such as hallucinations, delusional thinking, or mania may occur. May worsen peripheral vasculopathy, including Raynaud’s phenomenon.</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>Withdrawn in the United States (increased risk of serious cardiovascular events); still available in some countries such as Brazil.</td>
<td>Tachycardia, hypertension, palpitations, insomnia, anxiety, nervousness, depression, diaphoresis</td>
<td>Monitor HR, BP. Do not use with other drugs, MAO inhibitors.</td>
</tr>
<tr>
<td>Naltrexone ER + Bupropion ER</td>
<td>Approved for long-term use in adults.</td>
<td>Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea</td>
<td>Monitor HR, BP. Do not administer to patients with a history of seizure disorders or with anorexia or bulimia nervosa, to patients who are using opioids or abruptly discontinuing the use of alcohol, benzodiazepines, barbiturates, or antiseizure medications. There is potential increased risk of suicidality.</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Approved for long-term use in adults.</td>
<td>Headache, dizziness, fatigue, nausea, dry mouth, cough, constipation; back pain, cough and hypoglycemia in patients with type 2 diabetes</td>
<td>Risk of serotonin syndrome or neuroleptic malignant syndrome-like reactions. Evaluate patients for signs or symptoms of valvular heart disease. Euphoria, hallucination, and dissociation have been seen with supratherapeutic doses. Interactions with triptans, MAOIs including linezolid, SSRIs, SNRIs, dextromethorphan, tricyclic antidepressants, bupropion, lithium, tramadol, tryptophan, and St John’s wort.</td>
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Status</th>
<th>Common Side Effects</th>
<th>Monitoring and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine + Topiramate SR</td>
<td>Approved for long-term use in adults.</td>
<td>Paresthesia, dizziness, taste alterations, insomnia, constipation, dry mouth, elevation in heart rate, memory or cognitive changes</td>
<td>Contraindicated in glaucoma, hyperthyroidism, MAOIs. Concerns about teratogenicity (increased risk of oral clefts) mandate effective contraceptive use and pregnancy test monitoring in females. Metabolic acidosis, hypokalemia, and elevated creatinine have been reported, and periodic monitoring is advised. Abrupt withdrawal of topiramate may cause seizures</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Approved for long-term use in adults.</td>
<td>Nausea, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, increased lipase</td>
<td>Monitor HR at regular intervals. Contraindicated in patients with a history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2. Discontinue promptly if pancreatitis is suspected.</td>
</tr>
</tbody>
</table>

**Drugs in Development or Used Off-Label That May Act Centrally as Anorexiant Medications**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Status</th>
<th>Common Side Effects</th>
<th>Monitoring and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant human leptin, metreleptin</td>
<td>Investigational for use in obesity; FDA approved for generalized lipodystrophy.</td>
<td>Hypoglycemia, headache, abdominal pain</td>
<td>Useful only in leptin deficiency. Antibodies with neutralizing activity have been identified in patients treated with metreleptin. T-cell lymphoma has been reported in patients with acquired generalized lipodystrophy. A risk evaluation and mitigation strategy is in place to prevent inappropriate prescription.</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Not FDA-approved for obesity.</td>
<td>Nausea, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia</td>
<td>Acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis has been reported. Observe patients carefully for signs and symptoms of pancreatitis; discontinue promptly if pancreatitis is suspected. Contraindicated in patients with severe renal impairment.</td>
</tr>
<tr>
<td>Beloranib</td>
<td>Investigational.</td>
<td>Sleep disturbance, headache, infusion site injury, nausea, diarrhea</td>
<td>Teratogenic in animal models. Induces dose-dependent azoospermia and other sperm abnormalities, leading to infertility in males.</td>
</tr>
</tbody>
</table>

**Drugs Affecting Nutrient Trafficking**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Status</th>
<th>Common Side Effects</th>
<th>Monitoring and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>FDA-approved for treatment of obesity in adolescents ≥12 years old.</td>
<td>Oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, increased defecation, fecal incontinence</td>
<td>Contraindicated in chronic malabsorption syndromes and cholestasis. Choledolithiasis and, rarely, severe liver injury, including hepatocellular necrosis and acute hepatic failure leading to death, have been reported. Decreases drug concentrations of cyclosporine and levothyroxine. Doses should be temporally separated from orlistat. Fat-soluble vitamin absorption is decreased by orlistat. Use with caution in those at risk of renal insufficiency. MVI supplementation is strongly recommended. A low-dose preparation is approved for over-the-counter sale.</td>
</tr>
</tbody>
</table>
These agents are administered by subcutaneous injection, are approved by the FDA for adjunctive treatment of type 2 diabetes mellitus in adults, and have been shown to produce dose-dependent weight loss in both diabetic and nondiabetic adults [47–55], likely through central anorectic effects mediated via glucagon-like peptide-1 (GLP-1) receptors [56]. Liraglutide 3 mg (but not exenatide) is FDA approved for obesity management in adults on the basis of trials finding weight losses of ~8.4 kg (vs. ~2.8 kg for placebo) after treatment for 1 year [55]. Recent trials of two once-weekly GLP-1 analogs, albiglutide and dulaglutide, have shown glycemic improvement in select adult diabetic populations with modest mean loss in body weight [57,58] when compared with sitagliptin and liraglutide, respectively. Several small cohort studies in adults have also investigated the effect of combined GLP-1 agonist and metformin therapy, with promising results in glucose metabolism and weight [59,60]. Exenatide has been studied in 26 adolescents with extreme obesity during a 3-month, randomized, double-blind, placebo-controlled, multicenter clinical trial followed
by a 3-month open-label extension and produced weight loss of \(-2.9\) kg versus a \(+0.32\) kg weight gain in the placebo group, without regain during the open-label period [61,62]. One ongoing study examines the effects of exenatide on overweight adolescents with Prader–Willi syndrome [63]. At present, there are no pediatric liraglutide weight loss data available and insufficient long-term safety and efficacy data to recommend GLP-1 analogs for pediatric obesity.

**Agents with Action at Multiple Sites/Combination Agents**

Sibutramine, a combined norepinephrine and serotonin reuptake inhibitor, has substantial data indicating it reduces appetite and promotes weight loss in obese adults [64] and adolescents [9,65–74]. The largest adolescent multicenter trial [66], which enrolled 498 adolescents with BMI at least 2 units more than the US 95th percentile based on age and sex, but less than 45 kg/m\(^2\), found BMI decreased 2.9 kg/m\(^2\) in the sibutramine (10–15 mg) group versus 0.3 kg/m\(^2\) for placebo, after treatment for 1 year. Treatment with sibutramine also improved waist circumference, triglycerides, high-density lipoprotein cholesterol (HDL-C), insulin levels, and insulin sensitivity. However, cardiovascular adverse events (increased blood pressure [9,66,71] and heart rate [9,66,75–77]) were reported in sibutramine-treated patients, and the Sibutramine Cardiovascular Outcomes Trial (SCOUT) found that rates of nonfatal myocardial infarction and nonfatal stroke were significantly increased in adults treated with sibutramine [78]. Although withdrawn from the US market, sibutramine continues to be used and studied in other countries [74,79–81].

**Naltrexone Plus Bupropion**

Naltrexone is an opioid receptor antagonist approved to treat alcohol and opioid dependence. Bupropion is an aminoketone antidepressant with a structure similar to the appetite suppressant diethylpropion [82] that enhances both noradrenergic and dopaminergic neurotransmission via reuptake inhibition [83]. Bupropion is approved by the FDA as monotherapy for smoking cessation. Combination therapy with naltrexone-SR 16–32 mg plus bupropion-SR 180–360 mg/d was approved for adults, based on studies finding a mean weight loss of \(~6.8\)% of initial body weight (vs. \(~2.2\)% for placebo) [6]. The proposed mechanism for the beneficial effects of this combination is that bupropion stimulates hypothalamic pro-opiomelanocortin-producing neurons to release alpha-MSH, while naltrexone interrupts the autoinhibitory feedback loop that the endorphin products of pro-opiomelanocortin can induce, leading to a long-term synergistic effect on energy balance [84]. There are some short-term open-label studies in pediatric samples finding that bupropion monotherapy decreases body weight in subjects who are not participating in lifestyle interventions [85,86], there are as yet no available pediatric data for combination naltrexone–bupropion therapy.

**Phentermine Plus Topiramate**

In adults, the combination of immediate-release phentermine (3.75–15 mg/d) plus the extended-release (ER) GABAergic [87] antiseizure medication topiramate (23–92 mg/d), produced, together with lifestyle intervention, weight loss of 10%–11% compared with 1%–2% for those who received placebo [88–91]. These results make phentermine plus ER topiramate the most effective obesity pharmacotherapy that is FDA approved for adults [5,6]. This combination also improved glycemia, lipids, blood pressure, sleep apnea, and quality-of-life measures in adults. Of note, there is a warning of potential increased risk of orofacial clefts in fetuses exposed to topiramate [92] and a required risk evaluation and mitigation strategy [93] requiring monthly pregnancy tests, which may limit its use in adolescent girls. There are currently no pediatric weight loss studies of this combination available; there appear to be two ongoing randomized placebo controlled trials examining topiramate monotherapy in children and adolescents [94,95]. The most common adverse events associated with topiramate include paresthesias, taste impairment, psychomotor disturbances, and
impairment of cognitive function at dosages similar to those used to treat seizure disorders [96]. These adverse events limit the use of topiramate because of the higher doses needed for the medication to be effective as a stand-alone therapy for the treatment of obesity.

OTHER DRUGS IN DEVELOPMENT WITH POTENTIAL CENTRAL ANOREXIAN EFFECTS

The adipocyte-derived hormone leptin signals to brain regions that control energy intake, modifying the activity of hypothalamic appetite-regulating neurons [97]. In cases of congenital leptin deficiency, subcutaneous administration of leptin improves body composition, suppresses appetite, and normalizes the metabolic profiles [98–101] both short and long term. Leptin has also been used with some success to restore menses in leptin-insufficient women with hypothalamic amenorrhea [102] and to treat complete generalized lipodystrophy. In adult obesity trials, leptin has proved to be ineffective as monotherapy [103,104]. There is some evidence that leptin may reverse the muscular, neuroendocrine, and autonomic adaptations to the weight-reduced state in individuals who have achieved substantial weight loss [105–109]. However, in a small double-blind, placebo-controlled trial, when leptin was used in an attempt to promote further weight loss in the plateau phase following bariatric surgery, there were no significant effects of leptin treatment [110]. No trials have examined the effects of leptin in non-leptin-deficient obese children and teenagers attempting weight loss.

Tesofoxidine, like sibutramine, is a multiamine reuptake inhibitor. Due to its triple monoamine reuptake inhibitor properties, tesofenidine blocks the presynaptic uptake of noradrenaline, dopamine, and serotonin, thus increasing satiety and energy expenditure [111–113]. In one 6-month phase II trial of 203 adults, this medication resulted in dose-related weight loss, with the highest dose producing over 10% weight loss (vs. 2% in placebo) [114]. However, as with sibutramine, there were increases in blood pressure and pulse. There are no pediatric studies to date.

Amylin is a 37-residue pancreatic β-cell hormone that is cosecreted with insulin from the pancreatic β-cells. Amylin plays a role in glycemic regulation by reducing food intake, slowing gastric emptying, and reducing postprandial glucagon secretion in humans. Amylin has its own receptors in the hind brain that are hetero-oligomers with calcitonin receptors [115]. Its anorexic effects seem to be modulated through amylin’s interaction with other signals involved in the short-term control of food intake, including cholecystokinin, glucagon-like peptide 1, and peptide YY, by decreasing the expression of orexigenic neuropeptides in the lateral hypothalamus [116].

Pramlintide is a synthetic analog of amylin that has been approved for the treatment of both type 1 and type 2 diabetes and has been shown to result in small weight losses in obese and diabetic adults [117–120]. The main adverse effects of pramlintide are nausea and abdominal discomfort. There are a few pramlintide reports about adolescents with type 1 diabetes [121,122]; however, there appear to be no pediatric or adolescent weight loss studies.

Beloranib is a methionine aminopeptidase 2 (MetAP2) inhibitor and an analog of the natural compound fumagillin [123]. MetAP2 inhibition reduces fat biosynthesis and induces lipolysis and fat oxidation through unclear mechanisms [124]. It was originally developed as an angiogenesis inhibitor for the treatment of solid tumors [125] and it was observed to have weight-lowering effects at significantly lower doses than the ones used in cancer patients [126]. A phase II double-blind, randomized, placebo-controlled trial of three dose regimens of beloranib studying 147 obese adult patients (primarily women) showed weight loss of up to −11 kg in the high-dose group versus −0.4 kg in the placebo group [127]. Beloranib was associated with a dose-dependent reduction in the sense of hunger in these trials, suggesting a central mechanism of action that has yet to be elucidated. Animals treated with beloranib also exhibit reduced food intake [128,129]. Beloranib has also been reported to decrease weight in adults with hypothalamic injury-associated obesity [130]. A phase III double-blind, placebo-controlled trial of beloranib in pediatric and adult patients with Prader–Willi syndrome is now complete; results should be available by mid-2016.
**DRUGS AFFECTING NUTRIENT TRAFFICKING**

Medications affecting digestion in the gut include the following:

- **Orlistat** is a gastric and pancreatic lipase inhibitor that reduces dietary fat absorption by approximately 30% [131,132]. Orlistat is the only FDA-approved agent for the management of obesity in adolescents 12–16 years of age. There are multiple short- and long-term trials using orlistat in adolescents [131,133–138]. One of the largest randomized, placebo-controlled trials showed an overall $-0.55$ kg/m$^2$ decrease in BMI with orlistat versus a $+0.31$ kg/m$^2$ increase with placebo after 52 weeks ($p < .001$) [137]. The side-effect profile is primarily related to gastrointestinal issues, with oily stools, abdominal pain, and fecal urgency most commonly reported. Orlistat appears to affect the absorption of fat-soluble vitamins E and D [139], and users should also take a multivitamin. Some studies have also reported small but significant increases in serum liver enzyme concentrations [140]. Although orlistat has undergone two label changes due to reports of liver injury, cholelithiasis, and pancreatitis, a cause-and-effect relationship of severe liver injury with orlistat use has not been established [141]. Orlistat is the only FDA-approved drug for treatment of obesity in children aged 12–17 years to date, despite limited data on long-term (beyond 1 year) efficacy and its limited overall benefits. Orlistat must be taken with each meal, thus reducing its feasibility for school-attending adolescents. Available community data suggest half of the pediatric patients prescribed orlistat discontinue it within 1 month, 75% stop by 3 months, and only 10% remain on orlistat after 6 months [142,143]. Given its limited efficacy and low long-term use, orlistat appears of little benefit in practice.

- **Cetilistat** is another gastrointestinal lipase inhibitor currently under investigation [144,145]. It has shown similar weight reduction effects when compared with orlistat over 12 weeks among obese adults with type 2 diabetes treated with metformin, but may have a milder side-effect profile [144]. Cetilistat is approved in Japan for use in adults [146].

- **Acarbose** is a pseudotetrasaccharide that acts as a competitive inhibitor of intestinal alpha-glucosidases and compromises the uptake of monosaccharides, leading to lower postprandial insulin and glucose [147]. It is approved for diabetes management and has been shown to produce small weight losses in some adult studies [148–150]. There are no published pediatric trials for acarbose as an antiobesity drug.

**MEDICATIONS AFFECTING RENAL NUTRIENT REABSORPTION**

These drugs include dapagliflozin, canagliflozin, and empagliflozin, which are selective inhibitors of the sodium-dependent glucose cotransporter 2 in the renal tubule. They cause dose-related glucosuria by suppressing renal glucose reabsorption [151] and are approved for treatment of type 2 diabetes. Dapagliflozin induces relatively small but significant reductions in body weight, ranging from 2 to 5 kg [152–155] (vs. 0.95–1.55 kg reductions for placebo) in patients with type 2 diabetes [151]. Side effects include urinary tract and genital infections, volume depletion leading to increases in hematocrit and blood urea nitrogen, and hypoglycemia in those with diabetes. These agents are not approved for weight reduction in adults or children.

**DRUGS AFFECTING INTERNAL MILIEU/METABOLIC CONTROL**

None of the following agents have proved sufficiently potent to become FDA approved as therapy for obesity. However, modulation of the *milieu intérieur* is conceptually an important approach to ameliorate obesity. These drugs include the following:
• **Metformin**, a biguanide that inhibits intestinal glucose absorption, reduces hepatic gluconeogenesis, and increases peripheral insulin sensitivity [156, 157]. It is one of the cornerstones of treatment of type 2 diabetes in adults and children over 10 years of age [158]; however, it is not approved for the treatment of obesity. In nondiabetic adults it has been associated with modest weight loss and a reduction of insulin resistance [156] as well as the prevention or delay of type 2 diabetes onset [159]. Its use as a weight loss agent in adolescents has been studied in relatively few long-term trials (6 months or more). The largest trial in adolescents (92 subjects) showed a BMI change of −0.9 kg/m² in the metformin group versus +2.2 kg/m² in the placebo arm; however, metformin treatment did not produce a significant change in total fat mass, abdominal fat, or insulin [160]. A study of younger children aged 6–12 years with extreme obesity showed an average weight change over 6 months in the metformin group of +1.47 kg versus +4.85 kg in a placebo group in an intent-to-treat analysis [161]. The effect of metformin on BMI has also been studied in girls with polycystic ovary syndrome (PCOS) [162–168] and in adolescents receiving antipsychotic drugs [169, 170], with similar efficacy. Metformin has a modest impact on weight; its metabolic effects in nondiabetic children and adolescents are also inconsistent between studies [160, 161, 171–173]. Metformin remains one of the most studied drugs in pediatric samples. Currently, there are insufficient data to recommend metformin for weight reduction in children or adolescents.

• **Octreotide**, an octapeptide analog of somatostatin, is a potent inhibitor of growth hormone (GH), ghrelin, glucagon, cholecystokinin, and glucose-dependent insulin secretion [174]. Octreotide has been primarily studied for its weight loss properties in patients with hypothalamic obesity who are believed to have elevated insulin production in response to their brain injury–stimulated hepatic glucose production. In patients with Prader–Willi syndrome (who have marked increases in circulating ghrelin concentrations [175]), octreotide suppresses ghrelin; however, after 16 weeks of monthly octreotide administration, there was no significant change in BMI compared with placebo [176]. A small cohort of patients with hypothalamic obesity following cranial insults appeared to benefit from 6 months of octreotide therapy, with weight loss when compared with 6 months of prestudy observation [177], but a placebo-controlled trial suggested weight stabilization rather than weight loss in patients with hypothalamic obesity [178]. Among obese adults with insulin hypersecretion, treatment with octreotide for 6 months resulted in only ~2% more weight loss than in controls [179]. Octreotide appears reasonable to consider only in those with hypothalamic obesity, for whom it may be modestly effective.

• **Growth hormone**, which has multiple metabolic functions, increases hormone-sensitive lipase, stimulates adipocyte lipolysis [180], stimulates protein synthesis, and increases fat-free mass (both muscle and bone mass). GH is currently FDA approved for the treatment of patients with Prader–Willi syndrome and has proved to be efficacious at increasing height velocity [181] while decreasing fat mass and increasing lean body mass in such patients [182–184]. In GH-deficient adults and children, GH therapy has consistently resulted in decreased fat mass [185–188]. Despite its efficacy in these subset populations, a review of clinical trials of GH administration in patients with obesity showed no better performance for GH than for a hypocaloric diet [189]. The use of GH as a weight loss agent has also been limited due to the concerns regarding tumor development [190], changes in glucose metabolism [191], increased cardiac diameter [192], and exacerbation of respiratory symptoms (specifically sleep apnea) [193, 194]. Thus, GH is not approved for use as obesity therapy.

### Caffeine Plus Ephedrine

Ephedrine enhances catecholaminergic tone, with resulting thermogenic effects. This is augmented by the coadministration of methylxanthines such as caffeine, which inhibit phosphodiesterases [195].
In adults, a herbal caffeine–ephedrine preparation produced significant weight loss when compared with placebo [196]. This effect has also been observed in hypothalamic obesity [197]. One small study that randomized 16 adolescents to caffeine plus ephedrine and 16 to placebo reported significant weight loss (2.9 vs. 0.5 kg/m² with placebo) in a 5-month trial [198]. The most frequent side effects were nausea, insomnia, tremors, dizziness, and palpitations [199]. Ephedrine, however, was removed from use when it was found to cause significant cardiovascular effects.

CONCLUSION

At present, the only medication approved in the United States for use among adolescents for the amelioration of obesity is orlistat, which, when combined with lifestyle modification, has a moderate efficacy of approximately 3% additional weight loss relative to placebo, and is generally not well tolerated among adolescents in practice. Thus, at present, pharmacotherapy cannot be recommended for pediatric or adolescent obesity. Given the limited efficacy of even intensive behavior modification programs, however, there is a clear need for effective and safe long-term adjunctive drug therapy for children with severe obesity. FDA-approved drugs for long-term weight loss therapy in adults include combinations of bupropion and naltrexone, phentermine and topiramate, and monotherapy with liraglutide and lorcaserin. The percentage of adult patients achieving clinically meaningful (at least 5%) weight loss ranges from 37% to 47% for lorcaserin, 48%–66% for Contrave, 67%–70% for Qsymia, and approximately 51% for liraglutide. These encouraging results make them good candidates to be studied in randomized, controlled trials in pediatric and adolescent samples. In 2015, however, the literature on drug treatment for pediatric obesity remains quite limited and rife with issues (short intervention periods, high attrition rates, inadequate description of methods, and data analyses that use biased approaches to dealing with missing data) [5]. It is to be hoped that carefully designed, adequately powered clinical trials of the medications recently approved for long-term adult use will be carried out among pediatric samples in the near future.

REFERENCES


Advances in Pharmacological Treatment of Pediatric Obesity

Childhood Obesity: Causes, Consequences, and Intervention Approaches


Childhood Obesity: Causes, Consequences, and Intervention Approaches


Surgical Treatment of Adolescent Obesity

Andrew James Beamish and Torsten Olbers

INTRODUCTION
Today’s worsening global obesity pandemic affects a huge number of children and young people, with over 22% of children classed as overweight across the world [1] and almost 17% of children classed as obese in the United States [2]. While public health policy at the local, national, and international levels struggles to battle this crisis, the suffering at an individual level remains very real. For the obese teenager, life-changing and life-shortening comorbidities are highly likely in adulthood and often a reality long before [3]. The therapeutic options available to this vulnerable group are not only limited but often expensive and frequently ineffective. In this context, the emergence of surgical treatments is offering a promising and effective option for the severely obese adolescent. This chapter examines the background to bariatric surgery in adults and its use in adolescents, explores the selection processes, the role of the multidisciplinary team (MDT), pre- and postoperative considerations, and outcomes in this young and emerging field.

HISTORY OF BARIATRIC SURGERY
Surgery is currently a well-established therapeutic intervention for obesity and its comorbidities in adults. Bariatric surgery began in the 1950s with J. Howard Payne’s jejunocolic shunt [4]. This radical procedure involved the bypass of the vast majority of the small intestine. While the results were extremely successful in terms of weight loss, the negative effects on individuals were also profound. Patients often experienced major problems, such as diarrhea, dehydration, and gross and potentially life-threatening nutritional deficiencies, alongside myriad other complaints, such as gallstones and hair loss. A majority of patients required reoperation for complete or partial restoration of the intestinal anatomy [4].
To date, the most commonly reported procedure in adolescents is the Roux-en-Y gastric bypass (RYGB) [5]. The first reports of this approach came in 1966, when Edward E. Mason bypassed the majority of the stomach specifically to reduce weight [6]. Mason hypothesized that the powerful weight loss effects observed in patients undergoing gastrectomy for other reasons, such as peptic ulcer or cancer, could be replicated in patients suffering from severe obesity. In his early series, an impressive average weight loss of 44 kg across 1 year was achieved, but at the expense of a mortality in excess of 8% [7].

Building on this foundation, Mason set out to evaluate the early and long-term effects on metabolism and to develop the operation to achieve “safe control of obesity” [6]. Since then, surgical approaches to treat obesity have advanced enormously and, accompanied by advances in medical and anesthetic practice, the safe control of obesity using surgery has been made possible. Thirty-day mortality now lies below 0.1%, despite the presence of multiple comorbidities in many operated patients [8].

Less than a decade after Mason presented the first gastric bypass procedure, reports emerged detailing the results of surgery performed on children and adolescents [9,10]. When treating adolescents, a number of other issues must be considered in addition to the surgical approach. Adolescents’ growth and development is often not complete, and surgery confers lasting effects on eating patterns and nutritional intake. The long-term effects on micronutrient status and dependent systems, such as the skeleton, have yet to be documented in this population. However, for vulnerable individuals suffering from severe obesity, the negative impact of obesity is here and now. Where conservative measures are unsuccessful, surgery represents an effective and valid therapeutic option to reverse or improve multiple disease states and risk factors [5].

WHERE DOES SURGERY FIT IN?

Today, nonsurgical interventions predominate in the treatment of adolescent obesity, and the proportion of adolescents undergoing bariatric surgery is very small. Surgery is certainly not appropriate for every obese patient, but represents an essential and unparalleled option for a significant number of adolescents suffering from severe obesity and its comorbidities.

As covered in other chapters of this book, most nonsurgical interventions for childhood obesity are reliant on major lifestyle alterations involving dietary modification and physical activity programs. Surgery is not a first-line treatment for obesity. However, a referral to the specialist bariatric surgical MDT should be considered to evaluate surgical options when conservative measures persistently fail, generally after at least 6–12 months within a formal weight loss program.

PATIENT SELECTION

Selection criteria have been discussed in many papers in recent years and consensus guidelines are emerging, based predominantly on the original National Institutes of Health (NIH) guidelines [11]. However, these guidelines were developed in 1991 for adults with severe obesity and did not consider adolescents. The normal childhood body mass index (BMI) has been shown to increase with age [12]. Epidemiological analysis has determined appropriate global adolescent cutoff points for overweight and obesity, ranging from around 22 and 27 kg/m², respectively, at age 13 years, to the standard adult values of 25 and 30 kg/m² at age 18 years [12]. A BMI for age greater than the 99th percentile is associated with elevated cardiovascular and metabolic risk [13] and, in adolescence, this group includes all boys and most girls with a BMI exceeding 35 kg/m² [13].

The most appropriate candidates for surgery may well be individuals in later adolescence, whose physical development is more advanced compared with earlier in childhood. Therefore, the use of fixed cutoff points for selection is advocated in order to confer an increasingly conservative approach with decreasing age. In this context, the current guidance recommends that adult BMI cutoff points of 35 kg/m² with serious comorbidity and 40 kg/m² with other
comorbidity are appropriate primary criteria for surgery during adolescence [14] (Figure 31.1). Serious comorbidity is defined as type 2 diabetes mellitus (T2DM), moderate or severe obstructive sleep apnea (OSA; AHI >15 events/hour), pseudotumor cerebri, or severe steatohepatitis. Other comorbidities include mild OSA, hypertension, insulin resistance, glucose intolerance, dyslipidemia, and impaired quality of life or activities of daily living, as well as other conditions (Figure 31.1).

**FIGURE 31.1** Inclusion pathway for bariatric surgery. BMI, body mass index; MDT, multidisciplinary team meeting; T2DM, type 2 diabetes mellitus; CV, cardiovascular; OSA, obstructive sleep apnea; GERD, gastroesophageal reflux disease; ADLs, activities of daily living.
It is also largely accepted that surgical candidates should be developmentally mature, having reached Tanner stage IV or V and 95% of estimated growth [15]. An ability to demonstrate both motivation and a mature capacity for decision making, with a full understanding of the potential risks and benefits involved, is also necessary, along with commitment to a lifelong program of follow-up and micronutrient supplementation. Where psychiatric morbidity exists, it should be under formal treatment and be well controlled. Finally, and of crucial importance, the understanding and committed social support of the individual’s family or carers, and certainly the absence of abuse or neglect, are essential. Exceptions to the specific criteria exist and debate continues regarding the surgical treatment of younger individuals. Reports exist documenting surgery on children as young as 2 years old [16]. However, evidence in support of bariatric surgery in preadolescence is currently lacking and should be considered experimental.

A number of contraindications to surgery exist, especially among the psychologically vulnerable. Patients with unstable psychotic, depressive, and severe personality disorders would not normally be considered for surgery, although exceptional cases may be considered on formal advice from a psychiatrist and/or consensus within the MDT. An absent commitment to the lifelong postoperative program is also normally a contraindication, which also includes commitment from family members. The inability of the patient to understand the risks and/or to give informed consent also represents contraindications, although the MDT may identify exceptions to this rule where learning disabilities preclude full understanding.

THE MULTIDISCIPLINARY TEAM

An experienced MDT is essential for the effective function of a bariatric surgical service, particularly in the adolescent group. Skilled assessment and management of comorbidities and psychosocial well-being are key to achieving the optimal preparation for surgery and management afterward. Although formal evidence does not exist to back up this assertion, it represents the standard of care and is recommended unanimously across guidance documents. The American Society for Metabolic and Bariatric Surgery (ASMBS) suggests that several key members of the MDT are required [15]. These include a bariatric surgeon, a pediatrician, a dietitian, a mental health specialist, a physical therapist or exercise physiologist, and a dedicated coordinator. The surgeon may be either a bariatric surgeon experienced in pediatric surgery or a pediatric surgeon experienced in bariatric surgery. In fact, it is preferential that both a pediatric surgeon and a bariatric surgeon work together in combination. The pediatrician’s specialist expertise will typically be in one or a combination of endocrinology, gastroenterology, nutrition, and adolescence, but they may equally reasonably be an internal medicine specialist or a family practitioner experienced in adolescent medicine. The dietitian should be experienced in working with children and families, and the mental health specialist will typically be a psychiatrist or psychologist with adolescent or pediatric training, specifically experienced in obesity and assessment for obesity surgery. The physical therapist or exercise physiologist should be experienced in providing safe activity programs for severely obese adolescents. Finally, a coordinator must be responsible for coordinating the health-care pathway of each individual adolescent within the program, with particular importance placed on ensuring compliance with follow-up and treatments, such as nutritional supplementation. It is often appropriate for the coordinator to be a core team member who is in direct contact with patients and establishes a relationship of trust. This may be, for example, a nurse specialist or social worker. In addition to the primary team members, support should be available, as required, from specialists in pulmonology, gynecology, endocrinology, infectious diseases, cardiology, sleep disorders, gastroenterology, radiology, psychiatry, and hematology.

DIFFERENT SURGICAL PROCEDURES AVAILABLE

A wide range of bariatric surgical procedures exist today, but most modern reports of bariatric surgery in adolescents describe the use of the RYGB, sleeve gastrectomy (SG), and adjustable gastric band (AGB). Historically, the most commonly used procedure has been the RYGB, although
in recent years the use of SG has increased [15]. RYGB was first performed in adolescents in the mid-1970s [9], long preceding SG and AGB. It comes as no surprise, therefore, that the procedure with the greatest evidence base is the RYGB. As suggested by its name, RYGB involves bypassing the stomach by using an intestinal bypass, although no tissue is excised. The majority of the stomach is disconnected from the normal digestive route using a stapling device to leave a small (20–25 mL) gastric pouch in continuity with the esophagus. The jejunum is transected approximately 50–100 cm from the ligament of Treitz, and the distal end (Roux limb) is anastomosed to the gastric pouch, as a gastrojejunal anastomosis. The proximal end (the biliary limb) is attached approximately 80–150 cm distally along the jejunum, as a jejuno-jejunal (JJ) anastomosis. This Roux-en-Y construction means that ingested food passes directly from the esophagus through the small stomach pouch directly into the jejunum, bypassing most of the stomach, all of the duodenum, and the first part of the jejunum. Gastric, pancreatic, and biliary juices flow undiluted through the biliary limb to enter the jejunum at the JJ anastomosis, where juices meet ingested food.

SG involves the excision of the majority of the stomach on its greater curvature side, using a stapling device. The resection line begins approximately 5 cm proximal to the pylorus, proceeding to the angle of His to result in a tube or sleeve-shaped remnant stomach of approximately 25% its original capacity. A calibration tube, or bougie, is used to standardize the sleeve size.

The AGB is a synthetic restrictive device applied around the upper stomach to limit the transit of ingested food and therefore the volume that can be ingested. A balloon within the band is inflated with saline via a port-a-cath to achieve an adjustable degree of restriction.

There are currently insufficient data to make firm recommendations regarding preferred surgical technique in adolescents. In fact, this debate remains heated even regarding adult patients, and the answer will likely come from adequately powered randomized trials comparing procedures, which in adolescents have not yet emerged. Most bariatric surgeons appear to use the same surgical techniques for adolescents as in adults. The outcomes according to procedure will be discussed later in this chapter.

Proponents of AGB argue its reversibility as a benefit, although its mechanisms of action are more heavily reliant on restriction, compared with the profound gut–brain hormonal effects in RYGB. Surgeons preferring RYGB additionally argue that a long safety record, together with superior long-term weight and comorbidity control and favorable dietary compliance, suggest that this technique should suit adolescents best. SG, a relatively new bariatric technique, has been increasingly used in adolescents in recent years [17], and its short-term weight outcomes appear similar to those of RYGB. An advantage of SG may be a lower risk of long-term nutritional deficiencies, although long-term weight outcome remains unclear. The resection of a large portion of the stomach and the inability to restore normal anatomy after SG are disadvantages of this technique.

PREOPERATIVE WORKUP

A thorough formal overall assessment of the candidate’s eligibility should be undertaken. European guidelines [18] suggest that this should include an assessment of general health and nutritional status, a detailed explanation of necessary dietary changes after surgery, and an assessment of patient and family motivation and commitment to fully engage and comply with the lifelong follow-up program. Any existing comorbidities should be optimized with input from appropriate specialists.

Psychological assessment is especially important in the workup for surgery. Adolescents with obesity represent a particularly vulnerable group psychosocially, with exceptionally high prevalence of depressive symptoms, anxiety, and low self-esteem [19]. While these have been demonstrated to improve in many patients, a subgroup representing almost one-fifth of patients experiences ongoing symptoms [19]. It is crucial that full and frank discussions are held in advance of surgery, involving psychologically qualified professionals where necessary, to identify and address any identifiable psychological morbidity. It may be possible to mitigate the impact of mental health issues with close psychological follow-up and support. Some patients may be identified as candidates for cognitive therapies,
while others may be identified as unsuitable to undergo surgery at the current time point. It is essential that the patient and family fully understand the benefits, risks, and likely outcomes of surgery, as well as likely limits to its outcomes. Detailed health and nutrition assessment may include pulmonary function, sleep apnea, metabolic and endocrine function, helicobacter testing, body composition, bone density, and indirect calorimetry. A very low-calorie diet for 2 weeks prior to surgery has been shown, in adults, to reduce postoperative complications and improve the perceived difficulty of RYGB [20]. In adolescents, an example program has included a low-calorie diet (800–1200 kcal daily) for 2 to 3 weeks preoperatively [21].

**PERIOPERATIVE CARE**

Upon successful completion of the low-calorie diet, admission on the day of surgery is appropriate. Treatment should be in a specialist unit, with experience and expertise in providing adolescent bariatric surgical care. Ideally, the environment should be targeted at adolescents, rather than the general pediatric population. On the day of surgery, clinical aspects of management should mirror those adopted locally in adult bariatric surgery. These aspects should be discussed with anesthesiology colleagues and referenced alongside local guidance. Typical modern provisions include consuming clear fluids only from at least 6 h and nil by mouth for at least 2 h before surgery; appropriate thrombosis prophylaxis; and, of course, a final reassuring face-to-face discussion with the patient and his or her relatives to identify and alleviate any worries in advance of surgery.

Following surgery, care should be delivered in a ward environment with specialist experience in adolescent bariatric surgery. AGB, as the least invasive procedure, may be performed as an ambulatory procedure or, more likely, with a single overnight stay for observation. Following SG and RYGB, simple supportive measures, including analgesia and intravenous maintenance fluids, are required during the first 24 postoperative hours, but regular small-volume (20–25 mL) clear oral fluid intake is encouraged from the outset. Appropriate preoperative dietary counseling should allow patients to confidently upscale dietary intake, such that a small-portion soft diet is tolerated before discharge, typically on postoperative day two.

It is common to experience abdominal discomfort and even pain in the first 24–36 h postoperatively, which normally subsides rapidly and should be discussed in advance of surgery. It is not routine to perform a radiological contrast study to confirm adequate passage of fluid. Rather, attentiveness for warning symptoms of a hold-up is necessary. Should individuals regurgitate saliva or experience disproportionate pain levels after swallowing, a contrast study may be indicated. Clinicians should be vigilant for signs and symptoms of early complications, such as tachypnea, tachycardia, elevated oxygen requirement, fever, regurgitation, excessive pain, decreased conscious level, and anxiety. Complications that may be heralded by a combination of these symptoms include bleeding, gastric or intestinal obstruction, gastrointestinal leak, or pulmonary embolus.

Individuals should be well acquainted with a formal plan for obtaining advice and/or medical assessment and assistance in the event of difficulty after discharge. This may be in the form of a specific telephone contact, alongside electronic or paper information sources detailing expected and common symptoms and those symptoms requiring urgent attention. An appropriately staffed rapid-access clinic or suitable place for assessment should be available.

**POSTOPERATIVE FOLLOW-UP**

Intensive outpatient follow-up within the bariatric program should follow surgery. Regular early contact is important as patients become used to new eating patterns and abilities. A suggested program involves weekly or fortnightly patient visits for the first month, monthly visits up to 6 months, then 3-monthly visits until 2 years postoperatively. It is important to ensure effective and regular communication with the patient’s primary care provider, with a clear route of contact for advice and assessment, such that primary care staff members understand and are engaged with
the implications of the surgical intervention. This is made more important because of a tendency toward poor follow-up rates in bariatric surgery, as patients’ weight and comorbidities, and therefore their immediate need for health care, diminish. The standard for long-term follow-up in the United States is to achieve 75% patients attending at 5 years postoperatively, with all patients prospectively tracked [22]. Additionally, provision for long-term follow-up should plan for transition of care from the adolescent domain to an adult service as patients mature beyond pediatric or adolescent facilities [22].

OUTCOMES

The weight loss and comorbidity improvement resulting from adult obesity is well documented, the most recent meta-analysis incorporating over 160 studies and including 37 randomized trials [8]. This study demonstrated mean BMI reduction at 1 year to be between 11.8 and 13.5 kg/m² across the three procedures discussed in this chapter. The increasing body of evidence in adolescents shows similar BMI reductions beyond 6 months of 11.6 kg/m² after AGB, 14.1 kg/m² after SG, and 16.6 kg/m² after RYGB.

An area of particular interest in adult bariatric surgery is the impressive effect on T2DM. The risk of developing T2DM rises sharply with increasing BMI [23]. Furthermore, there is emerging evidence that adolescent-onset T2DM behaves more aggressively than adult-onset T2DM, with earlier failure of first-line therapies and requirement for insulin [24–26]. A mature literature base describes a marked improvement in glucose homeostasis after surgery, offering nondiabetics protection from developing T2DM [27] and inducing remission in 72% of those with T2DM, with the greatest benefit being when the T2DM diagnosis is new [28]. Adolescent studies, while limited thus far, show T2DM resolution in 79%–100% of cases following RYGB, 50%–94% following SG, and 100% after AGB [29].

Bariatric surgery has marked effects on cardiovascular risk factors, not least BMI, which is associated with a 10% increase in the risk of myocardial infarction per standard deviation BMI increase [30]. Overweight and obesity are associated with an increase in the risk of ischemic stroke of 22% and 64%, respectively [31]. Childhood levels of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) track into adulthood, and childhood LDL-C independently predicts carotid artery intima-media thickness in adulthood [32,33]. Obesity is associated with chronic, low-grade inflammation, and an elevated high-sensitivity C-reactive protein, even at low levels of ≥3 mg/L, is associated with a greater prevalence of coronary artery lesions [34]. There is growing epidemiological evidence in the adult literature of an association between overweight or obesity and breast, cervical, colorectal, endometrial, esophageal, gallbladder, kidney, liver, ovarian, pancreatic, stomach, and thyroid cancers [35,36]. Reversal of obesity may reduce the incidence of these cancers and long-term follow-up studies are needed to explore this in detail. Female-specific benefits include an increase in fertility and significantly reduced rates of gestational diabetes and eclampsia, with either no increase, or even a reduction, in risks to the neonate [37].

Additional comorbidity improvements have been shown in adolescents following bariatric surgery and are listed in Table 31.1 [5].

CONCERNS

Surgery can never be entirely without risk, yet bariatric procedures have an excellent safety profile in comparison with many other abdominal surgical procedures, such as cholecystectomy and hernia surgery, at least in adults. A number of potential complications require urgent reoperation in the postoperative period, such as anastomotic or staple line leak, bleeding, or bowel obstruction. Across all adult bariatric procedures, the published mortality rate is 0.22%–0.34% [38,39]. There is only one reported perioperative death following bariatric surgery in adolescents, which was a patient with significant cardiovascular comorbidity [40]. The choice of surgical procedure may be
influenced by such major comorbidity, since the operative time and physiological burden varies between procedures. Indeed, in a small number of eligible individuals the risk of surgery may feasibly outweigh the benefits, even in this young age group.

Adolescents with severe obesity often demonstrate nutritional deficiencies before bariatric surgery, which frequently persist postoperatively [41]. Protein deficiency is the most common macronutritional deficiency, but micronutrient deficiencies are more prevalent, such as trace elements, essential minerals, and both water-soluble and fat-soluble vitamins. Deficiencies may even be promoted by the consequences of surgery, such as small-intestinal bacterial overgrowth, especially in patients with T2DM [41]. RYGB removes the normal sphincter-controlled gastric emptying of digestive contents, permitting the rapid and unrestricted passage of calorie-rich food into the small bowel, which can lead to dumping syndrome. Symptoms include tremors, sweating, palpitation, fatigue, decreased conscious level, and diarrhea [42]. While symptoms are uncomfortable, most patients consider this to be a positive result of surgery as it can usually be controlled by dietary modification and offers a powerful feedback mechanism for avoidance of the wrong foods [43].

Some concern has been raised regarding the potential maternal and fetal health effects of micronutritional deficiencies during preconception and pregnancy. Testing for such deficiencies appears generally underperformed, although their true prevalence in preconception and pregnant women remains unknown [44]. Counseling regarding folic acid and other nutritional supplementation is, therefore, imperative in female adolescents under consideration for bariatric surgery. Iron deficiency anemia is also a risk in girls of reproductive age [45].

The impact of bariatric surgery on the adolescent skeleton is, as yet, unquantified beyond the first 2 years. Although bone mineral density (BMD) and bone mineral content have been shown to decrease within a year following gastric bypass surgery, levels fall from abnormally high values to reach normal or still above-normal levels for age [46]. Counseling, monitoring, and nutrient and mineral supplementation for bone health remain important after bariatric surgery [47]. The long-term skeletal impact is unknown and, therefore, warrants particular attention in follow-up studies, especially in young patients. Again, looking into the long-term implications of surgery in these young people, the required duration of action would be expected to be longer as the age at surgery decreases. It could therefore be expected that the requirement for reoperation at some future stage, with likely greater attendant risk than primary surgery [48], may be greater in this younger population. The implications of this will become more apparent from long-term follow-up studies in the adult population in the coming years, and similar studies in adolescent populations will provide evidence of its true implications.

### TABLE 31.1
Outcomes of Adolescent Bariatric Surgery by Procedure

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjustable Gastric Band</th>
<th>Sleeve Gastrectomy</th>
<th>Roux-en-Y Gastric Bypass</th>
<th>All Procedures (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI reduction (kg/m²)</td>
<td>8.5–11.7</td>
<td>13.0–17.2</td>
<td>13.3–22.5</td>
<td>13.5 (11.9–15.1)</td>
</tr>
<tr>
<td>T2DM resolution (%)</td>
<td>80–100</td>
<td>0–68</td>
<td>67–100</td>
<td>0–100</td>
</tr>
<tr>
<td>Insulin resistance resolution (%)</td>
<td>44–77</td>
<td>50–96</td>
<td>100</td>
<td>44–100</td>
</tr>
<tr>
<td>Hypertension resolution (%)</td>
<td>50–100</td>
<td>69–100</td>
<td>82–100</td>
<td>50–100</td>
</tr>
<tr>
<td>Dyslipidemia resolution (%)</td>
<td>35–100</td>
<td>0–58</td>
<td>87–100</td>
<td>0–100</td>
</tr>
<tr>
<td>Obstructive sleep apnea resolution (%)</td>
<td>20–100</td>
<td>56–80</td>
<td>100</td>
<td>20–100</td>
</tr>
<tr>
<td>PCOS resolution (%)</td>
<td>—</td>
<td>0</td>
<td>100</td>
<td>0–100</td>
</tr>
</tbody>
</table>

Note: CI, confidence interval; BMI, body mass index; T2DM, type 2 diabetes mellitus; CV, cardiovascular; PCOS, polycystic ovarian syndrome.
Anatomical implications of bariatric procedures must also be considered, since they can introduce relative inaccessibility to parts of the gastrointestinal tract. Conventional diagnostic and therapeutic approaches, such as gastroscopy [49] or endoscopic cholangiography, can be made more difficult or impossible. However, necessity has resulted in the development of novel techniques, including computed tomography virtual gastroscopy [48], double-balloon techniques for enteroscopy after RYGB [50], and even prophylactic cholecystectomy [51], which subsequently lost favor following meta-analysis [52]. Additionally, reversal of the RYGB is technically feasible, without significant complication in the short term [53]; however, the gastric excision of SG cannot be reversed.

**ADOLESCENT MORBID OBESITY SURGERY STUDY**

In Sweden, adolescent bariatric surgery has been investigated within the Adolescent Morbid Obesity Surgery (AMOS) study. This study examines the outcomes of 81 adolescents aged 13–18 years undergoing RYBG, comparing them with matched control adolescents undergoing nonsurgical treatment and matched adult controls undergoing RYGB. Alongside data regarding the effects of surgery discussed previously, which largely mirror the adult experience, some extremely valuable lessons have been learned pertinent to the adolescent population.

The adolescent population suffering with obesity represents a particularly vulnerable psychosocially morbid population, with disorders of mood, anxiety, and eating being particularly prevalent [54]. While the literature is limited regarding the effect of bariatric surgery on psychosocial outcomes, AMOS has demonstrated significant improvements in self-reported anxiety, depression, and self-perception across 2 postoperative years, alongside nonsignificant improvements in anger and disruptive behavior [19]. Services must be designed to actively seek, recognize, and intervene in vulnerable adolescents, as a 2% attempted suicide rate has been reported [21].

There is little evidence regarding compliance with prescribed mineral and vitamin supplements following bariatric surgery, perhaps largely due to the inherent difficulties in its accurate and reliable quantification. Within AMOS, compliance appears to be worse in adolescents than in the adult population, with incidences of rebellion and apathy toward supplementation. An example of the potential importance of this is the issue of bone health, discussed earlier in the concerns section. While AMOS has described an overall decrease in BMD for age, only a small proportion of patients (5%) reached subnormal levels over the first 2 years [55]. It was also seen in this cohort that individuals whose BMD was below normal for age (<−1) at 2 years had all started from a comparatively low baseline level (<0.5) [55]. These individuals may represent an at-risk subgroup to target with interventions to maximize compliance with supplementation. While effective interventions to achieve this are lacking thus far, compound tablet supplements have now emerged, permitting an all-in-one tablet to be taken, which may be preferable to taking multiple tablets.

In the adult population, excess skin represents a major psychosocial and physical problem. It was hypothesized that this might be less problematic in adolescents undergoing RYGB, since their younger skin was expected to retain more elasticity and, having been exposed to the stretching of obesity for a shorter duration, it may resume a normal contour more readily. However, the AMOS study has shown this not to be true. The majority of adolescents reported excess skin after bariatric surgery and the proportion desiring body-contouring surgery was at least the same as in an adult comparison group [56]. Objective measurements were significantly correlated with subjectively experienced excess skin [56]. Perhaps most surprisingly, only weak correlations were observed between the change in BMI and objective measurements, subjective experience, and discomfort from excess skin, rendering prediction of excess skin problems very difficult [56]. Therefore, adolescents undergoing bariatric surgery should be informed that there is a substantial likelihood that they will experience discomfort from excess skin following a major weight loss.
SUMMARY AND CONCLUSIONS

Although the literature base is limited at present in comparison with the adult evidence, bariatric surgery appears to offer adolescents unparalleled weight loss, and improvements to health and quality of life, which appear to closely match those reported in adults. The significant potential negative effects must be recognized, mitigated for, and further investigated in long-term outcome studies. Additionally, quantification of the possible benefits to society and health-care budgets is warranted. Surgery most certainly does not represent a stand-alone answer to adolescent obesity, and truly effective prevention and conservative treatment strategies are urgently needed. However, for the adolescent who is suffering from severe obesity and its incumbent wide-ranging health effects today, the likelihood of achieving a normal weight without surgery is very slim indeed. Bariatric surgery appears to offer significant benefits, present and future, while other therapies fail to match its effectiveness and struggle to achieve and maintain significant weight loss.

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Physical Activity Interventions for Treatment and Prevention of Childhood Obesity

Bernard Gutin and Scott Owens

INTRODUCTION

In principle, the strategy for the treatment and prevention of pediatric obesity is straightforward: (1) identify the causes for why some youths become fatter than others, (2) design interventions to counteract these causes, and (3) implement these interventions on a widespread basis. Unfortunately, none of the processes involved is simple. Thus, a 2015 review of determinants of childhood obesity in Europe concluded, “The true causes of the childhood obesity epidemic remain undiscovered, and the ability of research to identify effective prevention and treatment methods is compromised.”

One factor that might lead to ineffective preventive interventions is that our theories of the causes of obesity are often based on information that is valid for adults but faulty as applied to growing youths. For example, obese adults can successfully lose weight by creating an energy deficit through dieting, with moderate physical activity playing a supporting role. Thus, it is appropriate in adults to focus treatment interventions on how to help obese people restrict their dietary energy intake. However, for growing children, how to achieve weight loss is not the relevant question. Instead, we need to determine how to structure interventions so they help the youths to build more lean tissue rather than fat tissue, without necessarily restricting weight. In fact, a physical activity intervention that has a favorable effect on percent body fat (%BF) might increase bone and muscle mass to such a degree that the body mass index (BMI) of the active youths increases more than the BMI of the control subjects. To investigate this issue optimally requires the use of modern techniques to measure body composition. From a research perspective, new techniques are increasingly being employed in pediatric studies, allowing us to clarify the effects of physical activity interventions on various aspects of body composition. For example, dual-energy x-ray absorptiometry (DXA) provides data on three body composition compartments: fat mass, fat-free soft tissue, and bone mineral content. In addition, magnetic resonance imaging (MRI) and computed tomography provide information on potentially harmful visceral adipose tissue (VAT).
DESCRIPTIVE STUDIES EXAMINING THE LINK BETWEEN PHYSICAL ACTIVITY AND CHILDHOOD BODY COMPOSITION

Descriptive investigations typically involve relatively large numbers of free-living children and/or youths in whom physical activity and body composition have been assessed and correlated. For example, the Georgia Lifestyles Project examined the associations between adiposity and moderate and vigorous physical activity in a cross-sectional sample of several hundred adolescents in whom time spent in moderate and vigorous physical activity per day was measured objectively with accelerometry. Moderate physical activity was defined as activity that has a metabolic level of three to six multiples of resting metabolic rate (METS); in behavioral terms, this represents slow-to-brisk walking. Vigorous physical activity was defined as an intensity greater than 6 METS, which represents activities at jogging/running intensities. In this sample, the free-living adolescents did ~40 min/day of moderate physical activity and only ~5 min/day of vigorous physical activity. When the relations of moderate and vigorous physical activity to adiposity were analyzed separately in regression models, only vigorous physical activity was a significant predictor of DXA-derived %BF ($p = .001$ for vigorous physical activity; $p = .67$ for moderate physical activity). Subsequent to that study, a number of other projects in Europe and the United States have conducted similar projects with similar results. Thus, there seems to be something about vigorous physical activity that accounts for its inverse relationship to adiposity.

One line of investigation that may provide insight into the especially important role of vigorous physical activity in the development of a healthy body composition concerns its impact on various components of total energy expenditure. Because free-living youths participate in very little vigorous physical activity (i.e., ~5 min/day on average), the direct effect of the vigorous physical activity on energy expenditure would not seem to be an especially likely candidate as an underlying mechanism. Nonetheless, it is worth considering how vigorous physical activity might indirectly influence various aspects of total energy expenditure.

Resting metabolic rate (RMR) is the largest single component of total energy expenditure, and it is therefore noteworthy that vigorous physical activity stimulates the development of fat-free mass (FFM), the body compartment most highly correlated with RMR. Moreover, these findings are consistent with the results of two other lines of investigation: (1) free-living people with greater amounts of FFM tend to ingest more dietary energy; and (2) youths who engage in relatively large amounts of vigorous physical activity tend to be lean at the same time that they ingest more dietary energy than fatter youths. Another aspect of energy expenditure is the excess amount seen after the exercise itself is completed—the post-exercise energy expenditure. This is greatest following especially high-intensity exercise. Another component of total energy expenditure is the thermic effect of food (TEF)—that is, the increase in metabolic rate that follows a meal. The TEF is especially great following meals with higher amounts of food energy. Moreover, when people engage in some physical activity following a meal, the exercise and food interact, such that the exercise potentiates the TEF, with the TEF appearing to be greater in normal-weight than obese individuals. These aspects of energy expenditure are difficult to measure accurately, except in controlled laboratory settings. Therefore, they are seldom investigated in large-scale epidemiologic investigations. Nonetheless, taken together, they suggest that there are several pathways through which vigorous physical activity might be especially effective in raising total energy expenditure, thereby helping growing youths to avoid positive energy balance and develop lean bodies.

Another line of thinking, which is not directly based on energy expenditure, concerns the mechanical effects of vigorous physical activity on developing tissues—that is, the differentiation of immature stem cells into fat cells or lean cells. In culture, mesenchymal (bone marrow) stem cells can differentiate into various forms of mature cells; moreover, mechanisms that stimulate deposition of energy and nutrients into lean tissue tend to direct them away from differentiation into fat tissue and vice versa. Studies using mice have shown that daily exposure to mechanical signals, in the form of a vibrating platform, inhibited the development of fat mass while stimulating...
the development of bone; there were no dietary differences between the experimental and control groups.\textsuperscript{18} When the mechanical stimulation was introduced to the rodents at the same time as an obesogenic diet, it prevented the development of obesity; however, the stimulation did not reverse dietary-induced obesity. This suggests that the processes underlying prevention might be different from those involved in obesity treatment. To the degree that the mechanical effects produced by vibration and those produced by vigorous physical activity are similar, this line of research supports the potential efficacy of vigorous physical activity in promoting the development of lean bodies in growing youths.

It is important to emphasize that vigorous physical activity and appropriate diet play complementary roles in child development, in that active youths are able to ingest relatively large amounts of dietary energy and accompanying nutrients without necessarily becoming obese. This is illustrated by several studies showing that leaner youths tend to ingest more dietary energy than fatter youths.\textsuperscript{8,9,19} Moreover, a descriptive study of adolescents found that higher levels of bone mass and height were associated with vigorous physical activity, along with relatively high intakes of energy, calcium, and vitamin D.\textsuperscript{20}

Another important consideration is that physical activities undertaken in childhood, particularly activities that apply large forces quickly, convey optimal benefits to the development of bone mass.\textsuperscript{21} Examples of these activities include jumping, hopping, and tumbling.\textsuperscript{22} It also appears that increases in bone strength may be mediated in part by increases in lean mass associated with greater amounts of physical activity.\textsuperscript{23}

It is important to point out that although correlations provide valuable information about the relationships between physical activity and body composition, they have an important limitation in that they do not clearly indicate directional causality—that is, whether the correlation of high levels of vigorous physical activity with low levels of adiposity might be due to physical activity influencing adiposity or by adiposity influencing physical activity, or both.\textsuperscript{24} Therefore, findings from such studies should be considered as hypothesis generating rather than hypothesis testing. Randomized controlled trials are needed to test hypotheses generated by descriptive studies.

**RANDOMIZED CONTROLLED TRIALS EXAMINING THE LINK BETWEEN PHYSICAL ACTIVITY AND CHILDHOOD BODY COMPOSITION**

Within the category of randomized trials, an important factor to consider is where the trials fall on the spectrum of *efficacy* to *effectiveness*. At one end of the spectrum, we have trials that are tightly controlled and monitored to ensure that the subjects actually receive the doses of physical activity that are supposedly under investigation. For example, in some adult studies, subjects are brought into a research laboratory in which their individual physical activity prescriptions are supervised to ensure that they receive the exact dose of physical activity specified in the research design. In such projects, subjects may walk on treadmills at their specified physical activity prescriptions in order to determine the *efficacy* of different volumes and intensities of physical activity.\textsuperscript{25} Such trials are quite rare, especially in youths, because of the intensity of supervision needed to implement them. Nonetheless, they provide relatively definitive information about what types and amounts of physical activity should be incorporated into trials that go on to test the effectiveness of physical activity recommendations.

Within the pediatric literature, the trials conducted over the last 20 years at the Georgia Prevention Institute of the Medical College of Georgia provide examples of trials that are close to the efficacy end of the spectrum. To ensure that the youths actually receive the prescribed dose of physical activity, they are brought by bus from their schools to a research gymnasium to participate in a program that is offered every school day—that is, five days/week. In one of the early studies, it was found that youths preferred playing games that were modified to keep them active for the entire physical activity period, in contrast to exercising on treadmills or other machines.\textsuperscript{26} Thus,
subsequent studies used such games to provide the physical activity. The staff-to-subject ratio was quite high, ensuring that the youths participated actively. Moreover, every subject wore a heart rate (HR) monitor every minute of every session so that the intensity of their effort could be estimated. This enabled the investigators to show that the youths who maintained higher HRs during the sessions exhibited greater beneficial changes in the outcome variables. These analyses provided only indirect dose–response information because the youths were not randomly assigned to different intensities. Thus, youths who maintained higher HRs may have been predisposed to enjoy or profit from the higher intensities of physical activity.

As we move further along the efficacy–effectiveness spectrum, the conditions of some of the Georgia trials became closer to “real-world” conditions; that is, they had greater ecological validity. For example, in some trials, the youths remained in their regular schools at the close of the school day for the physical activity sessions, rather than being taken by bus to the research gym at the university. Nonetheless, the trials retained a high degree of supervision and HR monitoring, thus remaining toward the midpoint of the efficacy–effectiveness spectrum.

To the degree that the fidelity of the physical activity intervention is well controlled, and sensitive instruments are used to measure body composition, a clear picture of the true efficacy of the physical activity intervention can be obtained. Such information tells us what types of physical activity are appropriate to employ in real-world settings. However, in striving to learn more about the effectiveness of physical activity, interventions are typically less controlled, with the result that the distinctions between intervention and control groups in the physical training dose actually received may be less clear, leading to smaller group differences in the outcome variables. In this chapter, we are focusing on efficacy studies, while other chapters in this book discuss other effectiveness trials that have incorporated physical activity into the broader context of school or community-based studies.

To determine the efficacy of different intensities of physical activity, it would be ideal to randomize youths to different physical activity intensities and then supervise them carefully to ensure that they actually carry out the exercise prescriptions. Although the number of such studies is somewhat limited, two recent reviews concluded that vigorous-intensity physical activity is more efficacious than moderate-intensity physical activity for improving the body composition of youths. In addition, some indirect evidence of the value of vigorous-intensity physical activity has been provided by trials in which overweight/obese youths participated in vigorous aerobic physical activity interventions, and maintained average HRs greater than 150 bpm; this shows that even overweight youths can profitably maintain high physical activity intensities. Moreover, positive correlations were found between HRs during the training sessions and beneficial changes in body composition. Other recent studies have found similar results. Thus, it appears that obese youths can enhance their body composition without dieting by maintaining relatively high physical activity intensities for 40-min periods, undertaken for three to five sessions/week for 4-month intervention periods. This can be viewed as secondary prevention of obesity in the sense that it can prevent overweight/obese youths from going on to become even fatter.

However, in youths who were not preselected as overweight or obese, several projects failed to find that the interventions had a favorable effect on the adiposity of the subjects as measured with skinfolds. Although these results cast doubt on the value of physical activity alone as a form of primary prevention, they also led to consideration of another factor: how the exercise dose was administered. Perhaps (1) the intervention sessions needed to be longer than the 40-min periods previously used with the obese youths; (2) the intervention duration needed to be greater than the several-week period typically used; and (3) the fidelity of the intervention needed to be more closely supervised. Another possibility concerned the measurement of the outcomes; new imaging techniques such as DXA and MRI might be more capable of detecting changes in body composition.

Therefore, our Medical College of Georgia group undertook a series of studies in which the doses of physical activity were greater than previously used and the body composition changes were measured with high-technology imaging techniques. The first of these projects involved 8–12-year-old
black girls. African American girls were chosen because they were the demographic group in Georgia most likely to become obese and we wanted to investigate physical activity as the primary prevention. We imparted a physical activity dose of 80 min in duration: 25 min of skills development, 35 min of more vigorous physical activity, and 20 min of strength training and stretching. Subjects wore HR monitors, and were closely supervised. The sessions were offered 5 days/week and the intervention lasted for 10 months; average attendance was 54%—that is, slightly more than 2.5 days/week. DXA was used to measure total body composition and MRI was used to measure VAT. The intervention elicited favorable changes in %BF, VAT, and bone mass. Higher HR during the physical activity was associated with greater increases in bone mass and greater decreases in %BF. A follow-up study with black boys elicited similar results, but only in boys attending the physical activity sessions at least 3 days/week.

Recent controlled exercise interventions lend support to the value of vigorous physical activity interventions on measures of body composition in obese youths. In a group of 34 obese adolescent females randomly assigned to 12 weeks of either vigorous- or moderate-intensity interval training, post-training decreases in %BF were significantly greater in the vigorous intensity group than in the moderate intensity group. In another study, 48 overweight children were randomized to six weeks of either vigorous-intensity running, lower-intensity running, or a nonrunning control group. Total distance run per training session was equated between the running groups. Following training, decreases in the sum of skinfolds were significantly greater in the vigorous-intensity running group (−12%) than in the lower intensity running group (−0.5%) or the nonrunning control group (+8.0%).

Studies that have focused directly on bone development have found that the greatest osteogenic effects on the growing skeleton are provided by physical activity that has a high loading magnitude applied at a rapid rate—that is, vigorous physical activity.

Thus, it is clear that vigorous physical activity, without any restriction of dietary energy intake, can have favorable effects in helping both obese and nonobese youths to enhance their body composition. Almost all of the pertinent studies have used physical activity that was essentially aerobic in nature; that is, the activities involved large-muscle physical activity.

Another question for the design of physical activity interventions concerns the potential role of resistance training (RT). Because RT customarily involves taking the working muscles to momentary muscle failure, RT is high in intensity and might be classified as vigorous physical activity; thus, it might be expected to be especially effective in building muscle and bone mass. However, the literature related to this issue is sparse and it is not clear if incorporating RT into physical activity interventions has a positive effect on total body composition. In one recent study, the effects of 3 months of aerobic training versus RT were compared in a group of 45 obese adolescent boys. Total adiposity decreased significantly and similarly in the two groups.

Because of the especially significant role of VAT in cardiometabolic risk, a recent meta-analysis of diet and exercise interventions is noteworthy. The small number of interventions that involved diet alone did not show a significant effect on VAT. However, interventions that focused on exercise alone, or exercise plus diet, showed significant reductions in VAT. This meta-analysis supports the important role of physical activity in enhancing health-related body composition.

CONCLUSIONS

Based on this review of the scientific literature, how can physical activity be most effectively incorporated into interventions designed to treat or prevent pediatric obesity? The first recommendation is to recognize that children are not simply small adults. The biologic growth processes involved in the development of lean and healthy bodies are fundamentally different from the processes involved in adults. Thus, dieting for weight loss, which is appropriate for many adults, should not be the primary focus of preventive interventions in youths. Moreover, control of body weight should not be the primary index to evaluate the success of the interventions. Instead, the interventions should
focus on the development of lean tissue at the same time that they prevent excess accretion of fat mass. Because the development of lean mass is energetically expensive, children should be encouraged to ingest substantial amounts of nutrient-dense foods to support healthy growth. The diet composition that is optimal for this development is discussed elsewhere in this volume.

A second recommendation concerns the type of physical activity intervention that would be optimal for youths who are already obese and unfit. With respect to physical activity intensity, a number of studies have shown that such youths can engage in physical activity that elicits HRs greater than 150 bpm without excessive danger of injury. Nonetheless, it is reasonable to be cautious about engaging too abruptly in vigorous physical activity to avoid excessive fatigue and a resulting disinclination to continue in the exercise program.

Many of the descriptive studies reviewed here that concluded that vigorous physical activity was likely to be more beneficial than moderate physical activity used time–motion indices (e.g., accelerometry) to classify physical activity into moderate or vigorous categories. However, such physical activity categorization does not take individual differences in fitness into account. For example, lean/fit youths might find moderate physical activity, such as brisk walking, to elicit HRs of 120 bpm, while obese/unfit youths might reach HRs of 170 bpm while walking. Thus, in keeping with the overload principle, the lean/fit youths would need to incorporate running into their regimens to derive increased benefit, while the obese/unfit youths would be more likely to obtain benefit from a brisk-walking regimen. Regardless of initial fitness level, as fitness improves, the intensity of their regimens can be increased.

With respect to the duration of the physical activity sessions, dose–response studies of obese/unfit youths have shown beneficial body composition changes with regimens of 20–40 min/session, offered five times/week, with the physical activity interventions lasting 4–10 months. However, for youths who begin a physical activity regimen while relatively fit and lean, further improvements in body composition may require that the intervention sessions last longer, perhaps as long as 60–80 min/session.30,37,41 There is a need for a comprehensive meta-analysis to determine the precise effect of these types of interventions on the body composition/obesity of youths.

A final recommendation is that physical activity efforts involving youths be persistent and continuous in order to retain the beneficial effects. For example, in the 3-year FitKid study, the beneficial effects of after-school physical activity on %BF and cardiorespiratory fitness observed during the first and second school years (when the youths were active in the intervention) were lost over the subsequent summer months (when the intervention was suspended).42 This phenomenon has been observed by others as well.43 However, it is noteworthy that over the entire 3 school years of the FitKid intervention, DXA measurements showed that the youths who participated in the after-school program at least 2 days/week showed consistent and significantly greater increases than the control subjects in fat-free soft tissue and bone mass.2 More longitudinal studies in growing youths are needed to determine the patterns and magnitudes of effect for various aspects of body composition.

These recommendations can be incorporated into various specific activities. In our studies at the Medical College of Georgia, we have found that the youths prefer physical activity that is part of skills and games modified to include vigorous physical activity (e.g., soccer, basketball, dance), rather than exercising on machines that might be found in an adult fitness facility (e.g., treadmills, cycles, rowers). If facilities and leadership for these activities are provided on a widespread basis in clinical settings, schools, and community centers, then they can contribute to the treatment and prevention of pediatric obesity, leading to the improvement of public health into future generations.

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INTRODUCTION

The concept, called primordial prevention, that a condition such as childhood obesity can be prevented by avoiding the development of risk factors in the population raises several questions. First, to what extent do we understand the biological and other drivers or risk factors for obesity? Second, do we have available biomarkers of exposure to such drivers in individuals or groups and/or other means of assessing their susceptibility before the condition becomes manifest? And third, do we have the means of preventing the condition? The concept of such prevention inevitably focuses attention on interventions starting in infancy (as reviewed in Chapter 34), when the trajectory of weight gain appears to be particularly important [1], but such interventions will need to be sustained through childhood if they are to be effective [2]. Other research raises the possibility that maternal body mass index (BMI) at conception or weight gain in pregnancy constitute independent risk factors for childhood obesity [3], suggesting that interventions may need to be started before the child is born. In turn, this leads to the concept that attention needs to be given to the preconception period if the risk of obesity in the next generation is to be minimized.

There are now numerous animal studies showing that parental (both paternal and maternal) obesity, malnutrition (i.e., unbalanced macro- and micronutrient diets), and experimentally induced diabetes mellitus can pass risk of obesity to the offspring [4]. A range of epidemiological studies similarly support the concept of such transgenerational transmission of risk [5]. Translating these concepts into public health initiatives is challenging, as discussed in the last sections of this chapter, and is likely to necessitate a paradigm shift in our thinking about the prevention of noncommunicable diseases (NCDs) and their risk factors such as childhood obesity. These issues are encapsulated in the field of developmental origins of health and disease (DOHaD) [6], a relatively new area of biomedical science. The economic implications of non-communicable diseases are encapsulated in the concept of the passage of health capital from one generation to the next [7], and these are
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particularly important in low- and middle-income countries (LMICs) and populations undergoing socioeconomic transitions. This chapter describes aspects of the prevention of childhood obesity focusing on processes early in life with some emphasis on LMICs.

**LIFE COURSE BIOLOGY: NOT JUST DARWINIAN FITNESS**

Biologists are very familiar with the concept of the life cycle, whereby members of a species grow and develop to reproductive competence, reproduce, and then perish. This concept is enshrined in evolutionary biology as “Darwinian fitness,” by which beneficial adaptations in individuals promote their survival and fecundity in a given environment, giving them an advantage in passing on their genes to the next generation. While the nineteenth-century concept of the “survival of the fittest” [8] has been used to justify a range of human activities, and the metaphor of evolution is applied to a wide variety of aspects of human life [9], its application to medicine is not so straightforward [10]. The concept of fitness as an individual property is undermined by humanitarian considerations by which humans strive to preserve life, and provide opportunities for reproduction, in members of our species perceived to be weaker, unhealthy, or infertile. On the other hand, we are increasingly exposed to evolutionarily novel environments, offering calorie-dense and unbalanced nutrition, a sedentary lifestyle, 24 h access to entertainment, and exposure to a wide range of environmental toxicants—all of which are challenging our fitness because they can affect us during the phase of the life course when we are growing and commencing reproductive activity. Our evolved biology is simply not matched to these environments [11]. The problem is particularly acute in low-income countries (LIC) as they pass through socioeconomic transitions, leading to dramatic increases in obesity and NCD risk even in young people [12] (Figure 33.1).

In parallel with these changes, human life expectancy has increased dramatically over the last century such that, in, for example, the United States, it now stands at a mean of 76 years for men and 81 years for women, although these figures hide wide variations related to socioeconomic status (SES), both within as well as between populations and in attitudes to perceived longevity that affect behavior [13]. Nonetheless, survival into the postreproductive period means that a more complete life course concept of human health, as opposed to the more restricted life-cycle model, needs to be considered. This is particularly important as some of the factors influencing childhood health and risk of obesity are related to parental behaviors and are passed from generation to generation by a range of social as well as biological processes [14].

**FIGURE 33.1**  Risk of obesity is increased from birth in a low-income country (LIC), compared with a high-income country (HIC, gray line) as a result of parental malnutrition, low birth weight, and stunting, and so on. Greater mismatch occurs on the transition to a low-middle income country (LMIC, black line). In addition, teenage pregnancy passes greater risk to the next generation earlier, compared with HIC.
INTERGENERATIONAL PASSAGE OF OBESITY RISK

There is substantial evidence that early-life influences, in particular prenatal environmental conditions such as maternal adiposity, play an important role in the development of obesity in children. Young women are increasingly entering pregnancy with BMIs of more than 30 kg/m$^2$, which results in health risks to both the pregnant woman and her infant [15]. As reviewed in other chapters of this book, overweight or obesity, unbalanced diet, and preexisting conditions, such as type 2 diabetes or metabolic syndrome in the mother [16] and also to an extent in the father [17], are associated with greater risk of obesity in the child. These effects are amplified in first pregnancies [18]. In addition, conditions such as gestational diabetes mellitus (GDM) have been thought to be associated with greater risk of obesity in the offspring, although this is still uncertain [16,19]. There are reported ethnic differences in such risk [20] and in the extent to which such risk is passed even by mild diabetes [21].

Considerable research is underway into the mechanisms underlying such risk. The changes in phenotype in the developing individual, for example, in response to maternal malnutrition (either inadequate or excessive) involve epigenetic processes that relate to fat deposition and can be measured at birth [22,23]. The changes in the incidence of obesity between generations have occurred too rapidly to be accounted for purely by genetic predisposition, but nonetheless there are genetic–epigenetic interactions occurring in aspects of such phenomena [24]. It is important to realize, too, that these processes operate within the range of normal diets of the general population, at least in European populations. This is not surprising because fat deposition, at least in the neonate, can in terms of evolutionary biology be seen to be adaptive, providing a source of nutrition in the face of poor maternal care and assisting with the supply of fatty acids essential for brain development [25]. In this context, it is interesting that malnutrition in Indian babies is associated with greater abdominal fat distribution in proportion to body weight in comparison with Caucasian babies [26] and that in the Generation R study faster fetal growth was associated with greater childhood BMI [27]. The effects appear to be sustained across the life course, as in the Hertfordshire cohort low birth weight was related to greater central versus peripheral fat mass in men aged 64–72 years [28]. In a Western population, an imprudent maternal diet before conception and in early pregnancy is associated with greater liver blood flow and less shunting of blood returning from the placenta through the ductus venous in the late gestation fetus [29], a pattern linked to greater adiposity at birth and at age 4 in the child [30]. This emphasizes the importance of the liver in fetal metabolic and body composition development.

LIFE COURSE

A life course approach to disease is not a new concept, and its theoretical basis in terms of critical periods, accumulative damage, and pathway analysis is well established [31]. Taking a life course view of obesity highlights several aspects of the problem that are relevant to the prevention of the condition. The simplest view of the rising risk throughout life (as in Figure 33.1) is that this is due to the accumulation of damage due to lifestyle factors and a declining ability to repair such damage. From this viewpoint, the development of obesity is pathological from the beginning and has little adaptive significance. Moreover, reduction of exposure to factors that produce damage should reduce risk at any point in the life course. Although there is some validity in this concept, it cannot account for the entire trajectory of risk because, although some adult interventions have achieved positive results, others have proved to be disappointing [32–35]. For example, sustained weight loss in volunteers does not reset appetite and satiety control mechanisms even after a year [36], and there is considerable evidence that aspects of appetite, food preference, and taste are established in early life [37].

A second aspect of the life course concept is that components of the trajectory are set during “sensitive” or, if not reversible, “critical” periods of development. There may be some evidence for
this in childhood obesity [1], although the precise timing of any sensitive period is not established unequivocally. Some studies conclude that interventions should be focused in the primary school years or before [38], others that the major increase in fat mass occurs in older, teenage, children [39–42].

There is also evidence for gender differences with better cardiovascular risk profiles occurring in girls who changed to normal weight by adolescence than those who remained overweight. However, this was not the case in boys who kept an intermediate risk profile when altering their overweight status as they moved from childhood through adolescence suggesting the importance of intervention strategies during early childhood [43].

Once established, the implication of the critical- or sensitive-period concept is that obesity will occur later in life irrespective of later environment, behavior, and so on. This in sensu strictu relates to the use of the term trajectory, because the analogy with a ballistic trajectory is that, once set, its path and destination can be predicted. Clearly, this is not true for obesity in adults, which is likely to be a combination of early and later risk factors.

A third way of envisaging the life course model is that a condition “tracks” from childhood into adult life [44,45]. This might be because there is a limited opportunity to reverse the degree of the condition, which is analogous to the trajectory analogy, or because the response to a challenge at any point depends on the responses at the immediately preceding point. There is evidence for tracking of overweight and obesity within the childhood period [43,46,47]. This is a model of path dependency, for example, the response to risk at any point in time is not simply dependent on the level of the risk factors to which an individual is exposed (the ordinate in Figure 33.1) but also on the path taken to reach that point. A range of factors can affect this slope, in other words, the degree of tracking such as SES [48] and ethnicity [45]. There is also evidence for the tracking of lifestyle risk factors such as diet, sedentary activities, and exercise preference [49–52]. The resulting effect on obesity risk can be measured by the slope of the line relating risk to time. For type 2 diabetes, for example, the amplifying effect of low birth weight on the adult risk factors for ill health (diet, BMI, smoking, alcohol consumption) has been shown [53]. This is important as it reveals the importance of physiological testing of responses to small changes in risk, or to short interventions, in establishing where an individual lies on a particular risk trajectory. Advancing this field through the use of early biomarkers of later risk is, therefore, important [54].

CHILDHOOD OBESITY IN THE TRANSITION FROM HIGH- TO LOW- AND MIDDLE-INCOME COUNTRIES

Since the 1950s, economic development and major societal changes, such as modernization, individualization, and urbanization, changed lifestyles in high-income countries (HICs) [55]. These societal changes led to big increases in food availability and variety, as well as changes in the culture of food, such as flexible-eating patterns, solo eating instead of family meals, eating while watching TV, restaurant eating, irregular eating, and snacking [56]. In addition, there were significant changes in the way physical activity was incorporated into daily life. The so-called baby boomer cohort were the first generation to be exposed en masse to obesogenic risk factors and global marketing of foods as they entered adulthood, and this is likely to have contributed to obesity in the next generation. By the 1980s, the prevalence of obesity increased rapidly in both adults and children in HICs [57,58]. The overall mean BMI values in children increased and the heaviest children became even heavier [59]. Initially, obesity was mainly a problem among higher-SES children who had greater access to energy-dense diets [60,61]. However, since 2000 this trend has reversed in HICs and childhood obesity has become much more prevalent in deprived population groups [62]. For example, in the United States, racial/ethnic and SES-related disparities in childhood obesity had not changed from 2001 to 2010 [63]. In Europe, similar trends and patterns of social inequality in childhood obesity can be observed and are often grounded in parental risk factors [64]. For example, young low-SES mothers are less likely to breast-feed and, if they do, do so for a shorter
Life Course Approach to the Prevention of Childhood Obesity

Duration, while they are more likely to start early use of infant formula and cow’s milk consumption [65]. These mothers are more likely to be overweight and obese and less likely to adhere to lifestyle guidelines. This all implies a vicious cycle of “obesity begetting obesity”: a girl born to an overweight or obese low-SES mother is very likely herself to enter her first pregnancy being overweight or obese.

What happened in HICs in one generation (starting with greater affluence and urbanization in the 1950s) is now happening at a much faster rate in LMICs with much steeper and shorter trajectories (Figure 33.2) while the switch from rich to poor has already happened [66,67]. In contrast to the orderly transition of problems of undernutrition to problems of overnutrition in HICs, the distribution of childhood malnutrition is shifting from a predominance of undernutrition to a dual burden of under- and overnutrition [66]. This phenomenon is particularly seen in transition economies, where prevalence rates of obesity exceeding 15% in children and adolescents are common, such as Mexico (42%), Brazil (22%), India (22%), and Argentina (19%) [68]. Obesity may co-occur with stunting or anemia due to shared underlying determinants or physiological links, emphasizing the importance of the mismatch concept, and poses a novel public-health challenge [12]. In addition, LMICS are faced with a rapidly growing chronic NCD burden and continual high rates of infectious diseases [69,70]. These challenges may interact as some infections increase the risk of certain chronic diseases and vice versa. For example, diabetes has been associated with a threefold increased risk of tuberculosis, and both HIV and tuberculosis have been linked to an increased risk of developing diabetes; coincident HIV, tuberculosis, and diabetes are reported to worsen outcomes [70].

**WHEN MIGHT BE THE BEST TIME TO START INTERVENTIONS?**

Juonala et al. (2011) have reported that obese children who are able to become nonobese adults have no greater risk of cardiometabolic disease than adults who have never been obese [71]. However, within childhood, it is not certain how long the critical period is when it may be possible to reverse the risk extends, and there are methodological problems with the existing studies. The safest conclusion is conservative, viz. that interventions should start early and be maintained: this was one of the conclusions reached in the World Health Organization (WHO) ECHO final report [72].

A life course approach, targeting the developmental components of obesity risk, is crucial to curbing the obesity epidemic in both HICs and LMICs. Perhaps the most effective strategy would be to target the preconception period to improve prospective parents’ body composition and lifestyle, preferably resulting in women with a healthy prepregnancy BMI, lower gestational weight gain, and postpartum weight retention before conception [73]. In many societies, this means targeting...
adolescents, and there are several reasons for this. One simply concerns scale: there are 1.2 billion adolescents (aged 10–19 years) in the world today and the demography of some LMICs, such as much of sub-Saharan Africa, indicates that this age group already comprises 25% of the population and is increasing. Improving the health of this section of the population might provide an opportunity to redress the effects of a disadvantaged start to life [74] and improve their health and well-being, economic productivity, and longevity. It may reduce social inequalities in health and pass greater health capital to the next generation.

There are, however, some problems in effecting such a policy. The first relates to the fact that in most cultures, adolescents believe that they are fundamentally healthy and they do not access health-care services for screening or routine checkups. The life course model indicates that the adolescent section of the population does indeed enjoy good health and has low risk in absolute terms, but that nonetheless a substantial proportion of people at this age are on a steep trajectory of risk. Unfortunately, many adolescents discount future health against shorter-term goals, and this is particularly true of those of lower socioeconomic and educational status in migrant and displaced groups [75]. A high proportion of pregnancies in this age group are unplanned, and adolescent girls may not access health care until late in the first trimester, by which time it is too late to promote healthy development of the embryo [76]. Moreover, many women who have unhealthy lifestyles do not change their behaviour when they are pregnant [77]. In both HICs and LMICs there is a substantial gap in the provision of health care between contraception and antenatal services [78,79].

Opportunities for Global Action

There is an urgent need to address the problem of obesity in young people. The need is unlikely to be met through the formal educational system in many societies, although new methods of engaging adolescents and younger children in science literacy and investigative schemes, both in and out of school, offer promise [80–82]. Cost–benefit analyses of a range of interventions in younger and older children have been conducted [83], making an economic case for investment in this area.

The launch of the Sustainable Development Goals (SDGs) in September 2015 marks a new era in global health. While the foregoing Millennium Development Goals (MDGs) have not been completely met, there has been substantial progress in maternal and child health even though globally malnutrition and preexisting conditions, such as obesity, still account for nearly 45% of deaths of children under 5 years and more than 25% of maternal deaths, respectively [84,85]. We are moving into an era when the well-being and quality of life of those whose lives have been saved is a critical issue for humanitarian and equality as well as economic reasons. Unlike the MDGs, the SDGs have a focus on NCDs. For example, SDG 3.4 states: “By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and wellbeing.” There is also a clear focus on adolescents and prospective mothers, with SDG 2.2 stating: “By 2030 end all forms of malnutrition and address the nutritional needs of adolescent girls, pregnant and lactating women” [84].

The importance of the shift in emphasis is even clearer in the new Global Strategy for Women’s, Children’s and Adolescents’ Health launched under the United Nations Secretary-General’s Every Woman Every Child initiative [86]. The Global Strategy explicitly mentions adolescents and young people as one of their key target groups, also referring to the “SDG Generation,” and alludes to the economic benefits of this approach, in particular for sub-Saharan Africa. The WHO ECHO Commission was referred to in the last section. Other initiatives that have focused on a more holistic life course approach are the International Federation of Gynecology and Obstetrics (FIGO) Recommendations on Adolescent, Preconception and Maternal Nutrition [87], the Agency for Healthcare Research and Quality [88], the Doha Declaration of the World Innovation Summit for Health [89], United Nations Educational, Scientific and Cultural Organization (UNESCO) [90], and the National Institute for Health and Care Excellence [91].
CONCLUSIONS

Over the past 50 years, the effects of global transition and socioeconomic development have resulted in an increased exposure to the obesogenic environment, an evolutionary novel environment to which human populations were not previously exposed and to which they have not adapted. Initially, this transition happened only in affluent groups in HICs but in the past decades this pattern has reversed, rapidly affecting the poor in both developed and developing countries. As a result, the worldwide prevalence of childhood obesity has increased at an alarming rate while the onset of NCDs is now occurring much earlier in life [92,93]. A major concern in this scenario is the transmission of the risk of obesity to successive generations, in particular in LMICs where both over- and undernutrition fuels the epidemic. To reverse this trend in childhood obesity, interventions must therefore start very early in life, preferably before conception, and be sustained in a variety of ways thereafter. The life course approach of targeting adolescents and young people was recently recognized in global strategies as both a necessary and a cost-effective investment. Primordial prevention of childhood obesity may offer the best value for money and has the potential to minimize exposure to early-life risk factors in the next generation.

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INTRODUCTION

The obesity epidemic has affected individuals across the life span. It is of particular concern in early life, as 20% of children are already overweight and obese before they enter school, with higher rates among low-income children, and African American and Hispanic children [1,2]. The first years of life are a period of dramatic growth and developmental change, and early-life growth patterns, particularly more rapid weight gain during infancy and early childhood, predict increased risk for obesity later in life [3,4]. Rapid weight gain in infancy has also been associated with increased risk for hypertension [5], coronary heart disease [6], and type 2 diabetes mellitus [7]. Because rapid growth trajectories in early life increase risk for obesity and related comorbidities later in the life span, prevention of rapid weight gain is an obvious target for early intervention. However, at present, there is limited evidence on how to do this [1].

In infancy, as in later life, dietary intake is a key determinant of energy balance and weight gain. Unlike adults, who are able to make their own dietary choices, infants and young children are dependent on parents or other caregivers to provide developmentally appropriate foods that support healthy growth. With respect to factors affecting weight gain, parents control the timing and duration of feedings, as well as the quality and quantity of foods offered to the child [8]. Caregivers also structure children’s opportunities for other activities that can also affect energy balance and early growth, including sleep and active play [9,10]. All aspects of caregiving that can affect growth and energy balance are potential targets for early interventions to prevent rapid weight gain and reduce obesity risk.

This chapter will address interventions for obesity prevention during the first two years of postnatal life. The first section will highlight emerging evidence for opportunities to promote normative growth in infancy by influencing infant sleep and nutrition and feeding behaviors, and by the regulation of emotion. This is followed by a discussion of some of the recently completed and ongoing randomized controlled trials that involve multicomponent behavioral interventions in the first 24 months of life.
Emerging Evidence for Modifiable Risk Factors in Early Obesity Prevention

Sleep

Shorter sleep duration has been recognized as a factor in the development of obesity. There is an inverse association between shorter sleep duration and higher weight status that has been noted among adults, infants and children [11]. In the first weeks of life, infants spend the majority of their time sleeping, and typically wake every few hours to feed. Shorter sleep duration is therefore related to a higher frequency of feeding in early infancy, which can increase energy intake and growth [12]. Sleep duration also affects several hormones responsible for appetite regulation, and individuals with curtailed sleep duration have lower levels of leptin, a satiety signal, and higher levels of ghrelin, a hunger signal [13]. Moreover, shorter sleep duration may decrease energy expenditure by producing fatigue and low activity levels [14].

Observational studies provide most of the data on the association between shorter sleep duration and weight status in childhood. For example, Locard and colleagues first reported that 5-year-olds who slept less than 11 h/day were at significant risk of overweight [15]. Since that time, studies have demonstrated that shorter sleep duration in early childhood, between the ages of 3 and 5 years, predicts overweight in later childhood [1,16]. However, less is known about the association between shorter sleep duration and overweight or weight gain in infancy. Some studies have shown that shorter sleep duration is associated with body size in the first few months of life [17], and less than 12 h of sleep per day predicts overweight and obesity in early childhood [18]. Other studies, however, have reported null findings [19]. The potential for reverse causation also complicates matters, as it is possible that larger infants take larger feedings, which lead to increased sleep duration. While this relationship requires further study, shorter sleep duration has been recognized as a modifiable risk factor for obesity.

Randomized controlled trials have shown that interventions can be effective in prolonging sleep duration in infancy [3,12]. For example, parents and caregivers instructed on techniques to soothe breast-fed infants significantly increased hours of nocturnal sleep [12]. This is important, as sleep patterns are developing within the first few months of life, and strategies that improve infant sleep duration may prevent short- and long-term risk of both sleep problems [20] and obesity [21]. However, only a few studies have examined the impact of such interventions on growth patterns and weight status in the first 2 years of life [3,12]. Early-life sleep interventions hold promise, but there is a need for additional research.

Nutrition and Feeding Behaviors

Breast-feeding promotion is a popular strategy for the prevention of childhood obesity during infancy [11], and the links between breast-feeding and childhood obesity are reviewed in Chapter 11. Breast-feeding and human milk are considered the normative standards of nutrition in the first few months of life. Indeed, the American Academy of Pediatrics advocates exclusive breast-feeding for the first 6 months after birth because of several protective effects [22]. First, breast-feeding encourages self-regulation by the infant who is able to adjust milk intake to match energy needs, which has long-term behavioral effects [23]. Second, human milk contains nutritive and nonnutritive components that best meet the requirements of infant growth [24,25]. There is also emerging evidence that breast-feeding establishes healthy gut microbiota that affect metabolism [23]. Breast-fed infants also gain weight more slowly than formula-fed infants, and this early-life growth pattern is recognized as protective against obesity [26,27]. However, randomized controlled trials that have been shown to improve breast-feeding duration and exclusivity have not examined the effects on risk for obesity [10,28]. Indeed, the only randomized controlled trial that examined breast-feeding promotion and obesity risk found no association [28]. Because of the limited number of early-life interventions with growth outcomes, and the potential for confounding factors inherent in a woman’s decision to breast-feed that may also predict weight status (e.g., socioeconomic status), clear evidence that breast-feeding reduces
the risk of childhood obesity is currently lacking [11]. That being said, there is more definitive evidence that formula feeding increases the risk of childhood obesity [29], and though this may be tempered by formula composition [30], it suggests that breast-feeding may be the better alternative for its prevention.

The timing of solid food introduction has also been proposed as an opportunity for the early prevention of childhood obesity, although the findings are inconsistent [11,31]. It is recommended that the introduction of solids does not occur prior to ages 4–6 months, at which time solids may be added to the diet, along with continued breast-feeding or formula until at least age 12 months [22]. However, introducing solids prior to the recommendation is still a common practice among parents and caregivers that increases the risk of obesity [31]. While the underlying mechanism has not been established, it has been postulated that the early introduction of solids is associated with increased energy intake, as infants may not modify milk consumption when solids are also on the table. Evidence from observational studies indicated that earlier introduction of solids was associated with rapid weight gain in the first few months of life [32,33]. Earlier introduction of solids also predicts overweight and obesity at age 10 years [34], though findings over the long term are inconsistent [35]. Only one randomized controlled trial has investigated whether the timing of solids affects growth in infancy. Mehta and colleagues found that infants assigned to early (i.e., 3 months) versus late (i.e., 6 months) introduction of solids did not differ in weight gain by age 12 months [36]. In a recent longitudinal study, Vail and colleagues provided evidence for reverse causation, showing that heavier infants tend to be introduced to solid foods at an earlier age [31]. Additional research is needed, as strategies to delay the introduction of solids have been shown to be effective and may be a safeguard against childhood obesity [3,12].

The development of flavor preferences in infancy has garnered attention as it relates to weight status in childhood [1,11]. Infants have several innate responses that affect their acceptance of new foods, including a preference for sweet and salty tastes and a tendency to reject new, unfamiliar foods, especially foods that are neither sweet nor salty tasting. These predispositions may tip the scale toward greater intake of energy-dense foods (e.g., french fries, sugar-sweetened beverages) versus nutrient-dense foods (e.g., pureed vegetables, meats) in infancy; eating behaviors that have been shown to persist through childhood and increase the risk of obesity [37]. Fortunately, eating behaviors are malleable, and the first 24 months of life are an opportune time to promote acceptance of foods typical of a healthy diet [8]. For example, Birch and colleagues found that the neophobic response to new and unfamiliar foods is modified by repeated opportunities to taste them [12,38,39]. This practice was shown to increase intake of green beans, squash, and other vegetables in infants over the period of 1 week [12]. While repeated exposure has been shown to be efficacious in promoting food acceptance, few randomized controlled trials have examined how this affects growth patterns in infancy and risk of obesity in childhood.

**Regulation of Distress, Temperament, and Emotion**

Infants “come equipped” with different temperaments, or predispositions, to behave in a particular way. Temperament is determined through a balance in reactivity (ease of arousal) and self-regulation (control of arousal). High reactivity has been shown to predict weight gain and may be a risk factor of obesity, while high self-regulation has been shown to predict a lower weight status and may be a protective factor against obesity [40,41]. It follows that an infant with high reactivity and low self-regulation, or an infant with a negative temperament, may be more susceptible to rapid weight gain. This is because a negative infant is by definition prone to react with more negative affect and more frequent expressions of distress, and parents and caregivers are more likely to use feeding as a first response to fussiness [12,42]. “Feeding to soothe” an infant with high reactivity and low self-regulation increases opportunities for intake. It has been associated with energy imbalance and subsequent obesity [42]. Indeed, Stifter and colleagues found that feeding to soothe was a common practice among mothers of infants who were higher in negativity, and these infants were heavier in the first few months of life [42].
Because feeding to soothe can occur in the absence of hunger, it is possible that through their experience with feeding to soothe, the infant may learn to eat, not only in response to hunger, but to alleviate negative emotions. Particularly for highly reactive, negative infants, if caregivers respond indiscriminately to crying, fussing, and other expressions of distress with feeding, then the infant may learn to eat to reduce emotional distress. Studies suggest that the use of feeding in response to infants’ emotions, or to manage their behaviors, can have long-term effects on eating behaviors and weight status. For example, Blissett and colleagues found that children ages 3–5 years whose mothers frequently used food to regulate emotions (e.g., cookies), ate more sweet and palatable foods than children whose mothers used this practice infrequently. This relationship was exaggerated in response to negative emotions [43]. Moreover, Boggiano and colleagues recently found that adolescents who reported eating sweet and palatable foods to reduce negative feelings had an increased risk of weight gain over 2 years [44]. Taken together, these findings suggest that parent regulation of infant emotion through the use of feeding to soothe may lead to eating behaviors over the short and long term that increase obesity risk.

While it is possible that temperamental negativity can increase the risk for overfeeding through the use of feeding to soothe, it turns out that the caregiver’s response to infant negativity is key; results of one recent study indicated that negativity was only associated with higher weight status if mothers reported using higher levels of feeding to soothe, as infants high in negativity whose mothers used lower levels of feeding to soothe had normal weight status [45]. Taken together, these findings suggest the potential efficacy of interventions that target parenting and feeding practices, particularly the use of responsive parenting.

**Examples of Multicomponent Interventions for Early Obesity Prevention**

The preceding section of this chapter highlighted potential opportunities for the prevention of childhood obesity during infancy. Sleeping, feeding, and coping with distress are core components of infant life that develop dramatically in the first few years after birth [1,11]. These behaviors have been targeted in early interventions to promote normative growth in infancy, an important determinant of obesity in childhood and beyond. Over the last few years, the first randomized controlled trials have been conducted, designed to build upon the evidence presented in the previous section of this chapter. Most have been multicomponent interventions, focusing on factors hypothesized to prevent excessive growth in the first 12–24 months. The rationale for multicomponent interventions is that the multifaceted nature of obesity requires a multifaceted approach for prevention. Though preliminary findings suggest that multicomponent behavioral interventions for parents and their infants hold promise, data are not consistent [12]. Discrepant findings may be related to differences in the intervention components included, intervention dose, barriers to implementation, lack of a theoretical framework or preliminary data to inform study design, and lack of valid and reliable measures of parent–infant behavior hypothesized to mediate the intervention effects [11]. Nevertheless, an evaluation of multicomponent behavioral interventions to date shows the progress that is being made toward obesity prevention in early life and guides future studies for parents and their infants.

Paul and colleagues conducted a multicomponent behavioral intervention to promote healthy infant growth in the first 12 months through improved sleeping and feeding [12]. In the Sleeping and Intake Methods Taught to Infants and Mothers Early in Life (SLIMTIME) study, mother–infant dyads were randomized to one of four treatments delivered at two nurse home visits: “Soothe/Sleep,” “Introduction to Solids,” “Soothe/Sleep” plus “Introduction to Solids,” and control. The “Soothe/Sleep” intervention taught parents to discriminate between sources of infant distress. They learned alternative soothing techniques to reduce the use of feeding for nonhunger-related fussiness and increase infant sleep duration. The “Introduction to Solids” intervention taught parents to delay the introduction of solids and how to promote acceptance of new solid foods through repeated exposure. The study found that infants who received both interventions, designed to affect
feeding, sleeping, and soothing, had lower weight-for-length percentiles, a measure used to monitor normal infant growth, than did those receiving neither or only one intervention component. In addition, results from a second randomized trial by the same researchers who also used nurse home visits to deliver interventions has shown positive effects on infant growth, with infants in the parenting intervention growing less rapidly from birth to 6 months relative to control [46]. Taken together, these findings suggest that multicomponent behavioral interventions may have potential for long-term obesity prevention [12].

Wen and colleagues also conducted a home-based intervention to promote normal growth in the first 24 months through improved feeding [47]. In the Healthy Beginnings Trial, mother–infant dyads were randomized to intervention or control groups. The intervention group received eight nurse home visits to promote breast-feeding, delay introduction of solids, and increase food acceptance. This environment allowed nurses to first monitor parent–infant feeding interactions and then deliver one-on-one consultations. The study found that infants in the intervention group had a lower body mass index (BMI) versus infants in the control group at 2 years. However, a follow-up study revealed that there were no differences between groups 3 years later [47]. This suggests that multicomponent behavioral interventions can show efficacy in promoting healthy infant growth, particularly in the home environment. However, without continued intervention, the effects may not persist into early childhood [47].

While the multicomponent behavioral interventions just described noted effects on parental knowledge, practices, infant behaviors, and infant growth or weight status, several other trials have reported intervention effects on maternal and infant behavior but null findings with respect to weight status and growth. Taveras and colleagues designed a study focused on promoting parenting practices hypothesized to reduce obesity risk, with infant growth as a secondary outcome [3]. In the First Steps for Mommy and Me study, mother–infant dyads who were assigned to an intervention with motivational interviewing during well-child clinic visits, counseling with a health educator, and monthly parenting workshops reported later introduction of solids and larger increases in sleep duration compared with the control group. However, there were no differences between intervention and control infants in weight-for-length z-scores at 6 months [3]. In another intervention trial, Campbell and colleagues conducted a study to enhance parenting practices that focused on infant feeding and activity and included infant growth as a secondary outcome [48]. In the Infant Feeding Activity and Nutrition Trial (InFANT), mother–infant dyads who participated in dietitian-delivered education sessions on feeding style, timing of solid food introduction, and management of food rejection reported modest improvements in dietary behaviors of infants, but no differences in BMI z-scores compared with the control group at 20 months [48].

A recent study by Russell and colleagues was aimed at promoting healthy growth in the first year through improved feeding [49]. In the Greenlight study, mother–infant dyads were randomized to receive low-literacy materials covering six core topics at well-child clinic visits: satiety cues, sweetened beverages, delayed introduction of solids, portion sizes, nonsedentary activity, and breast-feeding. Preliminary findings suggest that while the intervention was effective in promoting parent acceptance of feeding behaviors that might prevent obesity, it did not result in significant differences between treatment and control in infant growth or weight status [49].

Finally, Daniels and colleagues recently completed an intervention using parent education and peer support to optimize feeding practices and food preferences for obesity prevention in infancy [50]. In the NOURISH trial, mother–infant dyads were randomized to two intervention modules timed around the introduction of solids and the emergence of autonomy and independence. In these modules, a dietitian and psychologist addressed topics including neophobia, portion control, timing of snacks, and hunger/satiety cues, and parents were instructed to help develop self-regulation in infants. The study found that infants in the intervention group had lower BMI z-scores and less rapid weight gain compared with infants in the control group from birth to 14 months. However, there were no differences between groups at age 2 years or at age 5 years [50]. There was, however, a nonsignificant trend toward lower BMI z-scores for infants in the intervention group [50].
Because multicomponent behavioral interventions to date have reported mixed findings, additional research is needed to identify efficacious interventions. A publication summarizing the proceedings of a National Institutes of Health Workshop on the Prevention of Obesity in Infancy [11] acknowledged the opportunities for intervention during the period from birth to 24 months, but concluded that there is little evidence for how to prevent obesity during this early period. A pressing research priority is to improve measures of parent and infant behavior, infant growth, weight gain, and body composition. Such measures are essential to providing evidence that will aid in determining which interventions impact early growth and thereby reduce obesity risk. Nonetheless, the committee determined that future interventions that address these challenges and develop parenting behaviors to promote establishing routines, healthy sleep patterns, and appropriate feeding practices have potential for obesity prevention [11].

CONCLUSION

Infancy is a critical period of development and a time of both opportunity and vulnerability for risk of obesity. Infants experience rapid changes in weight and growth outcomes in the first few months of life that may put them on a fast track toward overweight and obesity in the first few years. The link between rapid weight gain in infancy and later obesity risk is well established, but little is known about the mechanisms underlying this association, and this limits our ability to develop efficacious interventions. A lack of validated measures of potential mediators and moderators of the relation between early environmental exposures, particularly parental and infant behaviors, and weight outcomes in infancy is also a barrier to progress. These rapid changes in growth are paralleled by rapid changes in behavior, which may ultimately affect weight status. Multicomponent behavioral interventions in the first 24 months show promise in reducing early obesity risk. However, a great deal of additional evidence is needed to develop effective, resource-efficient interventions that are scalable and appropriate for high-risk, underserved populations. Because infant behaviors surrounding feeding, sleeping, and coping with distress are both malleable and putative contributors to early rapid weight gain, interventions that teach parenting and feeding practices may prevent obesity while also promoting positive behavioral outcomes, including responsive parenting, increased infant sleep duration, self-regulation, and infant dietary patterns, more consistent with current guidance.

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INTRODUCTION

Although a recent nationally representative study found a decline in obesity in 2- to 5-year-old children, this was not true for low-income and minority children [1]. In fact, 40% of low-income children enrolled in federally funded programs are already overweight or obese by age 5 [2]. This failure to effectively prevent the onset of obesity among at-risk children will only intensify and perpetuate health disparities, because once established, obesity is hard to reverse [3], and overweight youth have a 70% chance of becoming obese adults [4]. The stability of obesity across the life span, and the physical, psychosocial, and financial costs related to obesity for individuals and the larger society [5], raise the impetus to correct weight trajectories among at-risk children before they become overweight or obese. Unfortunately, extant childhood obesity interventions and prevention efforts have had limited success, especially among underserved children whose families are low income and of color.

In this chapter, we critically appraise existing family- or home-based obesity interventions and prevention programs, and highlight the key components of these efforts that we believe are essential in achieving positive outcomes in children; particularly children most at risk for obesity. Further, we present an innovative, sustainable, scalable, and potentially cost-effective model of delivery for obesity prevention initiated in infancy that we call COPE (Childhood Obesity Prevention @ homE/
Contrarrestar Obesidad: Programa para niños En casa). This collaboration emerged in response to the unmet needs and resources available to address the increasing prevalence of obesity among children enrolled in federally funded programs.

**OBESITY PREVENTION PROGRAMS SHOULD TARGET THE FAMILY AND THE HOME ENVIRONMENT**

Although the clustering of overweight and obesity in families is partially explained by shared genetics, familial behaviors and shared environments largely determine the expression and maintenance of obesogenic behaviors [6,7]. Thus, targeting the family and home environment is likely to impact the expression of obesity among families with and without genetic risk [8]. As a primary source of socialization for children, families, and in particular parents, have the opportunity to make certain foods and activities available, model and reinforce healthier food options and physical activity habits, and implement certain parenting practices. Because eating and physical activity habits established in these early years track into adulthood, early family influences have a lasting impact on children’s health [9,10].

Much research has been conducted on the advantages of modifying the family environment to “treat” obesity [11], as reviewed for example in Chapters 15 and 29. Family-based obesity interventions concurrently target parents (typically mothers) and children and focus on the adoption of a lifelong, healthy lifestyle to improve nutrition, physical activity, and psychosocial health [11–13]. The curriculum combines lifestyle and cognitive-behavioral techniques to improve nutrition, physical activity, and overall psychosocial health. Parents are taught multiple skills such as how to structure the family environment to support healthy behaviors, parenting practices conducive to children’s healthy changes, how to model healthy behaviors for their children, and how to problem solve in the face of challenges. Short and long-term studies have shown that targeting parents as active participants improves child weight trajectories over a 5- and 10-year follow-up, as well as the youth’s health-related risk factors, energy intake, and psychosocial functioning [11]. Although the family-centered model has been shown to be efficacious for weight loss in parents and children [14,15], the ability of this model to prevent the development of childhood obesity (as opposed to treating children who are already overweight or obese) is not clear. In fact, including parents and family members is less common for programs focused on preventing the onset of obesity (as opposed to “treating” obesity). Only 40% of childhood obesity prevention programs include a family component and only 5% explicitly target behavioral change among multiple family members [16].

In theory, the application of family-based approaches for obesity prevention appears to be promising; however, the question of treatment (weight loss) versus prevention (averting excessive weight gain) brings the issue of intervention timing. The vast majority of family-based obesity interventions have focused on school-age children when youth are already overweight or obese. This is unfortunate as there is now clear evidence that rapid weight gain as early as in the first 4–6 months of life is already associated with greater odds of child overweight or obesity later in childhood and adolescence [17–19].

**OBESITY PREVENTION EFFORTS SHOULD BE INITIATED IN INFANCY AND EARLY CHILDHOOD**

As reviewed in preceding chapters, early childhood is clearly a pivotal time for the formation of lifelong eating and physical activity habits [e.g., 9,10,20–24] and for the intergenerational transmission of obesity, yet controlled trials focusing on weight management or obesity prevention for children under the age of 5 years of age are scarce [25]. A small number of obesity interventions and prevention programs targeting infancy and early childhood have had some level of success in decreasing or preventing obesity, as reviewed in Chapter 34 [26–30]. However, the impact and sustainability
of these programs have been limited by their short duration (<6 months) and low dosage. The short duration of these interventions is problematic for the maintenance of healthy changes. Even when maintenance is directly addressed or planned as part of the intervention, the maintenance phase rarely (if ever) exceeds a few weekly 1 h sessions, which is doubtfully sufficient to ensure mastery of learned skills into lifelong healthy habits. Furthermore, the duration of existing efforts is not sufficient to cover the key developmental periods and nutritional transitions during and beyond early infancy, which are critical for obesity development [31].

EMBEDDING OBESITY PREVENTION EFFORTS INTO EXISTING HOME-BASED SERVICE SYSTEMS TO PROMOTE SUSTAINABILITY, SCALABILITY, AND COST EFFECTIVENESS

Few childhood obesity interventions and prevention efforts have been integrated into existing service delivery systems, creating significant barriers in their reach and impact. Existing programs typically require the parent and the child to attend intervention sessions outside their general daily routines (e.g., evening educational classes in outpatient clinics). As a result, less than 50% of families involved in obesity interventions complete follow-up visits, and attrition is especially problematic for low-income families and for those who live in remote areas [32–34]. The high rates of attrition, in both the initial intervention implementation and during the maintenance phase, seriously limit the impact of these efforts in achieving clinically significant long-term outcomes, particularly among at-risk children and their families [32,33]. Not only does the outpatient model impose a considerable burden on families, which likely interferes with treatment adherence, but it can also be argued that this modality is not optimal for the generalization of behavior change to the family’s natural environment.

A related limitation of current obesity interventions and prevention delivery models in specialized clinics or other medical settings pertains to the limited scope of these existing obesity efforts. Over the last decades, there has been a burgeoning of new programs tackling obesity management or the development of obesity risks. Unfortunately, the narrow focus on obesity makes it difficult to simultaneously address barriers such as a lack of access to resources and culturally competent services, poverty, unemployment, housing instability, food insecurity, family conflict and violence, and neighborhood characteristics—all of which profoundly affect the ability of at-risk families to engage in these programs and adhere to lifestyle changes. A more holistic approach to obesity prevention, which simultaneously addresses these barriers, could be adopted by embedding efforts into existing, comprehensive service delivery systems that target families. This is likely to be critical to developing effective and sustainable family-centered programs in real-world settings.

HOME VISITATION PROGRAMS: AN UNTAPPED OPPORTUNITY FOR PREVENTING CHILDHOOD OBESITY

Ideally, obesity initiatives should be (1) focused on the child’s ecological niche (family and home environment) to shape children’s health trajectories and promote generalizability and sustainability; (2) initiated in infancy and early childhood, when key eating and physical activity habits develop; and (3) embedded in existing service systems for an extended period of time to promote the consolidation of healthy habits for life among diverse families. Developing a nationwide obesity prevention program that provides in-home services to at-risk infants and their families for a sustained period of time, and which is effectively tailored for diverse families, would be cost prohibitive unless these services are integrated into an effective and sustainable service-delivery system.

Fortunately, home visitation programs (HVPs) already provide comprehensive home-based support, education, assessment, community linkage, referral, and advocacy to more than 500,000 low-income, underserved, at-risk children and their families in the United States annually. HVPs have
been in place for more than 40 years and currently have $1.5 billion annual investment from the Affordable Care Act [35], which speaks to the sustainability of the services provided. The free and voluntary weekly home visits begin during pregnancy, or shortly after birth, and continue until the child reaches 2–5 years of age. HVP sites/chapters are housed and overseen by accredited community health organizations or agencies. Locally hired home visitors provide services tailored for the cultural and linguistic needs of their constituents. HVPs are embedded in a comprehensive system of child and maternal health services designed to promote optimal child development and prevent adverse outcomes, including child abuse and neglect, academic underachievement, psychological maladjustment, and antisocial behavior [36–38]. Randomized controlled trials (RCTs) show that high-quality HVPs effectively improve children’s physical and psychosocial health, such as birth outcomes, breast-feeding, immunization rates, and overall cognitive and social development [36–38]. Despite the success of HVPs in improving the outcomes of at-risk children, there has been no explicit and systematic effort to target childhood obesity as part of these services. This is surprising as the HVP structure, with its strong partnership with WIC (women, infants, and children) programs, provides an ideal model for scalable and sustainable obesity prevention among underserved children:

1. The provision of in-home services removes barriers to accessing the program (e.g., transportation, childcare), promotes the generalization of skills to the home environment, and enables ethnically and racially diverse families to access culturally competent health services.
2. HVPs have existing partnerships with WIC programs nationwide.
3. The programs already address many barriers to healthy lifestyles such as unemployment, family conflict and violence, housing instability, and neighborhood characteristics.
4. The extensive time frame for service delivery (3–5 years) makes it possible for home visitors to transfer and reinforce health knowledge, skills and new behaviors, and to help families develop social and community networks promoting sustainability of health outcomes.
5. The widespread presence of HVPs across the United States, and established infrastructures in many urban and rural areas, are critical for the scalability of services across the United States.

COPE: CHILDHOOD OBESITY PREVENTION @ HOME/CONTRARRESTAR OBESIDAD: PROGRAMA PARA NIÑOS EN CASA

COPE is a collaboration, which emerged in response to both the limitations of existing childhood obesity prevention initiatives outlined in the last sections and the unmet needs and resources voiced by HVPs to address the increasing prevalence of obesity among children in their programs. Consistent with a capacity-building approach, COPE aims to extend the mission and capabilities of HVPs in delivering established nutrition guidelines and physical activity recommendations using an engaging, culturally sensitive, and community-forming model of delivery. It is important to note that COPE does not target weight loss; rather it focuses on the promotion of healthy behaviors in all HVP children and their families, regardless of weight status, and ultimately the prevention of the development of obesity in early childhood.

COPE CURRICULUM CONTENT

Nutrition
The curriculum promotes foods that support children’s healthy development:

1. Increase/promote intake of vegetables and fruits (≥5 servings/day of fruits and vegetables). Parents/mothers are given age-appropriate recipes and strategies to increase children’s fruit and vegetable intake.
2. Limiting intake of high-fat and high-sugar foods. Mothers learn to modify their families’ favorite foods and recipes to decrease fat and sugar content.

3. Eliminate sugar-sweetened beverage intake, including information and activities on sugar content of popular sweetened beverages, long-term effects of high sugar consumption, importance of drinking water, and impact of advertising [39].

4. Appropriate portion sizes for infants and preschoolers. Parents are taught to offer small portions, to follow a meal and snack schedule, and to help their children understand when they are satiated.

Physical Activity

Although there is no unequivocally accepted guidelines for the number of minutes young children (2–5 years of age) should be active each day [40], the US Department of Health and Human Services (DHHS) has summarized consensus recommendations among the National Association for Sport and Physical Education, the American College of Sports Medicine, and the National Institutes of Health that include (1) accumulate at least 60 min of structured physical activity each day (>3 years old); (2) engage in at least 60 min, and up to several hours, of unstructured physical activity each day; and (3) avoid being sedentary for more than 60 min at a time, except when sleeping. The American Academy of Pediatrics Expert Committee report for clinicians further suggests limiting screen time to a maximum of 2 h per day for children 2 years of age and older and removing televisions and other screens from children’s primary sleeping area [12]. These guidelines are consistent with the US Department of Agriculture (USDA) recommendations that “Children ages 2–5 years should play actively several times each day […] and that physical activities for young children should be developmentally appropriate, fun, and offer variety” [40].

The COPE intervention manual is premised on these guidelines and teaches parents to make activity and play a daily habit for their children and entire family by exploiting lifestyle activities (e.g., taking the stairs, walking to the shop). Home visitors are trained to help parents design activities around their local environment, schedule, and preferences, and to optimize their use of safe indoor and outdoor spaces that are suitable for structured and unstructured activities with children. Parents are provided with information about resources and free group activities conducive to physical activity (e.g., parks, walking clubs, outings) and classes they can take with their children and with other HVP families. The curriculum emphasizes the importance of parents coengaging in activities with their children to set a good example through modeling and to provide opportunities for their children to be physically active.

Developmental Considerations: Neophobia and Food-Related Tantrums

Young children are highly neophobic and resist trying new foods, which can be a barrier to their acceptance of healthy foods such as fruits and vegetables. Research has shown that parents typically present a rejected food 3–5 times before deciding that their child does not like the food, although 10–15 exposures is actually necessary to overcome food rejection by young children [41]. Similar to the approach used in the LAUNCH intervention [42], COPE includes behavioral strategies and activities to help parents address neophobia and increase children’s acceptance of novel foods: that is, repeated presentations and multisensory exposures (i.e., smell, touch, taste) of foods [43,44], gradual texture shaping, parents/caregivers modeling, and involvement of children in the selection and the preparation of new foods. Tantrums around eating can also be a barrier for healthy food consumption, and persistent tantrums around meals and food at age 3 has been found to predict obesity at age 5 [45]. COPE further targets strategies for mealtime behaviors [46] including redirection, extinction/planned ignoring, positive reinforcement of appropriate behaviors, scheduling of meals and snacks, and avoiding using food as reward or to soothe.

Format of the Education Delivered to Families

Through our formative work and pilot research it became clear that didactic and experiential approaches were needed to effectively reach, engage, and mobilize families.
Didactic Individualized Education
The didactic strategy focuses on in-home individualized coaching to help mothers implement changes in their natural environment. A strong emphasis is placed on gradual goal setting in which mothers set objectives for their children’s weekly activity and diet (e.g., decreasing by “x” the number of sugar-sweetened beverages; trying “x” new vegetables this week) and on parent modeling healthy behaviors (i.e., parent coengaging in healthy behaviors with their children). Parents are also taught behavior management and cognitive-behavioral strategies to change their home environment. For example, mothers receive individual shaping to gradually eliminate high-energy dense foods from the home environment and prevent mindless eating. Parents also work on modifying their home to make it more conducive to making choices that support exercising, such as removing computers and televisions from sleeping areas [12].

Social and Experiential Activities
These activities were developed based on families’ desire to engage in experiential/hands-on activities and strategies (e.g., concrete demonstrations, activities, and practices) to develop practical skills that generalize to their everyday life. They also requested social activities centered on health behaviors. The social and experiential activities that we created (Table 35.1) are similar to those delivered as part of the National Institute of Food and Agriculture’s Expanded Food and Nutrition Education Program [47]. These activities aim to promote the development of supportive, healthy social networks and communities to reinforce healthy changes and assist long-term sustainability.

CONCLUSION
In fiscal year 2009–2010, 46 states and the District of Columbia made $1.5 billion available for early childhood HVPs, with most states investing in at least two programs [48]. Investment in these services remains strong, with the Affordable Care Act allocating $1.5 billion for states to invest in these programs [35]. Given that 40% of children enrolled in federally funded programs are overweight or obese by the age of 5, it is expected that the Health Resources and Services Administration, Maternal, Infant and Early Childhood Home Visiting (HRSA MIECHV) program will mandate HVPs to address childhood obesity as a part of their services. COPE provides an innovative,

<table>
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<td>Communal cooking</td>
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scalable, sustainable, and potentially cost-effective approach to existing gaps. Once home visitors are trained to implement COPE, the material is delivered as part of the weekly home visits. This delivery model is designed to reach families who have historically faced disparities in services in order to improve the children’s health and reduce the financial burdens for society as a whole.

REFERENCES

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INTRODUCTION

Over the past 20 years, the socioecological model (SEM) [1] has emerged as the dominant and guiding framework for the development, implementation, and evaluation of community-based health promotion efforts. The SEM identifies the independent and interactive effects of factors at multiple levels that influence individual and population health. These factors range from individual-level factors (e.g., knowledge and behavior), interpersonal factors (e.g., family, peers), organizational factors (e.g., schools and work sites), environmental factors (e.g., built environment and social environment), and policy factors (e.g., health policy) [2]. The SEM has also been adapted to study several chronic diseases (e.g., cancer, type 2 diabetes, heart disease, obesity) [3–5], several health behaviors (e.g., cancer screening, physical activity, and nutrition) [6–9], and for use in specific population subgroups such as Latinos [10]. The wide use of the SEM has helped to identify opportunities to revert the current obesogenic environments and to identify areas where greater efforts are needed to create healthier communities [5].

As reviewed in several of the preceding chapters of this book, childhood obesity is the result of a constellation of factors that influence daily choices and opportunities for children to eat healthy and engage in regular physical activity [11,12]. Characteristics of the community environment such as the presence and proximity of parks, street connectivity, presence and proximity to grocery stores, neighborhood safety, and access to effective health promotion programs and resources can also influence children’s energy balance [12], as reviewed in Chapter 1. The home environment has a particularly strong influence on children’s health behaviors given the important role of the parent in modeling and supporting children’s health behaviors (e.g., parent monitoring of children’s eating behaviors and logistic support for physical activity) [13,14], as reviewed, for example, in Chapter 15. The aim of this chapter is to review notable school- and community-based childhood obesity prevention studies and some of the key factors that led to their success. Two specific studies are described in more detail in order to draw attention to the contextual and qualitative aspects of these efforts that may not otherwise be included in published scientific articles. This contextual information may provide greater insights for practitioners and researchers who work within schools and other community organizations to combat childhood obesity.
SCHOOL-BASED INTERVENTIONS

Schools play an important role in children’s lives and well-being. Schools provide children, not only with an important learning environment, but also with direct and impactful opportunities to establish healthy eating and physical activity habits. Not surprisingly, schools have been the predominant setting for implementing behavioral, environmental, and policy interventions aimed at preventing and reducing childhood obesity [15,16,17,18]. There are several examples of effective short-term and long-term school-based interventions. Specifically, school-based nutrition and physical activity curricula that are incorporated into existing curricula show significant effects on child obesity. The Planet Health program, for example, was a school-based nutrition and physical activity curriculum that showed significant reductions in the prevalence of obesity among girls and reductions in television viewing time compared with children in control schools [19]. Another school-based curriculum implemented in San Jose, California, resulted in significant reductions in children’s body mass index (BMI) and television viewing time [20]. Children who attend schools that participate in a coordinated program that incorporates school-based healthy eating recommendations demonstrate lower rates of obesity compared with children who attend schools without nutrition programs [21]. Beyond obesity outcomes, several school-based studies also demonstrate important improvements in children’s eating and physical activity behaviors. A large systematic, multisite trial (CATCH) resulted in significant increases in children’s physical activity and reductions in fat intake [22], and several of these outcomes were maintained over 3 years [23]. The TAAG school-based study also demonstrated significant improvements in girls’ physical activity [24]. Despite these successes, several review studies show mixed or inconclusive findings stemming from school-based efforts [25,26]. It appears that the success of these efforts are dependent on the level of “reach,” “penetration,” and “adoption” of such programs within the school system; in other words, the level of institutionalization. Institutionalization of school-based programs and policies requires the full buy in and participation from parents and school personnel (e.g., administrators, teachers, and staff). Programs and strategies must also be tailored to the contextual factors (e.g., language, cultural norms) relevant to the target population and community setting [27]. Programs that tailor messages and strategies to the gender and age of children are more successful at changing children’s behaviors given that social norms and social influences differ between boys and girls, and these social influences change as children age [26,28]. Thus, the success of each school-based study is largely dependent on the specific contextual factors where the intervention took place. To this end, researchers and practitioners are urged to share and publish more contextual information stemming from community interventions in order to better understand the factors that contribute to their success. In the following sections, we describe the implementation and evaluation of two multilevel school- and community-based childhood obesity prevention interventions among Latino families and describe the lessons learned and the important contextual factors that influenced successful outcomes.

The Aventuras Para Niños (APN) study was a unique and ambitious project designed to evaluate the independent and interactive effects of interventions occurring in the micro- and macroenvironments that were aimed at preventing and controlling childhood obesity among Latino children [14,29]. The intervention targeted the microenvironment, operationalized as the composite of the home environment, parental, and family influence. The macroenvironment intervention targeted physical, environmental, and policy changes within elementary schools, local restaurants, parks, and grocery stores in the communities where children (K-2nd grade) resided (South Bay, San Diego, CA). A total of 808 families and 13 schools were enrolled into the study. One of the first challenges to conducting large-scale community interventions is to successfully enroll the target population. APN recruitment efforts first focused on obtaining the buy in, approval, and participation of school principals, administrators, and other key stakeholders. This was accomplished through a series of meetings with school administrators and by engaging in discussions that emphasized the positive role that schools play in their students’ lives and the benefits of engaging in a mutually beneficial collaboration with the project team. Thus, a critical step for a successful community project...
is to establish a meaningful and mutually beneficial partnership between community organizations and the research team. Another important challenge in community-based health promotion research is to establish and maintain the trust between the practitioner/researcher and the community residents. Toward this goal, APN identified and hired eight community-health workers (also known as lay health advisors or promotoras) to work with the project team and serve as the communication bridge between the research team and the community residents. The work of promotoras has been identified as a key contributor to the success of many community-based studies, especially among diverse populations [30]. Promotoras can serve different roles depending on the goals of the project and skills/experience of the promotora. In APN, promotoras were paid project members who were also members of the target community. The promotoras were mothers of children who attended the intervention schools, lived in the target community, and were also demographically similar to the target population. The promotoras are able to offer unique insights about how to best implement meaningful and culturally appropriate changes in the target community given that they have firsthand knowledge of the cultural factors that can facilitate or impede change. Promotoras also have a unique understanding of the formal and informal social networks that can be leveraged to achieve the desired outcomes. This approach is particularly important when targeting communities that have historically experienced adversity (e.g., discrimination) that has led to systemic mistrust of state institutions and organizations. The promotoras in APN played an important role in both establishing trust and engaging community residents and leaders in project activities.

APN implemented several school-level strategies with mixed results. The most successful school-based strategies of APN were the “Start with Salad” cafeteria intervention and the “Peaceful Playground” intervention [31]. Start with Salad was a cafeteria intervention designed to reinforce children for eating a salad item from their plate prior to eating any other item. Adult volunteers (usually cafeteria staff or promotoras) monitored children's behaviors during lunchtime to ensure their safety and to help with the flow of students through the lunch line. These adult volunteers were trained by APN staff to monitor, identify, and reward children who consumed vegetables prior to any other item on their plate. Rewards were given to children in the form of stickers, which were placed on the child’s shirt/blouse, and verbal praise was given from the adult. Start with Salad was successful because it was easy to implement in all schools and was well received by the cafeteria staff and children. Peaceful Playgrounds was an effective school environmental intervention designed to encourage children to move more during recess time [32]. After several planning meetings with school administrators and parents, APN received approval to paint all intervention school playgrounds using the Peaceful Playgrounds stencils and artwork. Adult volunteers painted the surface of these playgrounds according to the Peaceful Playgrounds designs. Children showed an immediate positive reaction toward these new surfaces and began to play in and around these surfaces. These two school-based interventions highlight the positive and successful social and physical environmental changes that can occur quickly within schools. However, not all school intervention activities were successful. For example, the “Take 10!” classroom intervention did not appear to be successful because it detracted from academic activities and it was difficult for teachers to manage physical activities in small classroom spaces with 30 or more children per class [33]. Teachers prioritized classroom control over activities during instructional time, and only one teacher in a total of six schools maintained the effort for more than a week. Another strategy that was not successful was the “Walking School Bus,” which was designed to increase children's active commuting to school [34]. Mothers were asked to help escort their own and neighbors’ children to school; however, they were intimidated by the responsibility of keeping multiple children safe on busy streets and therefore none volunteered. These challenges highlight the need to test and refine multiple strategies and to allow for community residents to self-select the strategies that work best for them.

In line with the SEM, APN also targeted improvements in local parks in order to encourage greater use of those parks and increase physical activity opportunities for children. APN also implemented environmental prompts and incentive strategies within elementary schools, local restaurants,
and grocery stores to encourage healthy eating and purchasing of healthier options. APN project staff worked with the community *promotoras* on each of these efforts. One major success came directly from the work of the *promotoras*. Over the course of the 3-year study, *promotoras* received regular training in advocacy efforts from APN staff. The *promotoras* identified that local parks needed major renovations in order to make them safer and more appealing for community residents. APN worked with the *promotoras* to formulate an action plan that included obtaining signatures of support from community residents and advocating for these park improvements at city council meetings. The *promotoras* took photos of the poor conditions of the parks and presented these photos during city council meetings and they voiced their concerns over the conditions of parks. These efforts led to the city council's approval of almost half a million dollars to be used to renovate and upgrade one of the largest parks in the community. This success highlights the tremendous potential that is harnessed when working directly with community residents to achieve long-term environmental changes. More importantly, this underscores the importance of supporting and empowering community residents to take the lead in advocating for changes that are meaningful to their families and their own community. The restaurant intervention consisted of targeting locally owned restaurants and promoting changes in their children’s menu so that menu options were healthier. The *promotoras* identified several local restaurants and met with the restaurant owners. Over half of the 112 restaurants that were approached agreed to create and/or modify a healthy menu for children. In order to reduce barriers toward implementation, the *promotoras* worked with the restaurant owners to identify simple modifications to their existing menus, and the APN project provided restaurant owners with newly printed children’s menus that included healthier options. These new menus also displayed the APN project logo to highlight the project’s endorsement of the healthier menu options. In addition, these restaurants were featured in the school newsletters, which promoted the restaurant and their new healthier menus. The grocery store intervention consisted in the development and implementation of a frequent produce buyer program. The program was designed to increase the purchasing of fruits and vegetables through a frequent-buyer card in which the shopper earned a free pound of produce after nine separate purchases of produce. Few grocery stores agreed to participate in this program and as a result very few (<4%) families used the frequent-buyer cards. These examples, of varying success, provide insights into the complexities and the opportunities that arise when working in partnership with community organizations. One major challenge to school-based efforts has been the limited carryover of physical activity and healthy dietary behaviors beyond the school grounds and school time. This necessitates expanding efforts to include other community settings where children can be physically active and eat healthy (e.g., parks and recreation centers).

**COMMUNITY-BASED INTERVENTIONS**

Many modern urban cities have designated community spaces (e.g., parks) where children and adults can participate in leisure-time physical activity. Children who live in close proximity to parks, walking trails, and recreational facilities also use those facilities more often, engage in more physical activity, and have lower obesity rates [35]. Unfortunately, the distribution and quality of green spaces are not equally distributed across communities. Both the density and quality of parks is much lower within minority and low-income communities compared with more affluent communities [36]. Thus, the equitable distribution of parks and recreational facilities remains an important goal to achieve. Barriers to accessing parks and recreation centers and participating in physical activity within these spaces include lack of awareness that these facilities exist and of the programs they offer, living far from those facilities, having safety concerns, and lack of free age- and culturally appropriate programs [36]. To overcome some of these challenges, many cities have improved and expanded signage in order to inform residents of the location and the programs offered in local community centers [37]. Cities such as Phoenix, AZ have redesigned bicycle and walking paths, implemented the GRID Bike Share Program, and improved street safety features so that residents can more easily walk and/or bike to various locations. Other cities have reduced fencing around
Community and School-Based Interventions for Childhood Obesity

parks so that parks are more inviting and accessible, and have worked with local parent groups to increase adult supervision in parks in order to address safety concerns. Improvements in park quality and increasing the number of parks in a neighborhood also increase the value of the homes in those communities [38]. It is therefore mutually beneficial for private organizations, such as real estate agencies, to work with city parks and recreation departments to improve parks and recreational facilities. Shared use agreements between schools and local parks also provide expanded opportunities for children to engage in physical activity after school. These examples highlight the need to further expand collaborations between parks and recreation departments and other public/private organizations in order to improve access to, and use of, community spaces that promote physical activity for all children. Recreation centers also play an important role in children’s dietary behaviors. Recreation centers can influence access to healthier food options through items sold in vending machines and via the foods sold in sponsored events. In addition, recreation centers often provide children with meals as part of summer and after-school programs. This represents an important opportunity to influence the dietary quality of the foods that children are provided as part of these programs. Parks and recreation departments can work with local food retailers and distributors, local farms, and farmers market organizations to increase access to healthy and affordable foods within and around community centers. Despite the potential of recreation centers to impact the health of children, there are currently very few programs or initiatives that specifically target recreation centers for the implementation and evaluation of health promotion programs to increase children’s physical activity [39,40]. Next, we will describe the implementation and evaluation of a large citywide childhood obesity prevention intervention delivered in recreation centers.

The MOVE/me Muevo project was developed using a multilevel approach to target children’s physical activity, dietary behaviors, and child BMI [41]. The study enrolled 30 recreation centers in San Diego, CA and 541 families who lived within 2 miles of one of the recreation centers identified. Fifteen recreation centers, and the corresponding families who lived near the recreation centers, were randomly assigned to receive the intervention and the other fifteen served as a comparison group. Project team members met with center directors and administrators to identify recreation-level outcomes and develop an action plan to achieve those outcomes. Recreation center administrators identified that increasing the use of facilities and programs were the top priorities. To achieve these outcomes, the study team designated one team member to work directly with each center director to develop specific strategies that would improve the center’s visibility and attendance by community residents. These strategies included improving signage placement and information about programs within and immediately around the community centers, improving customer service via staff trainings, and identifying ways to expand program offerings to children and families. In addition, center directors were encouraged to identify policies that would increase healthier food options within the recreation centers and in sponsored events. For example, vending machine contracts were evaluated to identify changes that would improve the proportion of healthy snacks and beverage offerings. Two health coaches also worked directly with families in order to promote greater use and participation in programs offered in the recreation centers. Over the course of the 2-year intervention, several family workshops were held at the community centers in order to increase families’ exposure to the recreation centers and to implement interactive education activities related to healthy eating and physical activity. Similar to the APN study described earlier, important and sustainable macrolevel outcomes were achieved over the 2-year study. The existing city’s vending machine contract was evaluated and changes were made to the contract to explicitly require that at least 50% of the items in all vending machines meet healthy standards for snacks and drinks. Also, center directors enacted new policies that required that healthy options be offered during special events such as during staff meetings. Center informational brochures were also modified to include healthy-living tips related to physical activity and healthy eating. Lastly, the Parks and Recreation Department decided to offer yearly trainings for their staff who wanted to obtain specialized certifications (e.g., group fitness instructor). Similar to the APN study, these findings again highlight the importance of working with administrators and empowering them to advocate for systemic
SPECIAL CONSIDERATIONS AND RECOMMENDATIONS

The current trends in childhood obesity have resulted in greater efforts to understand the environmental (proximal and distal) and social factors that support an obesogenic environment. Several school-based programs and strategies have shown promise to reduce or taper childhood obesity [19,20]. However, there are equally several studies that have not been able to do so [25,26,29]. It is clear that interorganizational collaborations and coalitions provide the best opportunities to leverage resources and expertise across multiple community settings and that schools cannot undertake the challenges of combating childhood obesity alone [42]. The list of potential collaborators includes the YMCA, Boys & Girls Clubs, recreation centers, faith-based organizations, community clinics, and private businesses. For example, the Athletes for Life (AFL) project located in Phoenix, AZ, is a sustainable collaboration between Arizona State University and the City of Phoenix Parks and Recreation Department [43]. Through this collaboration, community residents have access to a free, culturally appropriate, and efficacious fitness and nutrition education program. Data support that recreation centers and other recreational facilities can positively influence children’s behaviors [41], yet there are still few studies to allow for the development of specific evidence-based recommendations. Important sources of information that are often overlooked or underreported in published studies are the contextual factors and macrolevel changes that can take place during community-based interventions (e.g., environmental and policy changes). These effects may be overlooked or underreported because they may not result in immediate or observable changes in child BMI. For example, the APN study described earlier did not demonstrate significant intervention effects on child BMI despite an intensive family- and school-based approach [29]. However, important improvements were made to a local park due to the advocacy efforts of promotoras. It is conceivable that those park improvements would stimulate greater park use and thus more physical activity among community residents living near the park. Similarly, the MOVE/me Muevo study did not show an overall effect on child BMI, but it did show a positive moderating effect on girls’ BMI [41]. The MOVE/me Muevo study also resulted in important policy and recreation-level changes that may influence community resident’s physical activity and dietary behaviors. These two examples (APN and MOVE/me Muevo) serve as case studies that highlight a possible mismatch between the intervention approach (i.e., community based) and the targeted outcome (i.e., child BMI). Specifically, community-based approaches may result in several important macrolevel outcomes (e.g., policy changes, structural changes, economic improvements) as a function of the levels being targeted (i.e., organizational and environmental). Yet, these macrolevel changes may lead to relatively modest, but potentially long-term, effects on children’s physical activity and dietary behaviors, which may or may not lead to observable or immediate changes in child BMI. Thus, we encourage researchers and practitioners who work in community settings to consider refocusing expectations away from individual-level outcomes, such as BMI, to focusing on designing and evaluating broader and macrolevel outcomes, such as changes in policies and environmental (social and built environment) factors that contribute to changing the current obesogenic environments. Special considerations should also be given to designing and implementing programs and strategies that contribute to increasing health equality and access to health-enhancing resources for all children and residents.

REFERENCES


INTRODUCTION

Recommendations to reduce dietary sugar have been part of efforts to promote public health\(^1\) and weight loss\(^2\) over the last 4 decades and thus are not novel. However, in recent years, recommendations have become more comprehensive and explicit. The first national nutrition guidelines, released in 1977 as *Dietary Goals for the United States*, included the recommendation to reduce the consumption of “refined and processed sugars and foods high in such sugars.”\(^1\) The 2015–2020 *Dietary Guidelines for Americans* advocate limiting consumption of added sugars, as defined in the next section, to less than 10% of daily energy (calorie) intake.\(^3\) However, a wide variety of sugary foods is readily available on the shelves of grocery stores, and children in the United States consume just over 85 g (more than 20 teaspoons) of added sugars per day, on average, equating to more than 15% of daily energy intake.\(^4\)
TABLE 37.1
Vignette: Data from Nutrition Assessment (with Potential Relevance to Dietary Intake of Added Sugars)

**Patient and Family History**
Julia is a 7-year-old Hispanic female living with her single mother and grandmother. Julia’s mother has a high-school education and works full time. She has a family medical history of obesity, type 2 diabetes mellitus, and depression.

**Anthropometric Data**
*Height:* 133.4 cm (84th percentile, z-score = +1.01), *Weight:* 52.7 kg (99th percentile, z-score = +2.89), *BMI:* 29.6 kg/m² (99th percentile, z-score = +2.64)
Patient BMI trend >95th percentile from age 2 according to electronic medical record

**Biochemical Data**
Hyperinsulinism

**Physical Examination and Medical History**
+Acanthosis nigricans (neck), constipation

**Food- and Nutrition-Related Data**
*Meals:* Receives free breakfast and lunch at school. Eats dinner at the table with family.
*Snacks:* Offered midmorning and after school. Snacking is significant for grain-based desserts (though Julia will eat vegetables and whole fruits).
*Beverages:* 24+ oz. SSBs (100% fruit juice, fruit drink, chocolate milk)
- 8 oz. of homemade juice with Metamucil in the morning, 8 oz. of homemade juice with dinner.
- 4 oz. carton of chocolate milk with lunch.
- 4 oz. juice box for afternoon snack. Julia often asks for more if feeling bored.
- No soda and water occasionally, but Julia states preferring the taste of juice.
*Desserts:* Cookies and grain-based fruit bars for afternoon and evening snacks.

*Beliefs and Attitudes:* Grandmother does not like telling Julia “no” when she asks for juice and snack foods. Mother believes that consuming 100% fruit juices (particularly homemade) is important for healthy growth and should be part of Julia’s childhood experience.

This chapter provides a reference for clinicians who counsel children and families on weight control, highlighting key research on reducing sugar consumption and considering pragmatic intervention strategies. A vignette is presented in Table 37.1 to set the stage for addressing clinically relevant questions pertaining to dietary sugar. At the end of the chapter, an approach to developing evidence-based care plans to reduce intake of added sugars is exemplified using the vignette.

**WHAT IS DIETARY SUGAR?**

From a biochemical perspective, the term *sugar* encompasses monosaccharides (glucose, fructose, galactose) and disaccharides comprising two monosaccharides linked by a glycosidic bond (sucrose: glucose–fructose, lactose: glucose–galactose, maltose: glucose–glucose). For the 2015–2020 *Dietary Guidelines,* the US Department of Health and Human Services and the Department of Agriculture defined *added sugars* as “sugars that are either added during the processing of foods, or are packaged as such, and include sugars (free, mono- and disaccharides), syrups, naturally occurring sugars that are isolated from a whole food and concentrated so that sugar is the primary component (e.g., fruit juice concentrates), and other caloric sweeteners.” This is consistent with the definition put forth by the Food and Drug Administration (FDA) when it proposed to include added sugars on the revised *nutrition facts* panel of labels. The World Health Organization (WHO) defines *free sugars* as “monosaccharides and disaccharides added to foods and beverages by the manufacturer, cook or consumer, and sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates.” The WHO strongly recommends limiting intake of free sugars to less than 10% of daily energy intake.
intake, consistent with the Dietary Guidelines, and further suggests a threshold of 5%. Although generally analogous, the definition of added sugars is less explicit than the definition of free sugars for fruit juices. We use the term added sugars throughout this chapter, to be consistent with the Dietary Guidelines, but agree with the explicit recommendation to limit consumption of fruit juice.

The sugars consumed most frequently in the United States are refined beet or cane sugar (sucrose) and high-fructose corn syrup (HFCS). Sucrose and HFCS are similar in sweetness and have the same energy content. While sucrose contains 50% fructose and 50% glucose as a disaccharide, HFCS contains free fructose and free glucose. The two forms of HFCS used by the food industry are HFCS-55 (55% fructose, 42% glucose, 3% hydrolyzable polymers of glucose) in sugar-sweetened beverages (SSBs) and HFCS-42 (42% fructose, 53% glucose, 5% hydrolyzable polymers of glucose) in solid foods. Although, some studies of measured sugar composition indicate higher levels of fructose in beverages made with HFCS. The glycosidic bond in sucrose is hydrolyzed by the enzyme sucrase in the brush border of the small intestine, yielding free fructose and free glucose for absorption. As such, while metabolic pathways for glucose and fructose are different, absorption of glucose or fructose is the same whether consumed as sucrose or HFCS. Interventions aimed at decreasing the consumption of added sugars should focus on the sum total of sucrose and HFCS.

**WHY IS DIETARY SUGAR AN IMPORTANT CONSIDERATION FOR WEIGHT CONTROL?**

The importance of limiting dietary sugar across the life span is underscored by data from observational studies indicating a direct relationship between the consumption of added sugars and risk for obesity, nonalcoholic fatty liver disease, type 2 diabetes mellitus, coronary heart disease, and periodontal disease. Studies also provide insights regarding the influence of early-life experiences with sweet taste on the propensity to consume diets high in added sugars. However, while most public health advocates and clinicians agree that dietary recommendations to reduce the consumption of added sugars may be effective for weight control and reducing the risk for chronic disease, the rationale for such recommendations is a topic of debate. With the consensus that added sugars are highly palatable sources of energy, the debate addresses the unique effects of added sugars, compared with other sources of energy, on metabolism. Representing one extreme of the debate, some argue that any adverse outcomes from consuming added sugars are largely a consequence of high-energy content. This perspective arguably may be influenced by ties with the beverage industry. Others have interpreted the published literature differently when considering the metabolic effects of glucose and fructose, the unique effects of consuming sugar in liquid versus solid form, and the hedonic appeal of added sugars.

**Metabolic Effects of Glucose and Fructose**

Glucose and fructose have the same number of carbon, hydrogen, and oxygen molecules (C₆H₁₂O₆) but different chemical structures and thus are metabolized differently. Each is absorbed into the portal circulation. A substantial portion of glucose passes through the liver and enters the systemic circulation, while most fructose is metabolized in the liver. Glucose triggers insulin release from the β cells of the pancreas, promoting hepatic glycogenesis and glucose uptake by skeletal muscle, adipose tissue, and other tissues throughout the body. When sugar is consumed in large amounts, postprandial hyperglycemia causes an exuberant insulin response and a marked increase in circulating insulin relative to glucagon. This hormonal milieu causes a drop in blood glucose below fasting levels, limited fuel availability, increased hunger, overeating, and ultimately weight gain. The same cascade of events occurs following the consumption of starch, particularly from refined sources, which is quickly metabolized to glucose. In contrast to glucose, fructose does not stimulate insulin secretion from the pancreas and requires energy in the form of adenosine triphosphate (ATP) for metabolism. Fructose metabolism is not regulated by hepatic energy stores. When sugar...
is consumed in large amounts, rapid absorption of fructose may overwhelm metabolic pathways leading to de novo lipogenesis and increased uric acid.\textsuperscript{20,21} Hepatic fructose metabolism has been implicated with cardiometabolic risk factors including hepatic steatosis, excess visceral adiposity, dyslipidemia, insulin resistance (hepatic and systemic), inflammation, hypertension, and endothelial dysfunction.\textsuperscript{18,20,22} 

The rate of absorption of fructose from added sugars compared with natural sources, most notably whole fruits, warrants comment. While fructose from added sugars is absorbed rapidly and has the potential to overwhelm hepatic metabolism when consumed in large amounts, fructose from fruits is absorbed more slowly and does not seem to have the same adverse effects.\textsuperscript{18} Slower absorption may be attributed to the integrity of the cellular structure and fiber content of whole fruits. Data from prospective cohort studies suggest that consuming whole fruit protects against cardiometabolic risk, while consuming fruit juice increases risk.\textsuperscript{23,24}

**Unique Effects of Consuming Sugar in Liquid versus Solid Form**

Sugar-sweetened carbonated beverages and fruit juices contain approximately 150 kcal per conventional 12 oz. can and 80 kcal per 6 oz. glass, respectively, but often are available in amounts much larger than conventional serving sizes. Several studies indicate imprecise dietary energy compensation following consumption of sugar in liquid form. Compared with solid foods containing the same amount of sugar, beverages require less oral processing (jaw and tongue movements to prepare food for swallowing), have shorter gastric emptying and gastrointestinal transit times, and may attenuate satiety signals and cognitive perceptions of energy intake.\textsuperscript{25} As such, children who consume SSBs may not compensate by decreasing other dietary sources of energy, leading to positive energy balance and weight gain. In a study of children aged 7–11 years who were randomly assigned to drink either a sugar-sweetened or sugar-free beverage, de Ruyter et al.\textsuperscript{26} found no difference in satiety at 15 minutes following the consumption of a single 250 mL (8.5 oz.) serving. Children who consumed the SSB daily for 18 months accumulated more body fat than their counterparts who consumed the sugar-free beverage, suggesting imprecise compensation.\textsuperscript{27}

**Hedonic Appeal of Added Sugars**

Humans have an innate desire for sweet foods and beverages from birth.\textsuperscript{15} Detection of sweet taste activates pleasure centers of the brain associated with reward and triggers strong hedonic responses. A preference for intense sweetness is particularly high in children and declines to adult levels during adolescence.\textsuperscript{28} Nevertheless, habitual sensory experiences early in life can modify preference and may have chronic effects on eating patterns and body weight. In a cross-sectional study, Pepino and Mennella\textsuperscript{29} observed that children aged 6–10 years who were routinely exposed to sugar water during infancy, compared with those who were not, preferred solutions with higher concentrations of sucrose. Liem and de Graaf\textsuperscript{30} reported that repeated exposure to a sucrose-sweetened beverage for 8 days enhanced preference for the beverage in primary-school children.

Research is needed to determine how early-life experiences and availability of sweetened foods interact to influence food preferences, energy consumption, and body weight over the life span. In a small prospective study, Weijs et al.\textsuperscript{31} found that the consumption of SSBs during infancy increased the risk of overweight at 8 years of age, independent of self-reported energy intake at the follow-up assessment. Ventura and Mennella\textsuperscript{15} point out that repeated exposure to sweet foods or beverages probably does not augment the hedonic response to the sensation of sweetness in general; rather, the context of repeated exposure likely is more important, as children develop expectations regarding the sweetness intensity of familiar foods and beverages in habitual circumstances. Using state-of-the-art methodology (functional magnetic resonance imaging) to evaluate neural responsivity, Burger and Stice\textsuperscript{32} noted the activation of taste and reward regions of the brain in adolescents following the consumption of a branded soft drink containing 17 g (just over 4 teaspoons) of sugar in
150 mL (5 oz.). For those who were regular consumers, simply seeing the brand logo activated a region of the brain thought to encode salience or attention to cues.

WHAT ARE THE PRIMARY FOOD SOURCES OF ADDED SUGARS IN THE DIETS OF CHILDREN?

Based on data from the National Health and Nutrition Examination Survey (NHANES), the primary food sources of added sugars for children and adolescents include soda (and energy and sports drinks), fruit drinks, candy, grain- and dairy-based desserts, ready-to-eat cereals, and syrups/toppings. Approximately 65%–70% of added sugars come from foods and beverages purchased at supermarkets or grocery stores as opposed to quick-service restaurants (including pizza takeout/delivery), full-service restaurants, schools, and other places (e.g., vending machines). More calories from added sugars are consumed at home than away from home. Data from a national cross-sectional study of schoolchildren indicate that the consumption of SSBs at home contributes the greatest proportion of calories from added sugars.

WHAT ARE CURRENT RECOMMENDATIONS FOR SUGAR INTAKE?

Previous editions of the Dietary Guidelines for Americans included warnings on the adverse health effects of consuming excessive amounts of added sugars with no recommendation for an upper limit. For the first time, the 8th edition of the Dietary Guidelines includes a specific recommendation to limit the consumption of added sugars to less than 10% of daily energy intake. The WHO strongly recommends limiting the intake of free sugars to less than 10%, and further suggests a threshold less than 5% of daily energy intake.

WHAT INTERVENTIONS ARE EFFICACIOUS FOR DECREASING SUGAR INTAKE AND PROMOTING WEIGHT LOSS AMONG CHILDREN AND ADOLESCENTS?

A variety of comprehensive obesity interventions have included recommendations to reduce the consumption of added sugars, frequently in combination with messages to increase fruit and vegetable consumption and physical activity and decrease sedentary time. In most intervention studies with a primary focus on reducing the consumption of added sugars, researchers have designated SSBs as a specific target. Interventions include public health initiatives, educational programs in schools, and alterations in beverage availability either at school or home. The impact and outcomes of these public health or research interventions provide insights on preventing and treating obesity in a clinical context.

Media campaigns typically do not lead to changes in behavior directly but can increase awareness, alter attitudes and perceptions, and, thus, enhance motivation and intention to change. Boles et al. evaluated the impact of a campaign involving mass media (messaging via web, television, billboards, and transit) and implemented over a calendar year to educate residents of Portland, Oregon, about SSBs. Adults who were aware of the campaign agreed that excess sugar intake causes health problems and reported the intention to decrease the amounts of SSBs that they offered to children. Jordan et al. explored the impact of public service announcements on the intention to reduce child consumption of SSBs in a national sample of parents with children aged 3–17 years. Perceived argument strength among parents was related to the intention to reduce child consumption, with announcements designed to convey messages of fear (e.g., “Are you pouring on the pounds?” with
information about negative health outcomes) or nurturance (e.g., “Know where the sugar is hiding,” focusing on boxed school lunches) deemed stronger than those that incorporated humor (e.g., “Soda might give you a temporary lift, but it can also make you crash,” with adolescents “crashing” their heads in various school settings).

The multifaceted approach taken in New York City to reduce the consumption of SSBs has been well publicized in the lay press. In addition to mass-media educational campaigns, this approach included nutritional standards for beverages (applied in schools, early child-care centers, and camps) and policy changes such as calorie counts on menu boards. A 27% decrease in the consumption of SSBs among high-school students from 2007 to 2013 was attributed to these public health initiatives. Proposals to cap the size of containers used to serve SSBs in food service establishments, tax SSBs, and eliminate SSBs as allowable purchases through the Supplemental Nutrition Assistance Program were rejected but nevertheless may have enhanced awareness of the deleterious effects of consuming SSBs on body weight and the risk for other chronic diseases.

EDUCATIONAL PROGRAMS IN SCHOOLS

Several studies indicate that educational programs can lead to decreases in the consumption of SSBs, and a couple of studies suggest that changes in consumption may have beneficial effects on body weight. James et al. conducted a school-based cluster randomized trial in England with 644 students aged 7–11 years. During four classes, a researcher with assistance from teachers encouraged reduced consumption of all “fizzy” beverages and increased consumption of water. Activities included taste testing of fruit to expose students to natural sweetness, a demonstration on how sweetened carbonated soda can adversely affect dentition, and producing songs and art around the message to “ditch the fizz.” Over 1 year, the prevalence of obesity decreased by 0.2% among children who received the educational program and increased by 7.5% in the control group, although change in body mass index (BMI) was not different between groups. The group difference in prevalence observed at 1 year was not sustained at 3 years. Sichieri et al. conducted a cluster randomized trial in Brazil with 1140 students aged 9–12 years. They provided education and encouragement to reduce the consumption of SSBs and increase the consumption of water using classroom activities (similar to those implemented by James et al.) during 10 sessions, banners displayed in the school, and water bottles portraying the campaign logo. Over one academic year, BMI decreased among overweight girls in the intervention compared with the control group, but the group effect was not significant in the full cohort.

ALTERATIONS IN BEVERAGE AVAILABILITY

Interventions that alter beverage availability arguably hold the most promise for preventing or treating obesity.

De Ruyter et al. randomly assigned 641 schoolchildren, aged 4–11 years, to receive a sugar-free beverage, artificially sweetened with sucralose and acesulfame potassium, or an SSB containing 26 g of sucrose and 104 kcal. The trial was conducted using a double-blind design. The two beverages had the same level of sweetness and were packaged in indistinguishable cans. Researchers instructed children to drink one can (250 mL, 8.5 oz.) per day. Among 477 children who completed the 18-month study, the increase in BMI z-score was smaller for the group consuming the sugar-free beverage compared with the SSB (0.02 vs. 0.15 units). Likewise, weight (6.33 vs. 7.30 kg) and fat mass (1.02 vs. 1.57 kg) increased less in the group consuming the sugar-free beverage.

Ebbeling et al. randomly assigned 224 overweight and obese adolescents who habitually consumed SSBs to intervention and control groups for 2 years. Participants in the intervention group received home deliveries of noncaloric beverages, as a strategy to displace SSBs, for 1 year. They were offered a menu of options that included water and artificially sweetened (“diet”) beverages. Registered dietitians conducted monthly motivational telephone calls with parents, focusing on
modeling healthful beverage consumption and stimulus control (removing SSBs from the home) and educational sessions with participants. During educational sessions, dietitians encouraged participants to “think before you drink” and provided information to increase awareness regarding the amounts of sugar in beverages; the benefits of drinking unsweetened water; the possible effects of SSBs in promoting excess energy intake, weight gain, tooth decay, hunger, and lethargy; and misleading beverage labels and advertisements. During calls and educational sessions, dietitians highly encouraged the consumption of water, presenting “diet” beverages as an option during the transition from SSBs to water. Consumption of SSBs dropped to almost zero, based on self-report, with the 1-year intervention. Between-group differences for changes in BMI (−0.57 kg/m²) and body weight (−1.9 kg) were significant, due to smaller increases in the intervention compared with the control group. After an additional 1-year follow-up period, discontinuation of the home deliveries extinguished group effects. Data obtained at 1 year reflect the effects of an active intervention and arguably are more relevant when considering the efficacy of altering beverage availability at home to promote weight loss.

ARE SOME INDIVIDUALS MORE SUSCEPTIBLE TO EFFECTS OF ADDED SUGARS ON BODY WEIGHT?

Some individuals may be particularly susceptible to the adverse effects of added sugars on body weight and may benefit more than others from interventions aimed at reducing added sugars. A combination of factors underlying susceptibility may include ethnicity and race, genetics, propensity to secrete insulin in response to sugar consumption, and disparities related to socioeconomic status and early-life feeding experiences. For example, Ebbeling et al. observed a significant difference in BMI between the intervention and control groups among Hispanic participants following a 1-year intervention with home deliveries of noncaloric beverages (−1.79 kg/m²) and also after an additional 1-year follow-up period (−2.35 kg/m²). The group effect was not significant among non-Hispanic participants. Consistent with this finding, a reanalysis of data from a 19-month prospective observational study of middle-school students also indicated a strong relationship between change in consumption of SSBs and change in BMI among Hispanics (p = .007) but no association among non-Hispanics. Effect modification by variables that may underlie susceptibility warrants additional research.

DEVELOPING EVIDENCE-BASED CARE PLANS TO REDUCE INTAKE OF ADDED SUGARS

Effective dietary interventions for preventing and treating obesity provide a scaffold for sequential changes in diet over time to eventually reach optimal intake. The order and time course of changes established collaboratively between individual patients and health-care providers in clinical settings are based on the unique needs and capacities of families. Often, devising care plans to reduce the intake of sugary foods and particularly beverages is a good place to start regardless of stance in the aforementioned debate. Although most studies of interventions aimed at reducing the consumption of added sugars for weight control have targeted SSBs per se, counseling patients to reduce their intake of added sugars from all sources is prudent based on the metabolic effects of glucose and fructose from refined sources and also the possibility of compromised micronutrient intake when foods containing added sugars displace more healthful options.

A reasonable approach to developing dietary-care plans targeting reduction in added sugars, based on evidence when available, includes a nutrition assessment, clear messages to reduce or eliminate the intake of target foods and beverages identified in the assessment, relevant education to foster behavior change consistent with messages, and counseling on modifiable factors associated with the intake of added sugars. Reducing consumption to less than 10% of daily energy intake, as
specified in the *Dietary Guidelines* and consistent with the WHO recommendation, is a pragmatic goal. The vignette presented in Table 37.1 captures the type of information that often emerges from a nutrition assessment, with particular attention to the consumption of added sugars, and an intervention pertaining to the vignette is presented in Table 37.2 to exemplify the approach described next.

The following list of target foods and beverages, based on the primary food sources of added sugars in the diets of children and corresponding messages to reduce or eliminate the consumption of these foods, can inform the design of tailored care plans.

- **Beverages.** Drink few or no regular sodas, sports drinks, energy drinks, and fruit drinks. Limit 100% fruit juice to no more than 4 oz. per day for children aged 1–6 years and no more than 8 oz. per day for children aged 7 years and older, consistent with lower limits specified by the American Academy of Pediatrics.\(^5^0\) Choose water, minimally sweetened beverages (no more than 1 g added sugar per oz.), and unsweetened milk according to general recommendations.\(^3\) (Regarding artificially sweetened beverages, while typically considered safe alternatives to SSBs,\(^5^1\) additional research is needed to evaluate the possible adverse effects of high sweetness intensity on taste preferences and body weight.\(^5^2\))

- **Candy and grain- and dairy-based desserts.** Limit candy and desserts with added sugars. Encourage replacement of candy and desserts with vegetables (no added sugars), whole fruits (natural sugar that is more slowly absorbed compared with added sugars), and whole grains (starch that breaks down to glucose more slowly than starch from refined products) that are more abundant in micronutrients.

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**TABLE 37.2**

*Back to Vignette: Intervention for Reducing Intake of Added Sugars (Based on Assessment in Table 37.1)*

<table>
<thead>
<tr>
<th>Messages to Reduce or Eliminate Intake of Target Foods and Beverages</th>
</tr>
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</table>
| **Beverages:** Drink water and plain milk. Limit 100% fruit juice to no more than 8 oz. per day. Eliminate fruit drinks.  
**Desserts:** Limit dessert intake. Replace with vegetables, fruits, and whole grains. |

<table>
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<tr>
<th>Relevant Education to Foster Behavior Change Consistent with Messages</th>
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| **Build Awareness to Increase Importance and Enhance Motivation for Change:** Link between the consumption of sugar, insulin secretion, acanthosis nigricans, and risk for type 2 diabetes mellitus. Importance of whole fruits, vegetables, and whole grains for relieving constipation.  
**Develop Knowledge and Skills to Operationalize Messages:** Based on estimated daily energy intake of 1640 kcal, prescribe upper limit of ~40 g per day of added sugars: \((1640 \times 0.10)/4\). Support label reading to identify sources and calculate grams of added sugars. Use visuals (e.g., sugar cubes) to enhance knowledge regarding sources of added sugars and motivation for behavior change. Review age-appropriate portion sizes. |

<table>
<thead>
<tr>
<th>Counseling on Modifiable Factors Associated with Intake of Added Sugars</th>
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</table>
| **Beliefs and Attitudes:** Explore family beliefs around the importance of consuming juice during childhood and use appropriate counseling strategies to adjust misconceptions. Assess alterations in beliefs and attitudes as a result of education and counseling.  
**Access to Foods and Beverages:** Replace juice and grain-based desserts from the home with vegetables, whole fruits, and whole grains to limit opportunities for consuming target foods and beverages and increase the likelihood of consuming more healthful options. Consider ways to improve selections at school breakfast and lunch to further reduce intake of added sugars.  
**Eating in Response to Boredom:** Explore appropriate parental responses to Julia’s boredom and support parental limit setting of juice intake in the afternoon. |
• **Ready-to-eat cereals and other packaged foods.** Limit cereals and other packaged foods with added sugars. Choose products with less or no added sugars. Choose vegetables, whole fruits, and whole grains without added sugars more often.

• **Table sugar and syrups/toppings.** Avoid adding sugar to foods and beverages during preparation and at the table.

**SUMMARY AND CONCLUSIONS**

Educational strategies and materials can be designed to build awareness regarding the adverse effects of added sugars on metabolism and risk for chronic disease, enhance motivation for behavior change, and develop knowledge and skills to operationalize messages. Studies of media campaigns and educational strategies used in clinical trials can provide ideas for messaging to build awareness. While added sugars currently are not listed on the Nutrition Facts panel of labels (FDA proposal pending), in May 2016, the FDA finalized plans to list added sugars on the Nutrition Facts panel of labels. Along with providing numerical information, educating patients and families to evaluate total grams of sugar and sources of added sugars in the list of ingredients can be beneficial for assisting patients and families in making food choices. In addition to HFCS, other examples of added sugars include corn syrup, dextrose, evaporated cane juice, fruit juice concentrates, honey, molasses, and syrup. An upper limit for grams of added sugar (10% of daily energy intake) should be estimated for patients: \[ \text{[(total energy in kcal} \times 0.10)/(4 \text{ g/kcal})] \]. Visual tools, such as sugar cubes or teaspoons of sugar, can be effective when educating patients and families. Knowing that a bottle (20 oz.) of cola contains more than 16 teaspoons (4 g per teaspoon) or 26 cubes (2.5 g per cube) of sugar is more impactful than knowing that it contains 65 g of sugar. Patients and families may be more likely to avoid consuming products with added sugars if they have guidance in converting abstract (grams of sugar) to concrete (teaspoons or cubes of sugar) information.

Sustained behavior change, leading to weight loss, often does not occur with education alone. Counseling on modifiable factors associated with the consumption of added sugars usually enhances the outcomes of interventions. The following list of factors, although not exhaustive, provides a starting point to explore the unique needs of each patient and family pertaining to reducing the consumption of added sugars: beliefs and attitudes; access to foods and beverages; eating atmospheres and environments; eating away from home; eating outside regular meal and snack times or “grazing;” behavioral responses to food marketing; using foods and beverages containing added sugars as rewards; impulsive intake of added sugars in response to boredom, stress, and other emotions; and the costs of healthful alternatives (particularly in the context of poverty).

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Lifestyle Interventions for the Prevention of Type 2 Diabetes in Obese Children and Youth

Micah L. Olson and Gabriel Q. Shaibi

INTRODUCTION

The pediatric obesity epidemic has contributed to the emergence of type 2 diabetes among children and adolescents, as reviewed in Chapter 25. Not only is type 2 diabetes in youth a recent phenomenon, but this phenotype is associated with a rapid onset and aggressive disease course. Unlike this diagnosis in adults, type 2 diabetes can develop within 1 to 4 years in otherwise normoglycemic youth [1]. Youth diagnosed with type 2 diabetes exhibit accelerated microvascular complications [2] and are projected to have a decreased life expectancy [3]. In addition, almost 50% of adolescents with type 2 diabetes are unable to maintain adequate glycemic control and will require insulin therapy within a few years of diagnosis [4].

The discouraging outlook for youth with type 2 diabetes underscores the need for prevention programs. While the most salient and cost-effective approach for diabetes prevention in youth is the primary prevention of obesity, millions of youth are already obese and would be best served by targeted diabetes prevention interventions. Multiple studies in adults have established the effectiveness of lifestyle changes in delaying or preventing the onset of type 2 diabetes in those with prediabetes [5]. The Diabetes Prevention Program demonstrated that an intensive lifestyle program with the goals of 7% weight loss through dietary modification and increased physical activity can prevent or delay the development of type 2 diabetes in those with prediabetes. After an average follow-up of nearly 5 years, those randomized to the intensive lifestyle program arm of the study exhibited a 58% reduction in the incidence of diabetes compared with controls [6].

To date, there are no comprehensive type 2 diabetes prevention studies described in the pediatric literature. In other words, there are no pediatric studies that are designed to directly test whether a lifestyle intervention is effective for preventing the onset of type 2 diabetes. There are a number of reasons for this including the heterogeneity in diabetes risk phenotypes even among obese youth [7], the unknown trajectory and time course of diabetes conversion [1], and the lack of data specifying behavioral and weight loss targets necessary to achieve diabetes risk reduction [8]. In this context, diabetes prevention is conceptually different from weight management. For weight
management programs, the primary outcome is weight loss (or prevention of weight gain) among obese youth, whereas diabetes prevention programs target high-risk populations (e.g., obese, minority adolescents with a positive family history) where risk stratification is derived from some indicator of glucose homeostasis.

Given these challenges in designing “true” diabetes prevention programs for youth, the majority of pediatric research focuses on the impact of lifestyle interventions on surrogate or proximal measures of diabetes risk factors. These studies manipulate diet and/or physical activity behaviors to induce changes in outcome measures that are either glycemic indicators of diabetes risk (i.e., fasting glucose, 2 h glucose, or HbA1c) or related to the pathophysiology of the disease. From a pathophysiologic perspective, insufficient insulin secretion relative to the degree of insulin resistance contributes to pancreatic β-cell dysfunction leading to the development of impaired glucose homeostasis and eventually type 2 diabetes [9]. Improvements in these glycemic indicators or pathophysiologic processes over a sufficient follow-up period could be indicative of reduction in diabetes risk (Figure 38.1).

Although emerging data support the potential efficacy of pharmacological [10] and surgical [11] approaches for reducing diabetes risk factors among obese youth, these studies are beyond the scope of this chapter and are covered in Chapters 30 and 31. The goal of this chapter is to review studies that have examined the associations between the key behavioral targets (diet, physical activity, and their combination) and measures of glycemia (fasting glucose, 2 h glucose, or HbA1c), insulin action (e.g., insulin resistance or insulin sensitivity), or measures of pancreatic β-cell function in populations with an increased risk profile for type 2 diabetes. We will use both observational and interventional studies to support the potential utility of lifestyle intervention to prevent or delay the onset of type 2 diabetes in youth. We will also discuss challenges to and opportunities for the translation of pediatric diabetes prevention programs into real-world settings in order to make the strongest public health impact on this growing epidemic.

**NUTRITION AND TYPE 2 DIABETES RISK**

Much attention has focused on nutritional factors and type 2 diabetes risk in youth. Macronutrient dietary content (the proportion of calories ingested from carbohydrates, protein, and fat), the makeup of dietary carbohydrates (e.g., glycemic index, fiber, and added sugar), and sugar-sweetened beverage intake have all been studied in relation to risk for type 2 diabetes. We will first review observational studies that evaluate relationships between selected dietary characteristics and markers of glucose homeostasis and later review interventional studies that test whether specific dietary changes can improve risk factors for type 2 diabetes.
OBSERVATIONAL STUDIES LINKING DIETARY PATTERNS WITH TYPE 2 DIABETES RISK FACTORS

A cross-sectional study of 285 healthy adolescents found a significant association between whole grain consumption, body mass index, and insulin sensitivity [12]. The relationship between whole grain consumption and insulin sensitivity was strongest among those adolescents with the highest BMI and suggests that eating whole grains may be protective against the development of type 2 diabetes in youth. Arslanian et al. examined 44 African American and white children and found that a higher dietary fat-to-carbohydrate ratio was associated with significantly lower insulin sensitivity suggesting that higher fat intake is associated with worsening insulin resistance [13]. However, a cross-sectional study of 63 overweight and obese Latino children failed to find any significant associations between macronutrient content and measures of insulin resistance [14]. Despite the lack of association with macronutrient content, higher sugar intake was significantly associated with lower pancreatic β-cell function. In a cross-sectional study of 630 Canadian youth, no associations between macronutrient content and insulin sensitivity or insulin secretion were noted [15].

In a longitudinal analysis of 226 healthy German youth, higher dietary glycemic index in adolescence was prospectively associated with increased insulin resistance over an average follow-up of 12.6 years [16].

As discussed in Chapter 37, dietary intake of sugar-sweetened beverages has received increased attention as a potential causal factor in the current pediatric obesity epidemic [17]. In contrast, the data examining the associations between sugar-sweetened beverage intake and markers of glucose homeostasis in youth are less abundant. Ambrosini et al. prospectively studied 1433 Australian adolescents from age 14 to 17 years but failed to find any significant associations between intake of carbonated drinks or fruit drinks with added sugar and insulin or glucose variables [18]. In a cross-sectional study using NHANES data from 1999 to 2004, sugar-sweetened beverage intake derived from a 24 h recall was associated with greater insulin resistance in girls but not in boys [19]. Similarly, in a study of 630 Canadian children, higher sugar-sweetened beverage intake was associated with measures of insulin resistance among overweight children (BMI ≥ 85th percentile) but not among healthy-weight children [20]. When this cohort was studied prospectively, a higher baseline consumption of added sugars from liquid sources was associated with increased fasting glucose and worsened insulin resistance at 2 years and those with a BMI ≥ 85th percentile were most affected [20].

The inconsistent findings from observational studies make it difficult to draw definitive conclusions regarding the associations between habitual dietary behaviors and type 2 diabetes risk factors in youth. This inconsistency may be attributed to the well-documented challenges in accurately assessing nutrition-related behaviors in youth [21]. Therefore, intervention studies offer a more direct approach to examine whether modifications in dietary patterns can reduce the risk for developing type 2 diabetes.

EFFECTS OF DIETARY INTERVENTIONS ON TYPE 2 DIABETES RISK FACTORS

Dietary interventions are inherently complex due to the interrelatedness of various dietary components (e.g., macronutrient composition and total caloric consumption). In addition, without completely sequestering participants and supplying all consumed meals during the trial, it is difficult to know how compliant participants are with achieving the intended nutritional targets that are being tested. Even with well-developed intervention fidelity plans, researchers are left with some degree of inherent uncertainty in quantifying the degree to which a nutritional behavioral change led to the observed outcome. With these limitations acknowledged, the fundamental importance of diet on the development of type 2 diabetes makes it essential that researchers continue to design and test the effects of various dietary interventions on type 2 diabetes risk among obese youth.

Ebbeling et al. randomized 16 obese adolescents to a reduced-glycemic-load diet or a reduced-fat diet [22]. The reduced-glycemic-load diet was ad libitum and targeted a proportion of energy...
intake between 45% and 50% from carbohydrates and 30%–35% from fat, and participants were counseled to consume low-glycemic foods. The reduced-fat diet was designed to elicit a negative energy balance of 250–500 kcal/day and targeted a proportion of energy intake of 55%–60% from carbohydrates and 25%–30% from fat. Despite the fact that the low-glycemic diet was ad libitum and the reduced-fat diet was energy restricted, the reduced-glycemic-load group exhibited a significant decrease in both BMI and fat mass at 12 months compared with the reduced-fat group. In addition, at 12 months the glycemic-load group had a significantly lower increase in insulin resistance compared with the reduced-fat group that was independent of changes in BMI. In a follow-up study of 113 obese Hispanic children, Mirza et al. adapted the dietary intervention to be tailored for Hispanic youth [23]. The intervention lasted 3 months and outcomes were obtained at baseline, 3, 12, and 24 months postintervention. Both the low-glycemic diet and low-fat groups exhibited significant decreases in BMI z-score that were sustained at 24 months. However, neither group experienced significant changes in fasting glucose or measures of insulin resistance.

In a similar approach, Krebs et al. randomized 22 severely obese adolescents to a high-protein low-carbohydrate (HPLC) diet or a low-fat (LF) diet [24]. The HPLC diet was restricted to <20 g of carbohydrates per day, but was not given a caloric restriction target. The LF diet was restricted to a calorie goal of 70% of resting energy expenditure and <30% of calories from fat. Both groups experienced a significant reduction in BMI z-score at 13 weeks with the HPLC group achieving a significantly greater decrease in BMI z-score than the LF group. Despite improvements in BMI z-score, no significant changes in glucose tolerance or insulin resistance were observed in either group.

Ramon-Krauel randomized 17 obese 8- to 17-year-old youth with fatty liver to either a low glycemic load diet or a LF diet [25]. The low glycemic load group was counseled to select carbohydrate-containing foods with a low-to-moderate glycemic load and targeted 40% of energy from carbohydrates and 35%–40% from fat. The LF diet targeted 55%–60% of energy from carbohydrates and 20% from fat, with <10% from saturated fat. Both diets were prescribed ad libitum and both groups exhibited similar decreases in liver fat, fasting glucose, and insulin resistance at 6 months.

Davis et al. enrolled 16 overweight and obese Latina adolescent females (12–17 years of age) in a 12-week nutrition education intervention focused on decreasing added sugar intake (goal of 10% or less of total daily caloric intake) and increasing dietary fiber (goal of 14 g per 1000 cal) [26]. Despite significant reductions in total calories, grams of carbohydrates, grams of fat, grams of added sugar, and the number of sugar-sweetened beverages, the intervention did not result in any significant changes in insulin sensitivity or insulin secretion. However, there was a trend noted between reductions in added sugar intake and insulin secretion (p = .075), suggesting that modest reductions in added sugar intake may reduce diabetes risk profile. In a follow-up trial, 53 overweight and obese Latino adolescents (14–18 years of age) were randomized to one of three groups for 16 weeks: (1) nutrition, (2) nutrition plus strength training, or (3) control [27]. The nutrition education consisted of weekly 1 h classes that focused on the same dietary targets as noted previously. The nutrition plus strength-training group consisted of the nutrition education classes plus a 60 min, twice-per-week, strength-training session. The control group received no intervention between the pre- and postintervention data collection. Both intervention groups achieved a decrease in glucose area under the curve during an oral glucose tolerance test, but there were no other significant intervention effects on BMI, body composition, or measures of insulin sensitivity or β-cell function. There was considerable individual variation in dietary changes within each of the study groups so secondary analyses were performed to compare outcome measures based on reported dietary changes across treatment arms [28]. Those who reported decreases in added sugar intake exhibited significant reductions in insulin area under the curve (p = .02) during an oral glucose tolerance test while those who reported increases in fiber intake exhibited reductions in BMI (p = .01) and visceral adipose tissue (p = .03).

The need for dietary intervention among obese youth aimed at reducing type 2 diabetes risk is evident. Despite a multitude of approaches targeting various aspects of dietary intake, there is insufficient evidence to recommend any one approach. It appears that modulating aspects of macronutrient content may hold promise for improving certain diabetes risk factors. Further studies are needed
to identify how changes in dietary patterns and caloric intake contribute to diabetes risk reduction and how to support obese youth and their families to successfully implement these recommended changes.

PHYSICAL ACTIVITY, EXERCISE, AND TYPE 2 DIABETES RISK FACTORS

It has long been established that adults who participate in regular physical activity have lower rates of type 2 diabetes than their sedentary counterparts [29]. Further, the protective effects of physical activity may be independent of weight status and appear to hold in lean, overweight, and obese populations [30]. These observations have led to an increasing body of literature supporting the benefits of exercise training on diabetes risk factors among obese youth. Several reviews [31,32] and a recent meta-analysis [33] have focused on the effects of exercise on insulin action in youth. Collectively, these publications support the efficacy of exercise training (both resistance and aerobic) to improve insulin action in obese youth and suggest that the health improvements are independent of changes in body weight or composition [32].

Bell et al. enrolled 14 obese, hyperinsulinemic normoglycemic youth (9–16 years of age) to participate in 8 weeks (3 days/week for 1 h) of supervised exercise training [34]. The training program included circuits of moderate to vigorous aerobic exercise on a cycle ergometer coupled with resistance exercises using a machine. Compared with baseline, participants exhibited a 12% increase in insulin sensitivity ($p = .02$) as measured by the euglycemic-hyperinsulminic clamp. This increase was observed in the absence of changes in weight or body composition and supports the concept that exercise alone can improve insulin sensitivity in obese youth. Shaibi et al. randomized 21 obese Latino adolescents 13–17 years of age to either progressive resistance training (twice/week for 16 weeks) or a nonexercise control group [35]. Participants were assessed at baseline and postintervention for insulin sensitivity, insulin secretion, and $\beta$-cell function by the frequently sampled intravenous glucose tolerance test. Compared with baseline, resistance-trained youth exhibited a 45% increase in insulin sensitivity while control youth experienced a small, nonsignificant increase. When data were compared across groups, the increase in insulin sensitivity was significantly greater in the intervention compared with controls and was independent of changes in total fat mass or total lean mass. Despite significant increases in insulin sensitivity following resistance training, there were no within- or between-group changes in insulin secretion or $\beta$-cell function.

In a series of related studies comparing the effects of aerobic versus resistance exercise on diabetes risk factors in obese youth, Lee et al. found that 3 months of aerobic exercise training (three 60 min sessions/week) led to significant increases in insulin sensitivity in boys and girls [36,37]. Aerobic exercise also led to reductions in total and regional body fat as measured by magnetic resonance imaging. Interestingly, the resistance-training program was only effective at increasing insulin sensitivity and reducing body composition in boys and did not result in diabetes risk reduction in girls. Collectively, these data suggest that sex may moderate the effects of exercise modality (aerobic vs. resistance) on diabetes risk reduction in obese adolescents. An additional important finding from these studies was that both forms of exercise led to reductions in percent body fat but did not result in weight loss.

These studies move the field beyond the conceptual basis for exercise to reduce diabetes risk into the prescriptive model that will be needed to further advance the translation of science into practice. Building on this model, Davis et al. randomized 222 overweight and obese children to receive 13 weeks of low-dose (5 days/week at 20 min/session) or high-dose (5 days/week at 40 min/session) aerobic exercise of similar intensity in order to examine the dose–response effects of exercise on diabetes risk factors in children. In addition to dose–response effects, several key features of this study included (1) the focus on a predominantly prepubertal cohort of children, (2) more than half of the population being an ethnic minority with a family history of type 2 diabetes, and (3) almost 30% of the total sample exhibited prediabetes at baseline. The authors found that both low-dose and high-dose aerobic exercise were equally beneficial for improving measures of insulin sensitivity but
that the high-dose exercise was superior to low-dose for improving β-cell function [38]. Despite the beneficial effects of exercise on insulin sensitivity and β-cell function, the prevalence of prediabetes was not changed over the course of the intervention.

Collectively, these studies support the utility of exercise to improve diabetes risk in obese pediatric populations and set the stage for future work to optimize the frequency, intensity, duration, and mode of exercise necessary to elicit beneficial health effects. These data will be instrumental for the translation of research into practice in order to support the concept that exercise is medicine [39].

**EFFECTS OF LIFESTYLE INTERVENTIONS ON TYPE 2 DIABETES RISK**

Very few randomized controlled trials have described comprehensive lifestyle interventions on type 2 diabetes risk factors in youth. The hallmark features of these comprehensive interventions include nutrition and physical activity components that are supported by evidenced-based behavior change strategies. An exemplar comes from the Yale Bright Bodies weight-management program where Savoye et al. conducted a trial of 209 obese children randomized to the Bright Bodies program or a control group [40]. The intervention group consisted of twice-a-week education sessions for 6 months followed by bimonthly sessions for 6 months. The program was family based and involved nutrition, exercise, and behavior modification. The nutrition counseling focused on better food choices of moderate portion sizes as opposed to a structured meal plan with calorie restriction. The control group consisted of standard weight management clinical visits where youth received general diet and exercise recommendations at baseline and 6 months. At 12 months, fasting estimates of insulin sensitivity significantly improved in the intervention group and worsened in the control group (p < .001) while there was no statistically significant change in fasting glucose in either group. Treatment effects were sustained at 2-year follow-up, despite discontinuing the formal intervention after 12 months [41]. A subsample of 23 children who were randomly selected to receive a standard oral glucose tolerance test (OGTT) at the beginning and end of the 12-month study demonstrated significant improvements in markers of insulin sensitivity and glucose tolerance in the intervention group versus the control group [42]. These data led to a follow-up study of the Yale Bright Bodies Healthy Lifestyle Program for obese youth with elevated 2 h glucose levels [43]. Seventy-five obese youth with prediabetes (defined as elevated 2 h glucose levels between 130 and 199 mg/dL) were randomized to a 6-month intensive lifestyle program or standard clinical care. The lifestyle intervention led to significant decreases in 2 h glucose, increases in insulin sensitivity, and greater reversion to normal glucose tolerance compared with the control group. Of note was that both groups experienced increases in weight over the 6 months, but the increase was significantly larger in controls (3.7 kg) compared with intervention youth (0.6 kg) for an overall treatment effect of −3.1 kg (p = .006). This series of studies supports the concept that comprehensive diabetes prevention programs can be efficacious for short-term and potentially sustained diabetes risk reduction among high-risk obese youth.

Shaibi et al. examined the impact of a 12-week culturally grounded, community-based lifestyle intervention on insulin sensitivity and glucose tolerance among 15 overweight and obese Latino adolescents aged 14–16 years [44]. The program included weekly nutrition education delivered in groups to families and 3 days/week of moderate-to-vigorous physical activity for youth. A key aspect of the theory-informed intervention was the delivery in the community at a local YMCA by trained community health educators rather than researchers. The program led to significant improvements in both glucose tolerance and insulin sensitivity even in the absence of weight loss. Although the sample size was small, the study supports the translational potential for diabetes prevention interventions to be extended to the community setting for vulnerable and underserved groups of youth at high risk for type 2 diabetes.

These promising studies suggest that comprehensive lifestyle interventions can result in diabetes risk reduction among high-risk obese youth and, contrary to what is known in adults, weight maintenance rather than weight loss may be critical for success. This distinction becomes increasingly
important in the context of normal growth trajectories where it may be physiological appropriate for youth to continue to gain weight until final maturation. Therefore, comprehensive diabetes prevention programs leading to reductions in diabetes risk among obese youth are likely the result of improvements in body composition, rather than weight loss per se, that are mediated by successful behavior change. Programmatically, this notion has implications for the design, implementation, and evaluation of comprehensive diabetes prevention programs for obese youth where emphasis should be placed on making and sustaining behavior changes and assessing outcomes that are proximal and related to the pathophysiology of type 2 diabetes.

CONCLUSION AND FUTURE DIRECTIONS

Obesity and type 2 diabetes remain challenging public health problems but the available data support the utility of lifestyle intervention for diabetes risk reduction in high-risk obese youth. Both dietary changes and increases in physical activity are essential to diabetes prevention with more research needed to ascertain the optimal dosing of these behavioral targets to result in diabetes prevention. More important than optimizing behavioral changes is the need for a greater understanding of how to operationalize and implement sustained behavioral changes in real-world settings. From a systems perspective, these programs must be developed to address family, social, environmental, and policy factors that influence downstream health behaviors and ultimately diabetes-related health outcomes [45]. This system-level approach is especially important for underserved and vulnerable populations of youth who will likely experience much greater barriers to achieving and maintaining optimal behavioral changes.

REFERENCES


INTRODUCTION

Modifying key obesity-related behaviors, as outlined in previous chapters, has been a prime focus of pediatric obesity prevention and intervention efforts. In recent years, the incorporation of mobile or wireless health technologies, also known as mHealth solutions, into pediatric obesity prevention and intervention studies has rapidly accelerated [1]. The rise of mHealth is partially fueled by the rapid growth in wearable device availability and mobile phone ownership across age groups, geographic regions, and socioeconomic strata. To date, there are an estimated 7 billion mobile phone subscriptions worldwide [2]. In the United States, it is estimated that over 90% of adults and 88% of youth aged 13–17 years own a mobile phone [3]. mHealth technologies have the potential to capture and transmit a wide array of participant data in an accurate and timely fashion. These data range from ubiquitously measured (via sensor) behavioral, biological, and other contextual data (e.g., social interaction and physical location) to self-reported survey questionnaires via ecological momentary assessment (EMA). These temporally dense data are also highly contextualized, taken in the course of daily life, where, when, and how it most matters for understanding and intervening in behavior. With technological innovations that advance both the hardware [4] (i.e., lower power requirement, wireless data transmission, smaller portable sensors) and the software aspects [5] (i.e., increasingly sophisticated algorithms) of mobile devices, mHealth solutions offer clinicians and scientists unprecedented opportunities to understand behaviors and diseases with more clarity and to intervene in complex behaviors and their antecedents in ways that would have been pragmatically impossible to achieve using traditional research methodologies [4].

Deployable and wearable sensors, such as accelerometers, have demonstrated high validity in measuring key obesity-related behaviors [5], including physical activity, time spent in sedentary
behavior, sleep patterns, and key risk factors such as blood pressure [6]. Other types of sensors, including deployable and ingestible sensors, can provide highly contextualized and temporally dense data on behaviors. Examples of these sensors include home-deployed sensors that track and transmit speed of gait within the home [7] and medicine-bottle sensors that can track and report on compliance with drug and data collection regiments in real time [8]. Some other key obesity-related behaviors, in particular dietary intake, remain challenging to measure with the current technology. However, progress is being made, for example, through photography and pattern recognition, crowd sourcing, wearable sensors, and other technology-driven mobile solutions [9–12].

In addition to capturing data using wearable and deployable sensors, mobile devices can also facilitate the collection of participants’ self-reported data in natural settings multiple times within a day. Experience sampling methods (ESM), such as EMA and other similar methodologies, capitalize on the capability of mobile devices to emit signals (audible, haptic, or embedded in the environment). These signals can be set up to prompt participants for information (1) at random times, (2) at a specific time or within a window of time, (3) in response to specific subjective experiences, or (4) triggered based on sensed events. Self-report and sensor data collected in real or near time and context (location and situation) of events and experiences are considered to be more ecologically valid and may be less prone to recall bias [6].

These and other mHealth solutions can be and have been applied to the prevention and treatment of childhood obesity, and offer four major advantages: (1) improved measurement capabilities and ecological validity, (2) innovative platforms for collecting and displaying data on obesity-related behaviors and their antecedents, (3) the capacity to deliver novel interventions in real time and in context, and (4) the capacity to deliver highly personalized interventions that adapt in an ongoing fashion to each individual’s needs. Taken together, these advantages provide the capacity to deliver what has been termed just-in-time adaptive interventions or JITAIIs [13]. JITAIIs are highly personalized mobile interventions that are delivered “just-in-time,” that is, when a person is available and in need, for instance after a sensed bout of more than 30 min of inactivity, and anywhere, that is, during the course of a person’s everyday life. JITAIIs use incoming personal data (from smartphones, sensors, the Internet, etc.) to adapt over time to that specific individual’s changing status and circumstances, with the goal to address the individual personalized needs. These highly precise interventions are likely the future of precision behavioral medicine.

While advancements in technologies and research methodologies allow clinicians and researchers to obtain high-resolution data about patients and participants, the use of these data and devices for understanding and changing behavior has been inconsistent across disciplines. The expectations of mHealth currently outshine the efficacy that the current state of evidence supports, leaving many to suspect that mHealth may not meet its expected potential [14]. However, the field is only beginning to understand how to use the temporally dense, highly contextualized data produced by mHealth technologies [15], and current mHealth interventions, particularly in pediatric populations, fail to take full advantage of the intervention capabilities of mHealth technologies [1,5,16]. This chapter will examine the literature on the use of mHealth solutions in preventing and treating pediatric obesity to date and the current technology used for measuring key obesity-related behaviors, describe the current limitations and challenges in using mHealth tools to change behavior, and conclude with suggestions on how researchers and clinicians could take fuller advantage of the sophisticated technologies now available, including implementing research designs that are more suitable to mHealth interventions [13,17,18].

**Current State of mHealth in Childhood Obesity**

**Text Messages or Short Message Service**

Text messaging, or short message service (SMS), is a commonly used channel for communication among the youth population. The PEW Research Center Teen Relationships Survey study conducted between 2014 and 2015 found that 91% of 13–17-year-old youths who owned a cell phone...
had engaged in conversations either through instant messaging mobile applications (e.g., WhatsApp and Kik) or SMS in their daily lives [3]. Although 33% of the phone-owning youth reportedly used instant messaging applications (apps) to communicate, SMS has been and continues to be an extensively used communication medium among the youth population [3,19]. Several SMS-based intervention feasibility trials in youth populations have reported that SMS is an acceptable [20–24] and, in some instances, a preferable intervention delivery method compared with other face-to-face or paper-pencil modalities [24,25]. Despite youth’s acceptance of and preference for SMS as a medium for communication, the effectiveness of interventions that use SMS as the sole or main intervention modality in pediatric obesity interventions to change adiposity (e.g., body mass index [BMI], BMI z-score, waist circumference, visceral fat, percentage body fat, etc.), metabolic health (e.g., insulin sensitivity), and behavior (e.g., physical activity and dietary intake) has been mixed [1,6,26].

mHealth pediatric obesity prevention and treatment studies published through 2014 were recently systematically reviewed by Turner et al. [1]. Among the 32 unique studies reviewed, eight of them focused on the efficacy of using SMS in changing adiposity, metabolic, and behavioral outcomes. Among these, three studies utilized a randomized controlled trial (RCT) study design to examine the efficacy of using SMS as a weight maintenance intervention condition, in addition to a group-based intervention [27], a face-to-face intervention [28], and other electronic communication methods (i.e., a website) [29]. The three RCT studies sent texts on a weekly [27] or biweekly [28] basis to promote self-reporting and self-monitoring of obesity-related behaviors [27], promote goal setting [28,29], provide tailored suggestions [28,29], and provide reminders for intervention adherence [28,29]. Overall, although one study reported lowered study attrition among participants who received the SMS-based intervention [27], all three studies concluded that the SMS-based approach did not provide additional effects in reducing adiposity, improving metabolic health, or obesity-related behaviors over the other face-to-face intervention modalities [1,27–29]. For the most part, the SMS in these studies was automated “one-size-fits-all,” with adaptation to self-reported data on a weekly basis in the more sophisticated studies [27,29]. In one of the two studies that did provide tailored feedback based on the weekly self-monitoring data, higher self-reported physical activity and improved dietary intake were observed among youths who were more compliant [27]. This suggests that using SMS as a channel to disseminate adaptive and personalized feedback may potentially be efficacious in changing obesity-related behaviors in youth. Similar results were found in two of the five pilot studies reported on in the Turner et al. review, as well as in four studies that were identified in an updated search, reported here. These studies used SMS to provide personalized feedback, on a daily basis, based on participants’ self-reported baseline characteristics [30] and on self-reported and sensor-based [16] data. The studies reported that personalized feedback exhibited preliminary efficacy in reducing time spent in sedentary behavior [25,31], time spent in physical activity [30], and increasing fruit and vegetable consumption [31].

Although the existing evidence may suggest that, overall, SMS-based interventions do not achieve significant improvement in obesity-related clinical and behavioral outcomes among youth [1], these studies represent early mHealth efforts. mHealth technologies are developing at a fast pace, and these early efforts are only beginning to scratch the surface of what can be done in a JITAI. While SMS has been shown to be an acceptable method for communicating with youth populations, guidelines on important experimental design factors, such as the effective dose and content of SMS for specific groups of youth, in time and in context, remain to be established [1,13]. Furthermore, most SMS studies to date have not used streaming data or available sensor technologies (for instance, those offered by the mobile phone) that could inform intervention delivery based on location, behavior patterns, context, time, and previous individual reactions to particular messages, timing, and other associated factors. Only one pilot study in children to date has used streaming data from wearable sensors to inform SMS messages in real time and in context, resulting in declines in time spent in sedentary behavior, as well as increases in physical activity [16]. Emerging evidence demonstrates that SMS with just-in-time, adaptive, and contextualized feedback may promote change in important obesity-related behaviors [16,25,30,31]. SMS may be an optimal channel to promote
obesity-related behavior change among youth when participant data are incorporated in an ongoing fashion to inform just-in-time and adaptive delivery.

**Interventions Using Mobile Applications**

Mobile apps provide a variety of functions beyond offering instant communication; that is, they provide interactive ways to collect and use self-reported data from external devices [32] and other sources such as social networks [33], act as platforms for more sophisticated data visualization [32], and offer the possibility of gamifying interventions [33,34]. Some of these advantageous functions offered by mobile apps have been adopted for the prevention and treatment of pediatric obesity. This is documented both by the increase in health-related “off-the-shelf” apps for pediatric obesity prevention and treatment that are available for a fee [35] and the evidence available on pediatric obesity prevention and intervention efforts using mobile apps [1,16]. While the body of evidence on the use of mobile apps to prevent and treat pediatric obesity continues to grow, the efficacy of using mobile apps to change obesity-related behavior or prevent pediatric obesity is considered preliminarily but moderately effective [1,5].

The mHealth pediatric obesity studies included in the review by Turner et al. [1] used a variety of mobile platforms, such as personal digital assistants (PDA), game consoles, and smartphone apps. These platforms were used mostly to deliver an intervention [33,36–41] or to collect data about obesity-related behaviors (either in conjunction with sensors [32,36–38,40–47] or as a medium for self-monitoring and self-reporting [39,40,48–51]). Although the evidence is preliminary, several pilot intervention studies [33,38–41,52,53] have reported intervention effects in changing obesity-related behaviors. These intervention studies used mobile apps as a channel to provide personalized feedback automated from preset algorithms [39,41,52], participants’ social circles [38,40], or virtual avatars in the app [33]. In these and a few more recent studies, personalized feedback was constructed using data captured by wearable sensors [16,33,38,41,52] and self-reported data [39,40]. These approaches were found to be efficacious in modifying obesity-related behavior, including increasing time spent in physical activity [40,41]; reducing time spent in sedentary behavior [16]; improving fruit, vegetable, and breakfast consumption [33,39,52]; and changing psychological antecedents to these behaviors, such as lowering the perceived effort in engaging in physical activity [38]. While these approaches have demonstrated some preliminary efficacy in changing obesity-related behavior, it is clear from the literature that the incorporation of user-centered design throughout the app or sensor development process is important in designing an effective mHealth pediatric obesity prevention or intervention study [1]. Using mobile apps and combinations of apps with sensors for changing obesity-related behavior among youth is often reported as acceptable [1,39,40,50,54] and preferable over the traditional paper-pencil modality [39,48]. Several user studies have reported that app designers need to pay attention to gender-specific preferences [42], and design to enhance motivation to continue using the application [36]. The ideal amount of engagement time with any specific app or mobile intervention has yet to be ascertained [44]. Finally, the measurement accuracy of apps, for instance, using apps to record dietary intake, needs to be improved [55].

While the evidence is limited to published pilot or feasibility trials, preliminary results suggest that interventions using mobile apps are not only acceptable [39,40,42,45,50], but also potentially effective intervention delivery methods that result in modifications of obesity-related behavior [33,39–41] and the associated psychological antecedents [37,56] in youth. Personalized feedback based on data ubiquitously captured by wearable sensors and participants’ self-reported data shows potential for modifying obesity-related behaviors [1,52,53]. Incorporation of wearable or other deployable sensors [57] will deepen our understanding of the dynamics of obesity-related behaviors in time and context [15]. This understanding will further aid clinicians and researchers in developing personalized, interactive, contextualized feedback necessary to intervene in obesity-related behaviors in real time using JITAls [13]. The incorporation of mobile apps and wearable devices/sensors to treat and prevent pediatric obesity is still a nascent field, and user-centered design is an essential step for program development.
Wearable and Deployable Devices/Sensors in mHealth Pediatric Obesity Studies

The use of real-time feedback has enormous potential for changing obesity-related behaviors in pediatric populations [16]. However, outcomes are dependent on feedback that is developed based on accurate and timely measures of appropriate (to the intervention) user information. Researchers and clinicians have been able to assess study participants’ self-reported behavior and experiences since the introduction of ESM and the invention of early mobile technologies such as PDAs [1]. However, data on key obesity-related behaviors, including sedentary behavior, physical activity, and dietary behavior, are susceptible to biases that stem from self-reporting, including memory lapses and purposeful omission [58]. The objective, accurate, contextualized, and real- or near-time measurement of obesity-related behavior is one of the central promises of mHealth solutions. The incorporation of validated wearable devices will help to realize these promises by providing insight into participants’ behavior with an improved ecological, as well as measurement, validity, and decreased user burden. Measuring complicated behaviors, such as physical activity and dietary behavior, however, is challenging even with wearable sensors. This section will provide an overview of the current use of wearable sensors in measuring key obesity-related behaviors, including physical activity, sedentary behavior, and dietary behavior, in pediatric obesity studies.

A recent review published by Bort-Roig et al. [5] used evidence published through 2013 to systematically examine the current use of technology in measuring and influencing physical activity. Among the 26 unique studies examined, Bort-Roig et al. found that external measurement devices (e.g., pedometers), external (waist- or wrist-worn) acceleration-based motion sensors, and accelerometers inside smartphones are the most commonly used equipment to obtain objective physical activity measurements [5]. Accelerometers, or microelectromechanical systems (MEMS-based accelerometers), are considered the current gold standard for objectively measuring physical activity and sedentary behavior. Accelerometers measure physical activity by converting acceleration captured by built-in transducers into a quantifiable signal [59]. Because many new accelerometers are providing raw data rather than preprocessed data such as “counts,” advanced algorithms, using signals captured by accelerometers, can now be processed to yield excellent measurement accuracy when the accelerometers are worn on the waist or hip areas [5]. Besides triaxial accelerometers, more complex approaches such as on-body sensing with a combination of multiple devices (e.g., an accelerometer with a heart rate monitor, gyroscope, and magnetic sensors) [5,32] and smart watches [5] are available to capture physical activity and sedentary behavior. Wearable technologies such as gyroscopes and magnetic sensors have also shown high accuracy in capturing key physical activity and sedentary behaviors such as sitting, standing, walking, and jogging [5]. However, evidence on using real-time data captured by wearable sensors to prevent and treat obesity in natural settings is limited [5], especially among pediatric populations [1,16]. Although Bluetooth and other wireless data transmission technology is available, to date, there is only one pilot study that has incorporated real-time physical activity data in promoting physical activity in a youth sample [16].

Accurate assessment of dietary intake is one of the greatest challenges in obesity research, and depends on the accurate estimation of portion sizes, the identification of ingredients, and the accurate identification of eating occasions. Accurate measurement, inference, and estimation of dietary intake using wearable and deployable sensors remains challenging [9,60]. Although a majority of efforts have been focusing on using mobile technology to enhance recall-based collection methodologies (e.g., providing visualized examples of portion sizes and fully automated self-administered dietary assessment [1,60]), there is a rapidly growing body of literature focusing on memory-independent collection methodologies using wearable sensors [9]. A recent work by Steele provided an overview of technologies that are currently being used for the automated capture of dietary intake information. Among the current technologies, portion-size estimation has largely relied on pattern recognition and image-analysis approaches [9,61]. Besides portion-size estimation, image analysis has also shown some promise in identifying types of food consumed and nutrient-intake estimation [61]. These data have also been accrued using bar code or quick response (QR) code scanners [9,60]. Nonetheless, as image-analysis approaches mainly rely on food appearance
features (e.g., color, texture, and shape) and largely ignore the structural features of food (e.g., density of the food in the image) [61], there are inaccuracies inherent in intake estimation using this approach. Another drawback of image-analysis approaches is that they require participant compliance; participants must provide a picture of food before and after consumption, and often need to include in the picture a reference card or fiduciary marker [61] as a reference in order to determine absolute size. Other wearable sensors are currently being developed that require less user effort and compliance including the wrist-worn bite counter (although this must be actively turned on by the participant at each eating event) [62], acoustic-based sensing [63], neck-worn, multisensor lanyards, and “smart” kitchen equipment [9]. Among these devices, wrist-worn bite counters and acoustic-based sensors have been able to fairly accurately measure the amount [62,64] or type [63,64] of food consumed. Nonetheless, each approach still faces some technical limitations. For instance, for pattern recognition, identification of the wide variety of food that participants consume in “free-living” situations remains a tremendous challenge. Although evidence on the usability and acceptability of wearable and deployable technologies in estimating dietary intake in youth is limited [1], the use of mobile health solutions do exhibit preliminary efficacy in the objective measurement of key dimensions of dietary intake [9,61,64].

**mHealth Challenges: Moving the Field Forward**

This chapter provides an overview of the current use of mHealth solutions to prevent and treat pediatric obesity. Several mHealth strategies, including the use of personalized feedback and interactive data visualization, have shown preliminary efficacy in changing key obesity-related behaviors and some of their antecedents in pediatric populations. These strategies capitalize on expanding mobile device ownership and the acceptability of using mobile devices as a means of communication. However, to date most mHealth interventions do not yet capitalize on the full capacities of mHealth technology to develop true JITAI's, providing personalized, adaptive interventions at the moment and in the dose and format that is appropriate for each individual. The true potential of mHealth resides in harnessing rich user information that is constantly streaming from and ubiquitously captured by wearable devices, as suggested in studies that incorporate real-time user information into interventions [16]. However, there are a number of challenges associated with capitalizing on mHealth solutions that need to be considered. These challenges include the need for improved transdisciplinary collaborations, a reconsideration of our measurement and modeling paradigms, and the need for agile and adaptive intervention strategies and evaluation methodologies.

**Technology, Transdisciplinarity, and Measurement**

mHealth is an inherently transdisciplinary endeavor, and continuing efforts to develop communications among researchers, clinicians, and engineers are essential for designing effective mHealth systems [4,15,65]. Particularly when working with children and minorities, a user-centered approach in designing mHealth systems can be critical in improving both the quality and the effectiveness of the study. Intended participants and patients with “experiential knowledge” can be considered as another one of the “disciplines” that need to be at the table [1]. Another major challenge associated with mHealth technologies is ensuring the security and privacy of data captured by and transmitted from wearable sensors or personal mobile devices [66]. Although ethical issues in mHealth are beyond the scope of this chapter, disciplines that cover data safety and security, as well as medical and research ethics, should be consulted where appropriate [67].

Ensuring the validity and reliability of data collected via wearable sensors and personal mobile devices is essential in attaining quality of the collected data [4,66]. However, using wearable devices and personal mobile devices for data collection in the free-living conditions of natural environments presents different challenges that cannot be simulated in controlled laboratory settings [4,68]. New data streams also bring new issues in measurement and modeling [15]. Although these new areas of research are beyond the scope of this chapter, one example is that, while ascertaining reliability at
the group level has been a major concern in measurement methodology, data from new technologies are providing unprecedented opportunities to understand the reliability at the individual level that will, in turn, eventually impact on what are considered “good” measures [69].

**Need for New Evaluation Methodologies**

Currently, technology development outpaces the evaluation of mHealth intervention across disciplines [1,4,15,16,26]. RCTs have long been the gold standard for evaluating interventions; however, these typically take years. Technology evolves so quickly that a study technology may be outdated or obsolete prior to the completion of a full RCT [4,70]. Agile research designs and agile evaluation frameworks are needed that can accommodate studies that use the full potential of mHealth solutions. An earlier report by an interdisciplinary group of mHealth researchers outlines various innovative research designs and evaluation frameworks that accommodate these needs [4]. This report presents some of the leading new evaluation frameworks, including multiphase optimization strategies (MOST) [18] and sequential multiple assignment randomized trials (SMART) [71]. These frameworks capitalize on the rapid personalization opportunities offered by new technologies to adapt interventions on the fly according to participants’ incoming data and to improve intervention efficiency by sequentially randomizing participants within the study.

**SUMMARY AND CONCLUSIONS**

This chapter discussed the current state of evidence and current challenges for mHealth pediatric obesity prevention and intervention studies. Innovative technologies have been repeatedly demonstrated to be acceptable and feasible tools for collecting objective, contextualized, and real-time data in youth populations [1]. Emerging evidence from recent pediatric obesity prevention and intervention studies has further suggested that personalizing interventions based on these temporally and contextually relevant participant data, whether it is acquired from self-report or ubiquitously captured by wearable sensors, offers promising strategies to change and maintain obesity-related behaviors [16]. To date, both SMS and mobile apps are commonly used platforms for participants to self-report data in a timely fashion through time-based prompting schemes (e.g., random time or stratified time-block prompting schedules) [1]. Nonetheless, pediatric obesity interventions and behavioral assessment studies based on the use of context-sensitive or “event-based” [6] data, whether via self-report or sensed events and contexts, have progressed at a slower pace [1]. The bulk of prevention and intervention science was necessarily built to seek the one best possible solution for the largest number of people [72]. New technologies can now support interventions that provide the best possible solution for each individual in time and context (JITAIs). Intervention dose, timing, content, and modality can be increasingly tailored according to individual needs and adapted over time as the individual changes [13]. These highly individualized and precise interventions are the very near future of personalized behavioral medicine.

**REFERENCES**


INTRODUCTION AND DEFINITIONS

This chapter introduces a broad range of complementary integrative health approaches to childhood and adolescent obesity. This is a relatively new field, and one with which many in the world of conventional medicine remain unfamiliar. Therefore, before delving directly into the specific modalities, the chapter will first deal with some of the basic concepts and definitions relating to alternative, complementary, and integrative health and medicine.

Multiple terms have been used over the last 20 years to describe the growing use of therapies that have been generally considered nonconventional in the context of Western, allopathic medicine practice. The term alternative medicine generally refers to those therapies and practices that are used in place of conventional medicine, while complementary medicine generally indicates those practices that are used as complements or adjuncts to conventional allopathic therapy. In recent years, the term integrative medicine has generally replaced these older terminologies, as a growing research evidence base has demonstrated the effectiveness of some of these therapies once considered alternative by the conventional medical field [1]. Integrative medicine therefore implies and promotes an integration of all health practices and therapies, whether Western based or complementary, using an integrated approach to the treatment of disease and/or the promotion
of health and wellness in human beings. Integrative medicine also represents an approach to the whole human being—body, mind, emotion, and spirit—recognizing and encompassing emotional, spiritual, social, cultural, and environmental influences on the overall health of the human organism. The term integrative health, in contrast to integrative medicine, may be used to designate those practices that promote health, wellness, and well-being, rather than emphasizing those therapies or medicines that treat specific pathological conditions within the Western medicine paradigm. Finally, integrative medicine/health is generally practiced as a collaborative relationship between the patient and a clinician who understands the benefits of both complementary and Western medicine and can guide the patient toward optimal health by integrating the benefits of both.

Given this general overview, the most widely used definitions today to describe these concepts can be taken from national and international institutions that are leading the field of integrative medicine and health. The National Center for Complementary and Integrative Health, part of the National Institutes of Health, uses the terms complementary health approaches to discuss non-mainstream therapies and integrative health when discussing the incorporation of complementary approaches into mainstream health care [2]. The Academic Consortium for Integrative Medicine and Health views integrative health care as that which promotes dignity and respect, includes a caring therapeutic relationship, honors the whole person—mind, body, and spirit—recognizes the innate capacity to heal, and offers choices for complementary and conventional therapies [3].

Taking all this into account, this chapter will consider integrative approaches to childhood obesity as those patient-centered or relationship-centered therapies that encompass the whole child—mind, body, and spirit—in the promotion of healthy body weight insofar as that is a part of the child’s overall health and well-being. This stands in philosophical distinction to the Western, allopathic model, which identifies obesity as a disease requiring a therapeutic intervention to eliminate it. The chapter will focus on those complementary, integrative modalities and approaches that have been demonstrated to be effective through evidence-based research. Due to the relative paucity of research evidence in children, evidence of effectiveness of some integrative modalities in adults will be discussed, and the chapter will conclude with a discussion of the new directions for research needed to build the evidence base necessary to confidently recommend modalities for obese and overweight children.

**PREVALENCE OF COMPLEMENTARY INTEGRATIVE MEDICINE USE IN PEDIATRICS**

The use of complementary alternative medicine (CAM) or complementary integrative medicine (CIM) in general for all medical conditions has been building steadily over the last 20 years in the United States. The prevalence of CAM use in children has generally been lower than that for adults. For example, in 2007, adult use of CAM therapies averaged close to 40%, with the highest use among Native Americans and Alaskan Natives, and the lowest among black adults [4]. In contrast, about 12% of children had used CAM therapy for any medical condition in the past 12 months, with natural product supplements and mind–body therapies being the most commonly used. Much higher prevalence of CAM use (above 30%) has been reported among children with chronic health problems and in those whose parents use CAM therapies [4–6]. There are no data for the prevalence of CAM use among children specifically for obesity or obesity-related disorders, but it is likely to be relatively low, since the use of CAM modalities in obese adults is known to be similar or lower than in the general population [7].

**INTEGRATIVE ASSESSMENT OF THE OBESE CHILD**

A proper integrative assessment of an obese child should include not only an assessment of dietary intake and physical activity, but should also pay attention to such other lifestyle factors as degree of life stress and other psychological issues, adequacy and quality of sleep, and social factors such
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as food insecurity and access to safe places to play or exercise. Family history, maternal history of obesity or diabetes during pregnancy, and exposure to environmental toxins such as bisphenol are further likely to impact childhood obesity status through genetic and epigenetic mechanisms, though a history of exposure to specific environmental toxins may be difficult to obtain [8].

It has become clear that chronic life stress is another potential factor in the development of obesity and its related complications. It is therefore important that the integrative assessment of the obese child evaluates stressors in the child’s life and the means by which the child manages such stress. Stress results in a preference for and the ingestion of higher calories, more fat, and calorically dense snack foods, as well as in cortisol secretion [9,10]. Studies in primates [11] and human adults [12,13] suggest that chronic stress, via neuroendocrine mechanisms producing hypothalamic–pituitary–adrenal axis activation and subtle hypercortisolism, can result in a pseudo-Cushingoid obesity phenotype characterized by visceral adiposity, insulin resistance, and metabolic syndrome [14]. These factors appear to be present in children as well. Thus, among overweight/obese Latino adolescents, those with metabolic syndrome have higher morning serum cortisol levels [15], and higher serum cortisol predicts future deterioration of insulin sensitivity [16]. Additionally, a blunted diurnal salivary cortisol pattern is linked to increased carotid intima-media thickness—that is, preclinical peripheral vascular pathology—independent of age, height, systolic blood pressure, and ethnicity [17]. Finally, higher morning cortisol levels and dietary sugar intake may interact to promote increased visceral adipose tissue stores [18].

Other psychosocial factors need to be part of the evaluation of the obese child. Decreased sleep duration has been linked to increased body mass index (BMI) in children [19,20]. Depression, history of physical or sexual abuse, disrupted family structure, lower socioeconomic status, food insecurity, neighborhood crime, and gang activity all promote obesity in children and will not easily respond to routine dietary or physical activity recommendations [21]. These factors will generally require attention from other health professionals (e.g., social workers, psychologists) in order to successfully address the psychosocial issue that is physically manifesting as obesity.

SPECIFIC COMPLEMENTARY INTEGRATIVE MEDICINE MODALITIES FOR OBesity

MIND–BODY APPROACHES TO OBESITY IN YOUTH

Mind–body therapies encompass a diverse array of methods that all utilize the connection of mind, imagery, and attention in ways that affect physiological processes. These therapies include guided imagery (GI), mindfulness-based approaches, meditation, hypnotherapy, biofeedback, relaxation training, and others. GI and mindfulness-based approaches, in particular, have been reported on in recent years in the context of childhood and adolescent obesity.

Guided Imagery

GI is a complementary/alternative, mind–body healing modality that typically involves a series of relaxation techniques followed by the generation of mental images to evoke a state of relaxation (i.e., reduced stress) or achieve a specific health outcome (e.g., reduce pain, lower blood pressure, enhance immune function) [22]. GI is also a proven stress management technique in a wide array of clinical circumstances [23]. In adults, GI has been shown to improve unhealthy eating behaviors, including binge–purge activity in bulimia [24].

The potential to change eating behaviors as well as reduce stress makes GI an attractive target therapy for obese children. Stress reduction–GI was found to be an acceptable and well-liked modality in obese Latino adolescents who were previously quite naïve to any mind–body modalities, as well as leading to acute reduction in salivary cortisol levels [25]. A follow-up study in obese Latino adolescents utilized a 12-week guided-imagery intervention in order to reduce stress, as
well as to motivate improved obesity-related lifestyle behaviors. Findings replicated the ability to acutely reduce salivary cortisol levels by approximately 40%, as well as demonstrating significant reductions in sedentary behaviors and increases in moderate physical activity across the 12-week intervention [26]. Larger follow-up studies of this population are currently underway to determine the effects of GI on objective measures of physical activity and eating behaviors, longer-term stress management, adiposity, and insulin resistance.

**INTEGRATIVE LIFESTYLE APPROACHES: NUTRITION, PHYSICAL ACTIVITY, STRESS, AND SLEEP**

The mainstay of conventional management of the obese child remains attention to lifestyle behaviors to improve eating and physical habits. This is true as well in the integrative approach to the obese child. As conventional nutrition and exercise approaches are covered extensively in other chapters of this book, this section will focus on those integrative approaches that move beyond standard “eat less, exercise more” physical activity prescriptions.

**Integrative Nutritional Approaches: Intuitive Eating and Mindful Eating**

It is clear that the first approach to childhood obesity must be to ensure adequate nutritional education for both parents and children. However, it is also clear that nutritional education alone, while absolutely necessary, is unlikely to have a sustainable benefit in terms of weight reduction in most cases. True health behavior change—that is, making healthier eating choices and increasing physical activity and movement—takes motivating internal factors that actually change one’s relationship to the behavior in question.

*Intuitive eating* and *mindful eating* (also referred to as *mindfulness-based eating*) represent two very similar *nondieting* approaches to eating that seek to radically change the relationship of an individual to his or her eating behaviors and choices. Intuitive eating is a nondieting philosophy whose major principles include (1) rejecting the *diet mentality* to give oneself unconditional permission to eat when hungry, and to eat whatever food is desired; (2) using internal hunger and satiety cues, rather than external rules on portion size, to determine when and how much to eat; (3) eating for physical rather than emotional reasons; and (4) seeking satisfaction in the eating experience [27,28]. By supporting autonomy in eating and physical activity decision making, intuitive eating is developmentally ideal for adolescents, for whom the pursuit of autonomy is a critical developmental milestone [29]. Multiple studies in young adults, both cross-sectional and longitudinal, have shown positive associations between intuitive eating practices and lower BMI, improved psychological outcomes, and other physical health indicators [30,31]. When intuitive eating was used as one component of an integrative mind–body intervention in obese adolescents, intuitive eating attitudes and practices were increased, and there were no increases in intake of calories, sugars, or fats despite the nondieting intuitive-eating curriculum [26]. Combined with the findings in adults showing positive relationships between intuitive eating practices and BMI and other health markers, these findings suggest that intuitive eating can be used in obese adolescents without fear of sustained consumption of unhealthy foods or worsening obesity status. Further studies are clearly needed to directly test the intuitive-eating approach against conventional dietary approaches.

*Mindfulness*, a meditation-based mind–body CAM modality, has been defined as paying attention, on purpose, in the present moment, nonjudgmentally, to the unfolding of experience moment by moment [32,33]. One of the key concepts in mindfulness is the lowering of reactivity to stress triggers. Mindful eating, also known as mindfulness-based eating, extends general mindfulness approaches directly to the field of obesity and eating disorders. Mindfulness-based interventions in adults have been found to be effective for obesity and for altering obesity-related eating behaviors such as emotional eating, binge eating, and dietary intake [34,35]. Such approaches have specifically been useful for treating binge-eating disorder [36,37] and obesity in adults [34,38]. A recent report showed that among obese women, a mindfulness intervention for stress-related eating led
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to a reduction in morning cortisol responses, which was associated with a reduction in abdominal fat [39].

With respect to children and adolescents, recent years have seen increases in mindfulness training programs for a variety of clinical conditions [40]. A recent review exploring theoretical considerations for mindfulness training for obesity and obesity-related eating behaviors in youth suggested that improved executive function, increased attentional control, emotional and cognitive flexibility, and acknowledgment of impulses without reaction might all be mental capacities developed through mindfulness that could result in improved eating behaviors and benefits for obese youth [41]. To date, however, there have been no published reports on the effects of mindfulness-based eating interventions in obese children.

Integrative Physical Activity Approaches: Yoga, Tai Chi, and Qigong

Conventional approaches to physical activity are covered elsewhere in this volume. This section covers complementary approaches to movement and physical activity, including yoga, tai chi, and qigong. It must be noted, however, that these practices each involve a major component of mindfulness, and thus, rather than representing a strictly physical activity approach, they each represent an integrative mind–body therapy in and of themselves.

Yoga, though primarily viewed as a movement practice in the Western world, typically involves significant mindfulness, stress reduction, and breathwork, linking all components of mind, body, emotion, spirit, and meaning together, and thus is a fully integrative practice. Early studies suggest that the benefits of yoga in obese adults may include the reduction of BMI and waist circumference and improvements in metabolic outcomes [42–44]. In children, yoga has been reported to reduce stress, improve classroom behavior, prevent eating disorders, foster self-esteem, and have multiple beneficial health effects [45,46]. The minimal information from small intervention studies in obese youth has demonstrated reductions in body fat, BMI, and some lipid parameters [47,48].

Tai chi and qigong represent low-impact movement meditations from the Chinese medicine tradition that each contain both physical activity and mindfulness components. Tai chi has shown reductions in BMI in older adults [49], and adolescents taught tai chi as a “control” exercise intervention showed similar stabilization of body fat during growth to an active kung fu martial arts intervention group [50]. In obese adults with type 2 diabetes, qigong led to reduced weight, waist circumference, insulin resistance, and hemoglobin A1C [51,52]. Studies are absent regarding the use of qigong in obese children or adolescents.

Stress Management

Because of the links between chronic life stress, obesity, and obesity-related morbidities, the assessment and management of stress represents an important part of the integrative approach to the obese child. As discussed in previous sections, most mind–body modalities utilize stress reduction techniques as a major component. These can be as simple as focused breathing, which has been used successfully to reduce stress and stress biomarkers such as cortisol in children for a variety of clinical conditions, including obesity [26]. Other integrative stress management activities, such as music, exercise, gardening, or hobbies can be recommended as determined in collaboration with the individual child or adolescent. These need to be determined collaboratively in the integrative assessment of the child, listening closely to the child’s narrative of what he or she has previously found useful in managing stress, and then tying that activity into the overall obesity prescription.

Sleep

As reviewed in Chapter 28, sleep is another critical piece of lifestyle behavior that is often overlooked in the assessment of the obese child, despite clear evidence that decreased sleep duration is
associated with both increased BMI and insulin resistance [19,53,54]. Recommendations to improve sleep quality and duration should thus be given as part of obesity treatment.

**Herbs/Botanicals and Dietary Supplements**

Dietary supplements are the most common CAM approach used by obese adults [55]. However, the majority of weight loss supplements advertised and sold have not been demonstrated to be effective and safe in adults, much less in children [56,57]. In adults, some data for modest effects on weight reduction exist for fiber supplements and green tea catechins [58]. Glucomannin and other soluble fiber supplements have been found to be of benefit in weight management in adults [59]. The data are inconclusive or negative for other common supplements such as chromium picolinate, chitosan, conjugated linoleic acid, or *Garcinia cambogia* (hydroxycitric acid) [60].

There is evidence to support a number of herbal therapies in adults with obesity-related complications such as metabolic syndrome and type 2 diabetes. Thus, ginseng (*Panax ginseng*), green tea (*Camellia sinensis*), milk thistle (*Silybum marianum*), and nopales (prickly pear) cactus have all shown glucose-lowering effects in type 2 diabetes or other benefits in obesity-related conditions [61]. Cinnamon has been shown in animals to increase insulin sensitivity, and a recent meta-analysis concluded it has a significant, though modest (~9 mg/dL), effect on reducing fasting glucose values in adults with type 2 diabetes or prediabetes [62]. Finally, preliminary evidence suggests a possible role for other supplements in treating obesity-related insulin resistance and/or type 2 diabetes, including vitamin D, folate, B12, B6, and zinc [1].

Few of these herbal products have been investigated in children with obesity, prediabetes, or diabetes. Zinc has been found to reduce fasting insulin and glucose levels in obese prepubertal children [1]. Fiber supplements have been considered for weight loss in children. The rationale for the use of fiber is supported by the long-known weight loss effects of diets high in fruits and vegetables in children [63]. In general, the current state of knowledge would suggest that fiber is beneficial to children as part of a good healthy diet, and that the major beneficial source of fiber remains natural food sources. The role of additional fiber supplementation beyond dietary fiber in children remains to be determined.

In summary, it is important to state that the evidence to date is not strong enough to clearly establish herbal and dietary supplements as effective therapies in obese children, and there is an absence of good data on the safety profiles of most dietary supplements in children.

**Body-Based Integrative Therapies: Acupuncture, Chiropractic, Osteopathy, and Massage**

Among these body-based integrative therapeutic approaches to obesity, an evidence base exists only for acupuncture. Acupuncture, though grouped here in the category of body-based approaches, is often instead categorized as a mind–body integrative intervention. Recent meta-analyses and systematic reviews have shown that acupuncture results in significant weight loss (approximately 1.7–4 kg) compared with either sham-treated or lifestyle controls [64,65]. However, most previous trials suffer from suboptimal design and small numbers. There are few data on the use of acupuncture in children, though one uncontrolled, longitudinal study showed significant reductions of 3.5% in BMI (29.03–28.08 kg/m²) and 16% in visceral adipose fat volume (measured by magnetic resonance imaging [MRI]) in children undergoing acupuncture for obesity [66].

**Narrative Medicine and Integrative Behavioral Approaches**

These approaches are difficult to categorize in the usual framework of what are considered integrative modalities. Nonetheless, these represent approaches that may hold future promise for obesity treatment in children and teens. Narrative medicine encompasses the field of personal story and
how it may relate to healing [67]. Having patients tell their story to the clinician, to peers, to family members, often in writing, helps the person feel heard, promotes self-understanding and insight, helps the clinician understand the individual nuances involved, and promotes a much deeper rapport and relationship from which to engage the salient issues. Integrative behavioral approaches include such modalities as motivational interviewing, integrative health coaching, support groups, and other group approaches. Motivational interviewing represents a behavior modification approach that has been used with success in obese adults, and has also been incorporated into pediatric obesity interventions [68,69]. Self-help support groups have been utilized in obesity treatment programs and are highly valued by participants [70]. Finally, the facilitated group process of council, based primarily on Native American processes and preliminarily shown to improve well-being and psychosocial outcomes in young adults with diabetes [71], could readily be applied to the treatment of obese adolescents. All of these behavioral approaches rely on the building and nurturing of relationships between patients and intervening professionals, and the use of the integrative model of collaboration and promotion of whole health rather than the disease-based allopathic approach to the individual child with obesity. Much more future research is needed to determine the ultimate benefit of these integrative behavioral approaches.

CONCLUSIONS

It is clear from the discussion in this chapter that while complementary integrative therapies present a promising and hopeful philosophical approach to the obese child or adolescent, for most of the integrative modalities there remains too little evidence base at this time to strongly substantiate the benefits of their use. Despite this, many of these therapies offer promising potential benefit with very little risk in terms of adverse side effects, particularly among the mind–body and integrative-lifestyle modalities. Such therapies can be used in individual children as part of an integrative approach to their obese condition, as long as reasonable discussion is undertaken between the health-care provider and the child/parent in terms of what is known and what remains unknown with respect to any given integrative therapy. Thus, using the integrative health model of assessment and treatment, a collaborative approach can be utilized that takes into account the whole child, addressing obesity as one physical aspect of the child’s whole being—mind, body, emotion, and spirit. Such an approach can help minimize the stigma of obesity in the mind of the child, deflect attention from any failure to lose weight immediately, and launch the child on a personal journey to health and wellness, which over the long term can improve the obese child’s well-being and potentially his or her overall health, whether or not the obesity itself is reduced. Clearly, much more research is needed in the area of integrative obesity management of children and adolescents in order to substantiate the potential benefits offered by the various forms of integrative therapies. This represents a wide-open area of investigation for those physicians and scientists interested in pursuing an integrative approach to childhood obesity.

REFERENCES

Section VI

Public Health and Policy Based Interventions
The marketing of foods and non-alcoholic beverages with a high content of fat, sugar or salt reaches children throughout the world. Efforts must be made to ensure that children everywhere are protected against the impact of such marketing and given the opportunity to grow and develop in an enabling food environment—one that fosters and encourages healthy dietary choices and promotes the maintenance of healthy weight.

Dr. Ala Alwan

Assistant Director-General, World Health Organization, 2010 [1]

INTRODUCTION

The prevention of child overweight includes moves to encourage children to eat a healthy diet, and in most countries of the world the national food-based dietary guidelines recommend plentiful consumption of fruit, vegetables, pulses, and wholegrain foods, while recommending limiting the consumption of energy-dense, micronutrient-poor processed foods. Yet, in most countries, the mass media shows high levels of commercial promotion of energy-dense foods and relatively little promotion of more healthful foods. In this chapter, we consider current moves to limit children's exposure to such commercial messaging and to rebalance commercial rights in favor of the reduction of risks to children.

POLICY CONTEXT

For more than two decades, concern has been expressed about the commercial promotion of food and beverage products, especially when those products have a nutritional profile that may undermine the healthfulness of diets, and which are not recommended for increased consumption in national dietary guidelines. Campaigns by civil society organizations to restrict the promotion of such unhealthy foods and beverages date back at least to the 1970s and have gained increasing support as
the rise in diet-related chronic disease has an impact on health service costs and economic output, in developed and developing economies alike.

“Marketing approaches matter for public health,” stated the then director-general of the World Health Organization, Dr. Gro Harlem Bruntland, addressing the World Health Assembly in 2002. “They influence our own—and in particular our children’s—patterns of behavior. Given that they are designed to succeed, they have serious consequences for those at whom they are targeted” [2]. This statement triggered official recognition in WHO member states that the promotion of foods that undermine healthy choices represented a major threat to population nutrition security. It was followed a few months later by the WHO’s Technical Report 916 [3], which considered the evidence on the nature and strength of the links between diet and chronic diseases, and which classified as “probable” or “convincing”:

- The adverse effect of high intake of energy-dense, micronutrient-poor foods
- The adverse effect of high intake of sugar-sweetened beverages
- The adverse effect of heavy marketing of energy-dense foods and fast-food outlets

The technical report was followed by a “Global Strategy on Diet, Physical Activity and Health,” endorsed by the World Health Assembly in 2004 [4], which explicitly stated that food advertising influences dietary habits, and that “messages that encourage unhealthy dietary practices or physical inactivity should be discouraged, and positive, healthy messages encouraged.” It urges governments to work with stakeholders to develop “multisectoral approaches to deal with the marketing of food to children and to deal with such issues as sponsorship, promotion and advertising.”

While policy development was being urged by health advocates and by international health organizations, national governments faced resistance from commercial operators, and in order to take action, needed more concrete evidence to show that market interventions could be justified. For example, one of the counterarguments suggested that advertising of products served only to encourage an exchange from one brand to another, and did not increase overall consumption. The evidence, however, showed that marketing served to increase product sales not only through competition with similar products but also through increased sales of the entire category. A systematic review conducted in 2003 for the UK Food Standards Agency (FSA), concluded:

> Overall, there is evidence that food promotion causes both brand switching and category effects, with stronger support for the latter effect. Although no study provides a thorough comparison of the strength of both types of effect, both types of effect have been examined independently, and there is reasonably strong evidence that both occur. In other words, the effects of food promotion are not limited to brand switching [5].

A second evidence review undertaken by the US Institute of Medicine in 2005 [6] found evidence that television advertising had an impact on overall diet in the short term for children aged 2–11 years, with insufficient evidence for older children. There was also moderate evidence of long-term effects on children aged 6–11, with weak evidence of long-term effects on younger children and weak evidence of no effect for older children. The review also noted strong statistical associations between higher exposure to television advertising and obesity in children aged 2–11 and in youth aged 12–18 years.

Subsequent reviews have largely confirmed and strengthened these associations. A systematic review published by the World Health Organization in 2009 [7] supported the findings of the UK and US reports, and a further review of reviews published in 2013 concluded:

> Food promotions have a direct effect on children’s nutrition knowledge, preferences, purchase behaviour, consumption patterns and diet-related health. Current marketing practice predominantly promotes low nutrition foods and beverages. Rebalancing the food marketing landscape’ is a recurring policy aim of interventions aimed at constraining food and beverage promotions to children. [8]
Several countries have responded with varying degrees of regulatory action. In the United Kingdom, the communications-regulating agency Ofcom introduced a set of measures implemented over the period 2007–2009 [9] that restricted television advertising for specified foods during children’s programming: the age of a child was specified as 16 years, and the definition of the food products that could be advertised was the first example of a nutrient-profiling system defined by a government agency to distinguish acceptable and unacceptable products, based on diet-related public health criteria. In Spain, the government initiative Código PAOS (Código de Corregulación de la Publicidad de Alimentos y Bebidas Dirigida a Menores, Prevención de la Obesidad y Salud) [10] consisted of a coregulatory action in which the industry operated a set of definitions and monitored compliance, with government oversight. A similar procedure was developed in Denmark [11]. Several such statutory actions by governments and coregulatory actions (government-agreed, industry-run initiatives) have been developed in several countries in the last decade (see Table 41.1).

Across the globe, sections of the food industry have recognized the need to respond, and some of the largest food-producing companies have offered voluntary pledges to limit their marketing activities in several regions around the world, from 2006 onward [14]. These moves have been welcomed for showing willingness to act and as a method for addressing cross-border advertising concerns. The details have, however, been criticized by civil society organizations on several counts, including the lack of an enforcement structure, the nonbinding nature of the pledges, the lack of application of the pledges to nonsignatory companies, the low threshold for allowing advertising, the limited number of food products that are excluded by the nutritional criteria, the narrow

<table>
<thead>
<tr>
<th>Country, Year of Implementation</th>
<th>Regulatory Controls</th>
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<tbody>
<tr>
<td>Iran, 2004, 2014</td>
<td>Statutory prohibition on broadcast advertising of soft drinks; proposals to prohibit 24 food products.</td>
</tr>
<tr>
<td>Spain, 2005</td>
<td>Coregulation operated by food industry with government oversight; restricts marketing specified foods and beverages.</td>
</tr>
<tr>
<td>United Kingdom, 2007, 2008</td>
<td>Statutory prohibition of the advertising and product placement of specified foods during TV and radio programs with 20% more viewers under 16 years old relative to the general viewing population.</td>
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<tr>
<td>Denmark, 2008</td>
<td>Coregulation operated by food industry under government approval; restricts promotion of specified food and beverages to children aged 13 and under via media including TV, radio, Internet, SMS, newspapers, and comic books.</td>
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<tr>
<td>South Korea, 2010</td>
<td>Statutory prohibition of TV advertising of certain categories of food 5:00–7:00 p.m.; further restrictions on advertising on radio and Internet.</td>
</tr>
<tr>
<td>Ireland, 2013</td>
<td>Statutory prohibition of the advertising, sponsorship, teleshopping, and product placement of certain foods during TV and radio programs where over 50% of the audience are under 18 years old, and at any time a restriction of such advertising to no more than 25% of total advertising.</td>
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<tr>
<td>Norway, 2013</td>
<td>General statutory prohibition on advertising to children, with additional coregulatory agreement on the promotion of specified foods and beverages in a wide range of media.</td>
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<tr>
<td>Mexico, 2014, 2015</td>
<td>Statutory prohibition on advertising certain foods and beverages 2:30–7:30 p.m. on weekdays and 7:00 a.m.–7:30 p.m. on weekends, if over 35% of the audience is under age 13.</td>
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definition of advertising, and the restricted set of media (primarily TV and some Internet activities) included in the pledges [15].

**PROMOTIONAL METHODS**

The promotion of food products toward children occurs in a variety of forms and in many different settings. Parental food messages are among the first and continue to be significant throughout childhood. Messages from schools are also important and carry cultural significance, as they are in effect authorized by a school’s staff, the governing body, and the educational authority. Messages from peers become increasingly influential as children mix socially and develop friendship networks and group loyalties.

Messages from commercial interests are also important, and recent scientific research has strengthened the evidence base demonstrating links between the exposure of children to marketing messages and consequential changes in their dietary behavior, thus reinforcing the case for intervention. At the same time, the technology for advertising has changed, with new and rapidly expanding forms of media (digital TV, online marketing, cellphones and smartphones, and social networking) becoming available to larger numbers of children and offering low-cost, effective means of reaching them directly for marketing purposes.

Food purchase choices and food consumption behavior depend on a range of external factors, including price, availability, and adequate information about the products, as well as the individual’s personal preferences and cultural values. For both adults and children, food marketing can influence all these factors: prices (e.g., through promotional “special offers” and discounts), availability (e.g., through positioning at the checkout), information (generally through food advertising and specifically through, e.g., health claims), presentation (e.g., the packaging, labeling, and formulation of the product), personal taste (e.g., through the use of coloring or flavoring additives in the foods), and cultural values (e.g., through the use of celebrities and sports personalities in product promotions).

Messages are delivered by food producers and food service operators as part of their general marketing strategy. Promotional marketing is an economic activity in which organizations promote demand for their goods or services, using paid-for advertising in third-party media or internal activities such as company-owned websites and product and packaging design. Examples of the various ways in which commercial messages about food and beverage products may be delivered are shown in Table 41.2.

**EXTENT OF ADVERTISING**

Food and beverage advertising during both children’s and family TV schedules and during peak and nonpeak viewing hours is largely for unhealthy foods [17–19]. An international survey [17] examined TV food advertising to children in 11 different countries—Australia, Brazil, Canada, China, Germany, Greece, Italy, Spain, Sweden, the United Kingdom, and the United States—and found that, during peak children’s viewing time on the three commercial channels most watched by children, food advertising comprised 11%–29% of total exposure to advertising. The proportion of advertisements for unhealthy foods varied between countries but was always the dominant form of food advertising, with little airtime devoted to the promotion of healthy products. Items such as fast food, sugar-sweetened beverages, high-sugar breakfast cereals, cookies, salted snacks, sweet desserts, and confectionery dominate advertising during children’s peak viewing times. While advertisements directed at children and at adults differ in theme, they differ little in nutritional value [20], with food products and restaurant experiences being marketed to children on themes of fun and taste, often featuring promotional characters and cartoon animals of particular appeal to children and adolescents [21].

A high level of advertising for unhealthy food has been seen during children’s viewing in the United States [22] during a period when voluntary pledges by the food and beverage industry were supposed to reduce children’s exposure to such marketing. In the United Kingdom, between 2008 (a period of partial regulation) and 2010 (when full regulation was effective) there was a clear fall in
TABLE 41.2
Examples of Media through Which Children Are Exposed to Product and Brand Promotion

**Broadcast**
- TV and radio advertising
- TV and radio program sponsorship
- TV program product placement

**Nonbroadcast**
- Cinema advertising
- Film product placement
- Posters and advertising boards
- Print media: e.g., magazines and comic books
- Branded books: e.g., counting books for preschoolers
- Internet: e.g., email clubs, chat rooms, free ringtones
- Websites: e.g., puzzles, interactive games
- Promotional sales by telephone
- Text messaging to mobile phone
- Direct marketing: e.g., home catalogs, mail shots, leafleting
- Sponsorship of events and venues
- Sponsorship of teams and sports “heroes”
- Cross-branding of logos on household goods
- Branded toys: e.g., a fast-food store as a playhouse
- Branded computer games, product placement in computer games

**In Store**
- On-shelf displays
- Displays at checkout till
- Special offers and pricing incentives
- Purchase-linked gifts, toys, and collectibles
- Free samples and tastings

**On Or in the Product**
- Product formulation: colors and shapes
- Product portions: e.g., “king size”
- In-pack promotions: e.g., gifts, vouchers
- On-pack promotions: e.g., games, puzzles, vouchers
- Packaging design: Imagery, colors, play shapes

**In School**
- Sponsorship of educational materials and equipment
- Vending machines in schools and youth clubs
- School participation in promotion and sampling schemes

food advertising during children’s TV programming but no reduction in food and beverage advertising during family scheduling, which is when most children are watching television.

Analyses of trends in expenditure on food and beverage advertising to children in the United States indicates that TV expenditure is falling, but children and teens still see 12–16 TV advertisements per day for products generally high in saturated fat, sugar, or sodium [22,23]. In addition, marketing using newer digital media is increasing, as is expenditure on advertising using product placement, movies/videos, cross-promotion licenses, athletic sponsorship, celebrity fees, events, and philanthropy [23]. Content analysis of food and beverage advertising on popular children’s websites found 84% of products were high in fat, sugar, and/or sodium [24], while food companies’ own websites can be highly attractive to children but promote nutritionally poor choices [25].

In a study conducted in Canada [26], 24 websites sponsored by 10 food and beverage companies (all of which were members of the Canadian Children’s Food and Beverage Advertising Initiative [27]) were examined, and most (83%) were found to target children below the age of 12 years. Half of the websites had a mechanism for children to recommend them to a friend. Brand and product imagery permeated all these sites, with spokescharacters (brand equity characters) being by far the most common device used. Brand logos appeared and were used to link to games, as game pieces, scenery, and as game “buttons.” This is of some concern, as this age group may lack the ability to recognize advertising content on the Internet compared with broadcast media.

A systematic review published in 2013 of children’s exposure to the marketing of foods and beverages found that high levels of advertising of less healthy foods continue to be found in many different countries worldwide, despite the evidence provided in industry-sponsored reports that indicates a remarkably high adherence to voluntary codes [28]. The authors concluded “adherence to voluntary codes may not sufficiently reduce the advertising of foods that undermine healthy diets, or reduce children’s exposure to this advertising.” A second review reached similar conclusions: “Statutory regulation could reduce the volume of and children’s exposure to advertising for foods HFSS, and had potential to impact more widely. Self-regulatory approaches showed varied results in reducing children’s exposure” [29].

**EFFECTS OF ADVERTISING**

The 2003 systematic review of the impact of advertising on children’s food preferences, choices, and diets, undertaken for the UK FSA noted earlier [5], identified over 29,000 potentially relevant papers, from which it selected 55 of sufficient relevance and quality. The Institute of Medicine, in its 2006 report, based its conclusions on 155 relevant papers [6]. The subsequent decade has seen a substantial increase in scientific research specifically examining the extent of food advertising and brand promotion, children’s recognition and understanding of advertising messages, and the effect of advertising on children’s preferences, eating patterns, and dietary behavior. We give a brief narrative summary here.

The recognition of commercial brands and logos starts early in childhood and by the age of 4 years is associated with different expressions of eating behavior and weight status. Robinson et al. [30] showed that brand imagery on food packaging affects children’s perceptions of the taste of food they are eating. Forman et al. [31] showed that overweight children in particular react to branded food packaging by increasing their food consumption. The inclusion of licensed characters (such as those from children’s films) on food product packaging improves children’s ratings of the product’s taste [32,33].

There is a strong link between TV viewing and obesity in children. Using data collected in a survey of TV advertising to children, Lobstein and Dibb [34] compared the prevalence of overweight among children in nine participating countries with the extent of advertising of energy-dense foods, and the extent of advertising of healthier foods and nonfood products. They found a significant positive correlation between overweight prevalence and the promotion of energy-dense foods but a weak negative correlation with the promotion of healthier foods and nonfood products, indicating
a specific association with the types of products being advertised. More direct evidence of a link is shown in one study [35] in which viewing of advertisements was a predictor of subsequent excess body weight, even when physical activity and eating in front of the TV were taken into account. These data indicate the powerful influence of the commercial content of TV on children's health.

The quantity of TV viewed may be an indicator of susceptibility to advertising. A study in the United Kingdom found that the food preferences of children and young adolescents who habitually viewed a large amount of commercial TV were more affected by experimental exposure to food advertisements than those of children who watched less commercial TV [36]. This was particularly apparent in their selection of branded food items following the viewing of food advertisements. Parental concern may not help and could make matters worse: a study in the United States [37] found parental input to have little impact on food choices following exposure to advertisements, and a Dutch study [38] found that children reporting the highest maternal encouragement to be thin ate the most food when exposed to advertisements for energy-dense products in the absence of their caregivers.

The effectiveness of advertising may lie outside direct cognitive control, especially for those most susceptible. A study by Bruce et al. [39] of neural responses to images of food brand logos showed greater motivational responses from children who were obese and greater cognitive control responses from children of normal weight. There is evidence that children at least as old as 12 years may not recognize online advertising for what it is [40]. A Swedish study using eye tracking showed that while adolescents (14–16 years) were surfing the Internet, food and beverage advertising had a relatively greater impact on their attention than other forms of promotion [41]. The adolescents were unaware of much of the advertising to which they had been exposed.

**RIGHTS AND RISKS**

The protection of children from exploitation has a long legislative history. Marketing to children has been described as inherently exploitative because children may be incapable of discerning its commercial intent and yet are susceptible to its influence [42]. A rights-based approach builds on the United Nations Convention on the Rights of the Child [43], the right to adequate food [44], and the right to freedom from obesity [45]. The rights-based approach is based on the concept of a civilized society’s responsibility to protect its citizens, especially the more vulnerable.

An alternative is the risk-based (or risk/benefit-based) approach, where an attempt is made to weigh up the multiple likelihoods of harm and benefit in terms of outcomes, to minimize the risk of harm and maximize the benefit. It recognizes conflicting interests and the costs to different stakeholders, and the need for proportionate action to balance commercial and economic costs against health gains.

In the World Health Organization’s 2010 recommendations on marketing to children [46], the approach is primarily one of reducing health risks while not constraining responsible marketing. Specifically, the document calls on member states to adopt policies that reduce the extent of exposure to, and the power of, marketing messages that promote the consumption of “foods high in saturated fats, trans-fatty acids, free sugars, or salt” in order to reduce the risk of noncommunicable diseases.

Risk-based policies have been enacted in France, the United Kingdom, and several other countries (see Table 41.1). A rights-based approach is more comprehensive in nature and can be more easily formulated. A risk-based approach has to define which marketing messages are and are not allowable, based on an evaluation of the likelihood of harm, and it has to specify the products permitted to be advertised, the age group whose exposure is being protected, and the methods, media, and messages being used. Such a risk-based set of specifications may also need to be set against costs and an evaluation of the proportionality of the market restriction in order to justify the measures taken; an example of this is provided by the UK communications regulator, Ofcom [47].
A rights-based approach usually puts human health and well-being ahead of economic interests and so is likely to be intrinsically more favorable to the protection of children, whereas a risk-based approach offers some protection to the free working of markets and commerce. In practice, rights-based policies have already been enacted in several countries to protect children from commercial marketing messages generally, including Canada (the province of Quebec) and Sweden. A broadening of the rights-based approach to justify restrictions of the commercial promotion of unhealthful food products has been recommended by several international civil society organizations and supported by leading international lawyers, including UN special rapporteurs on cultural rights [48], rights to health [49], and rights to food [50].

REFERENCES

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INTRODUCTION

The opening article of the second Lancet “Obesity” series describes the false dichotomies behind conventional approaches to obesity prevention [1]. These false dichotomies include either/or arguments around the significance of individual responsibility or government policies, prevention or treatment interventions, and public- or private-sector actions, for example. However, as this and other papers [2–6] in the Lancet “Obesity” series point out, the reality is that solutions to the obesity problem require the integration and coordination of all these approaches. Nevertheless, how these diverse approaches can and should be integrated remains a daunting challenge. This dilemma lies at the heart of the complexity of obesity. Systems approaches provide a way to address this dilemma.

In the last decade, there has been increasing interest in the concept of systems approaches to obesity prevention and control. The term systems science in the context of obesity and chronic disease was first coined and solidified by the Office of Behavioral and Social Sciences Research at the National Institutes of Health (NIH) [7]. Although the science of systems approaches to complex problems has been in development since at least the mid-twentieth century, its introduction to the chronic disease–prevention field has been fairly recent. Many competing schools of thought and methodologies exist within the broader field of complexity science. In an effort to bridge these differences and adopt a more applied approach to solving modern-day public health problems that seem so intractable, the NIH proposed a relatively neutral term—systems science—to embody the overarching principles and methods of complex systems as a whole.

Around the same time as systems science was introduced to the biomedical and public health research community, the Eunice Kennedy Shriver National Institute of Child Health and Human
Development at the NIH hosted an international conference entitled “Beyond Individual Behavior: Multidimensional Research in Obesity Linking Biology to Society.” This was the first attempt at the NIH to bring together basic, clinical, population, and policy scientists, along with representatives from government and industry, to discuss how interconnections across these diverse silos could be cultivated and how a new roadmap for childhood obesity prevention and control could be developed through a systems lens. The conference yielded insights into new cross-disciplinary research questions, the need to integrate individual and policy research, the capacity required to undertake such a systems approach, and the importance of learning from a global mindset [8,9]. A subsequent series of papers stemming from this discussion focused in greater detail on how biology–society interactions [10], developmental trajectories [11], and multistakeholder partnerships [12] could all cohere around a common systems framework [9].

Much progress has occurred since the 2000s on the field’s thinking around systems approaches to obesity prevention and control. The goal of this chapter is to review and summarize the complex dimensions of childhood obesity, how systems thinking and systems insights can inform innovative solutions, and how to implement a systems framework in real-world settings.

**CHILDHOOD OBESITY AS A COMPLEX PROBLEM**

The UK Foresight Programme first published the complexity map of obesity in 2007 (Figure 42.1) [13]. This map illustrates several features that are inherent in a complex problem. First, there is a great deal of heterogeneity in the actors, factors, and sectors that contribute to energy balance. The map shows how energy intake and output are connected to, for example, the food and the built environment; diverse social, economic, and political forces; and multiple institutions and sectors that have greater control over these environmental dimensions than individuals alone. Many publications on obesity in the last decade have focused on dissecting this heterogeneity; fewer, however, have focused on how the heterogeneous components are linked [9]. This leads to the second obvious attribute in the map—that is, the multiplicity of feedback loops that connect these actors, factors, and sectors. These feedbacks give rise to system behaviors that are not simply the addition of all the system’s parts—also known as emergence. The phenomenon of emergence makes it difficult to use traditional reductionist methods to isolate cause and effect. In addition, feedbacks in a complex system create delays in system behaviors. Much as how there is a delay in getting hot water when we turn on the faucet, delays are everywhere in a social and public health system. Consideration of delays is critical for intervention design so that undesirable delays in effects can be managed and appropriate outcomes to capture intervention effects within a specific time horizon can be selected.

The heterogeneity and feedbacks in the complex system of childhood obesity contribute to the formation of highly interactive and dynamic networks of actors and actions. Recent research has shown how obesity in the population “spreads”—or emerges—through such a network effect [14]. The complexity of this effect is that individuals are usually embedded in multiple networks that may all influence individual energy intake and output. For example, a recent paper showed the simultaneous effect of peer and parental influence on children’s unhealthy behaviors and how this in turn affects prevention and treatment intervention outcomes [15]. Another aspect of network complexity is the fact that they are dynamic, meaning they change, learn, and adapt over time. Just as the body adjusts its energy metabolism, where diet- or physical activity–induced weight loss occurs in a downward exponential fashion and eventually plateaus after 3–4 years [16], a social system also adapts to changes in the actors, factors, and sectors involved over time. This has important implications—such as how obesity intervention strategies should be combined and sequenced—that need to be considered a priori. The obesity field is quite far yet from taking obesity intervention research to this next level, but there are emerging methodological advances in adaptive interventions—albeit limited to experimental models thus far—that can be of utility [17].

Predicting system behaviors is challenging. As such, public health researchers and practitioners often cannot anticipate the unintended consequences of obesity interventions. Yet,
unintended consequences occur more frequently than we think. In the 1980s and 1990s, there was a strong public health emphasis on reducing fat intake because of research showing its association with heart disease and the fact that fat carried more calories per unit than other macronutrients. Inadvertently, the industry responded by reformulating packaged foods with less fat but more sugar to preserve the palatability, consistency, and texture of manufactured foods. As a result, while fat intake in the United States plateaued during this period, sugar intake went up [18]. Recently, the United States Department of Agriculture (USDA) introduced new school breakfast and lunch guidelines to add more fruits, vegetables, and whole grains and reduce sodium in students’ diets. No one in public health would dispute this as a sound and needed change in policy. However, no one anticipated the backlash that came from students and school food service personnel alike in response to the changes. Videos from high school students suggesting the new guidelines were making them go hungry went viral. The backlash eventually led the USDA to revisit and revise some of the guidelines to give more flexibility to some of the more stringent criteria. Although some may argue that the backlash was short-lived, as students and school personnel eventually moved on, the ramification of this has been much more broad reaching. At the time of this writing, a fight over the renewal of the child nutrition programs is looming large in the US Congress [19].

Given these important attributes of a complex problem, we need new thinking and new tools to address childhood obesity. Approaches attempted to date have been large in quantity and diversity. However, a high prevalence of childhood obesity persists in most developed countries and is growing in many developing ones [20]. Note that although childhood obesity is a multilevel problem by nature (linking biological and societal factors), taking a systems approach is not necessarily the same as taking a multicomponent, multisetting, or multilevel approach. Current approaches encapsulate more the latter than the former. Systems approaches go beyond addressing the main effects (isolated causal factors) that exist at each level of a socioecological model [9]. Rather, systems approaches relate to intervening directly on the feedbacks, structures, and goals of a system. In so doing, a fundamentally different set of questions emerges. In the following sections, we will illustrate how systems thinking informs innovative solutions for childhood obesity.

**DESIGNING SYSTEMS CHANGE STRATEGIES**

Building on earlier work by Meadow [21], Finegood [22] has proposed a useful framework to think about systems intervention strategies. Through a systems lens, obesity interventions can be roughly categorized into five different systems dimensions: elements, feedbacks, structures, goals, and paradigm of the system. The complexity of the task increases as we move along this spectrum, but the impact on systems change also increases. Most of the research to date has focused on system elements (i.e., main-effect risk factors), as these are the easiest to identify and target. In the last 10 years or so, there has also been a push in strategies related to environmental and policy change with the hope that we can modify the system’s structure to make healthy eating and active living the default behaviors. However, the problem in this effort is that little attention has been paid to feedbacks or goals within the system simultaneously. As such, traction around environmental and policy change has been very limited. While we do not attempt to cover all the possibilities on how to leverage systems dimensions for change, we offer some examples here to illustrate these dimensions, with a focus on systems dimensions other than elements.

**INTERVENING ON FEEDBACKS IN THE SYSTEM**

Feedback mechanisms regulate systems by providing “information” to the source of an action about the outcome of the action [23]. Interventions at this level can change the structure, flow, or strength of information channels within a system. Feedback interventions can enhance positive feedback mechanisms, disrupt negative feedback mechanisms, or create new feedback loops.
Intervening on feedback mechanisms is not necessarily a new approach to childhood obesity prevention and reduction. However, most of the attempts to date have focused on individual-level information feedback, with the assumption that information alone, along with rational mental processing, would lead to behavior change. For example, interventions based on cognitive behavioral therapy (CBT) help participants better understand and change the thoughts, attitudes, or expectations that influence their actions and well-being, thereby altering the psychosocial feedback mechanisms related to health behaviors [24–28]. Other intervention strategies with modest success have focused on stimulus control (i.e., disrupting an obesogenic feedback) or self-monitoring (i.e., establishing a new information feedback loop) of weight, eating, and physical activity [29–34]. Mindfulness-based interventions have gained popularity in recent years, and preliminary findings appear to be positive [35,36]. Biofeedback therapies provide another example of existing interventions at the individual level that may help mitigate the stress-coping mechanisms associated with obesity. Visual biofeedback (e.g., electrodermal activity) paired with food stimuli has shown positive effects on food-related self-efficacy and perceived stress in obese adults by desensitizing the reward value of food or redirecting coping strategies among participants [37]. A similar approach has shown potential benefits in girls with anorexia [38], but the impact on children with obesity is unknown.

The impact of interventions targeting feedbacks can be enhanced if such feedbacks are reinforced by additional social or environmental strategies. For example, it has been shown that the facilitation of social support further increases the effectiveness of CBT-based interventions on reducing child adiposity and obesogenic behaviors [26,39–41]. Other novel, promising strategies include Pushcart, an app being developed by the Small Data Lab at Cornell Tech, which harnesses consumer information through online grocery purchases (popular in many large US cities) and maps this information to users’ health goals (e.g., fruit and vegetable servings per week) to guide future food purchases [42]. Presumably, such a system can incorporate nudging or choice architecture principles in a virtual environment to prompt consumers with specific purchase options that are more likely to help them meet their dietary goals, thus reinforcing the positive information feedback loop toward greater behavior change. Recently, the Children’s Use of the Built Environment (CUBE) study showed that adolescents increased their physical activity when GPS- and accelerometer-captured activity patterns were fed back to participants along with strategies for increasing physical activity within the context of each participant’s built environment (e.g., taking a different transit path) [43]. The same researchers are exploring scaling this up and adding social networking and environmental change opportunities to such a feedback platform [44].

Sometimes, when we intervene on system feedbacks, especially feedbacks at an institutional or community level, such interventions over time alter the structure of the system. For example, farm-to-school initiatives create a new demand–supply feedback loop at the local level in hopes of improving student awareness of where foods come from and increasing access to fresh ingredients in school meals [45,46]. Though currently still experimental on a small scale, there is a broader local foods movement that can shift the structure of the food value chain [47]. Calorie menu-labeling initiatives add transparency to foods at the point of purchase; however, the greatest impact of such initiatives may not be at the level of individual purchase behavior but rather at the level of food reformulation by restaurants [48–51].

**Intervening on Structures in the System**

Interventions on the system’s structures alter the interactions or interconnections between components or actors within the system or between subsystems [23]. Interventions can introduce new elements into the system, such as enhanced built-environment infrastructure, to increase opportunities for healthy foods or physical activity [52,53] or to alter individuals’ interaction with the environment, such as through choice architecture [54–57]. For example, active design interventions in schools can alter students’ interactions with the built environment and impact physical activity behaviors [58,59]. Switching to more healthful default side options for children’s meals can impact...
eating behaviors [60–62]. One study in San Francisco found a significant decrease over time in the total fat and sodium content in children's orders after a chain restaurant switched to a more healthful default side dish and replaced the accompanying low-fat beverage with a fat-free beverage [60].

Many policy strategies advocated by public health are also designed to alter the system's structure [63]. Policy strategies can create new economic incentives or disincentives for consumer behavior and accelerate environmental changes deemed important to healthy lifestyles. Because of the population reach of policies, such interventions, when effective, can tip the system toward a large-scale shift in system behavior. However, policy interventions are also likely to create unintended consequences (i.e., compensatory responses elsewhere in the system) that need to be anticipated and managed.

Interventions on the system's structures can also shift existing structural dynamics by fostering collaboration and/or competition among actors to increase productivity or innovation. It is possible to leverage collaboration and competition simultaneously if they work on different levels to create a virtuous cycle [64]. Competition between teams leads to the selection of players that are more collaborative within teams, and in turn, this leads teams to become more competitive. This has important implications for how we structure different community organizations or government agencies, for example, to create both synergy and innovative solutions to obesity. One example of this at work relates to the Access to Nutrition Index (ATNI), which rates and ranks food and beverage companies in terms of their contribution to global nutrition [65]. While ATNI creates a new public information feedback loop to hold companies accountable, where ATNI may exert its most powerful impact lies in its adoption by value investors who are increasingly looking to put their money in companies that contribute to social good. Indices on environmental sustainability, access to medicine, and corporate social responsibility are used in a similar fashion [66–69]. ATNI also fosters collaboration across divergent voices (e.g., sales vs. public affairs) within companies in order for each company to be more competitive against others in ATNI rankings.

Last but not least, interventions on structure can include efforts to align the capacity of actors with the complexity of the tasks by either scaling up actor capacity, reducing the complexity through distributed actions, or both. Healthy Together Victoria, a statewide initiative in Victoria, Australia, created a new prevention infrastructure that embedded defined programmatic, evaluation, communication, and outreach functionalities both horizontally across communities and vertically between the local and state levels (i.e., distributed actions with coordination). In addition, the scaling up of systems-thinking capacity among its prevention workforce was central to the initiative, so that the individual actors were equipped to cope with the complexity of the system [70]. Elsewhere, the Missouri Foundation’s Social Innovation for Missouri initiative seeks to alter the existing infrastructure by integrating health strategies into a holistic paradigm (e.g., tackling tobacco cessation and obesity prevention together) and investing in multisectoral partnerships to increase the system's capacity [71,72].

**Intervening on Goals of the System**

The goals of a system inform all of the interactions and feedback mechanisms within the system. Interventions on system goals can alter the aim of the system with the potential for considerable impact. In order for the overall paradigm to shift, new targets must be set and met [23]. The true goals of the system are not always the goals identified by actors within the system [21], so it is critical to examine the system's actual goals and set new goals if the existing goals contradict the desired paradigm shift. As mentioned at the start of this chapter, the obesity prevention field has grappled with various dichotomous goals—for example, prevention versus treatment, obesity versus hunger, food regulation versus individual preference, multisectoral approaches versus no collaboration with industry, and so on. However, these are false dichotomies that are incompatible with the complexity of the system in which obesity arises. Top-down goals cannot be at the exclusion of creating the demand for healthy products, policies, and places [2]. There has been relatively little
attention paid to the demand-side strategies. Huang et al. [2] describe several examples showing how public demand can be mobilized through political strategies including streamlined messaging, media advocacy, the harnessing of citizen engagement and protest, and investment in a favorable political environment. As Hawkes et al. [3] point out in their paper on food policies and food preferences, the goal of the system is not to make the healthy choices the default choices; rather, the goal ought to be making the healthy choices the preferred choices. Reemphasizing the system goal around demand-side issues necessarily introduces a whole new set of system elements thus far not considered. The paper by Huang et al. [2] illustrates how the fundamental questions for each sector shift as a result. For example, rather than focusing on obesity specifically, a recent study focused on enhancing the readiness of a Latino community to embrace health as an issue in general through the use of youth activism and social media [73,74]. In the burgeoning field of school design, there have been efforts to dovetail school goals around learning and sustainability to incorporate design-based strategies for healthy eating and physical activity [58,59,75–77]. Thus, shifting system goals opens up new opportunities for both research and practice as we move toward systems solutions for childhood obesity.

**SHIFTING THE PARADIGM OF THE SYSTEM**

Shifting the system’s paradigm is the most difficult place to intervene in a complex system but also has the potential to create the most substantial impact. Shifting the system’s paradigm requires changing the deep beliefs and values that inform the goals and the many interactions, interconnections, and structures within the system [23]. An important paradigm shift in the obesity context relates to moving from a problem-oriented to a solution-oriented frame. Recognizing the “causes” of obesity does not necessarily lead to ideas about how to solve it [78]. For childhood obesity specifically, we need a shift from a cost/savings perspective to a moralistic or human rights perspective. In the United States, we also need to go from a system created to generate health care to one that values and generates health. These paradigm shifts happen gradually but require systematic planning and effort. We recently published a commentary illustrating how lessons from the gay marriage movement in the United States can be adapted to create a movement that leads us to healthier lifestyles and communities [79].

**MODELING AS A TOOL TO MANAGE COMPLEXITY**

Systems modeling (SM), with a strong tradition in engineering, business, ecology, and some corners of the social sciences, is an emerging methodology in the field of chronic disease. Researchers increasingly recognize its potential to frame and analyze the complex systems involved in obesity and related chronic diseases. SM can be qualitative or quantitative. It allows researchers to better understand complex interactions, identify potential intervention levers, predict system behaviors, test or generate new hypotheses, model intervention effects, and anticipate unintended consequences. SM is particularly powerful because it can accommodate nonlinear dynamics, feedback mechanisms, time delays, multiple interactions, and diverse sources of data, all of which are challenging using conventional research tools [22,80,81]. A review of SM in the obesity prevention field demonstrates the versatility of SM to explore different facets of the complex systems dynamics related to obesity and to generate compelling, actionable new knowledge.

In the context of childhood obesity, one particularly useful function of SM is its ability to model the potential impact of policies or interventions. The knowledge generated from SM can be an invaluable tool for informing researchers’ and policymakers’ work. The Baltimore Low Income Food Environment (BLIFE) model is an agent-based model of the Baltimore City food environment [82]. Researchers have used it to simulate the potential impact of different types and combinations of small food store interventions to reduce obesity in adolescents [83]. They found that while healthy food availability interventions in corner stores were more effective than in takeout
restaurants, a combined approach to address healthy food availability in both settings was the most effective and had the potential to reduce adolescents’ BMI by an average of 3.9 centile points over a 5-year period [83]. This new knowledge can help policymakers leverage the ideal combinations of interventions to create the most impact or prioritize the best use of limited resources.

SM can also help inform how interventions may impact different subpopulations or how environmental or socioeconomic characteristics may influence interventions’ effectiveness. An agent-based model of walking behaviors explored the interactions between different intervention approaches, walking behaviors, income differentials of walking behaviors, and aspects of the built environment [84,85]. One simulation found that while interventions to increase positive attitudes around walking may initially improve walking behaviors, they are unsustainable if the built environment is not conducive to walking [85]. Another simulation from this model focused on travel costs, such as parking tickets and gas prices, and found that changes in travel costs may impact the walking behavior of individuals in lower socioeconomic groups, but that high-income groups are relatively insensitive to changes in travel costs [84].

A third example by Hammond et al. [86] illustrates how individual neurological and physiological development can be integrated with different environmental contexts in a virtual, agent-based environment to help anticipate how environmental exposures might influence future behaviors. In this study, researchers showed that early-life exposure to a highly palatable and highly rewarding food environment strongly shapes the individual reward valuation system over time and that such early exposure may be more important than current exposure.

SM can be a helpful tool in better understanding the complexity of childhood obesity and its potential interventions. However, SM is only a tool to manage complexity. Systems thinking is a much broader philosophy to master and can be pursued by modelers and nonmodelers alike.

IMPLEMENTING SYSTEMS CHANGE

Though systems change provides a powerful approach to conceptualizing and addressing childhood obesity, the complexity of the task can be daunting. Once systems change has been identified as an important course of action, where does one start? Just as SM provides a way to better understand the complexity of the childhood obesity system, implementing and operationalizing systems change may greatly benefit from the lessons of frameworks and approaches in other fields.

Though not explicitly developed as a systems thinking tool, the philosophy and aims of the collective impact (CI) model dovetail in a compelling and mutually beneficial way with the systems-thinking approach. The CI model identifies the components necessary to create change at a systems level and scaffolds the design, implementation, and evaluation of each component [87]. The CI model comprises five main ingredients: a common agenda, a shared measurement system, mutually reinforcing activities, continuous communication, and a strong backbone organization [87]. Stakeholders can use these five elements to identify common goals, align their expertise and resources, and create change by synergistically working across the systems levels.

Stakeholders can leverage each component of the CI model to manage the complex task of systems change interventions to address childhood obesity. By defining a common agenda, stakeholders establish a shared understanding of the problem, agree to a course of action, and identify the goals needed to resolve the problem. The process can help participants better understand the existing paradigm, scrutinize whether the actual goals of the system match the desired goals, and, if not, articulate the new goals necessary to shift the paradigm.

By establishing a backbone organization and aligning activities so that they are mutually reinforcing, multisector stakeholders can coordinate and leverage their combined efforts. This synergistic approach has the potential to shift the systems’ structure and alter the existing interactions and feedback loops between different actors and sectors. Mutually reinforcing activities help harness the power of the complex system dynamics in support of the desired goals. A shared measurement platform and continuous communication develop new feedback mechanisms to further shift
interactions between systems actors and subsystems and ensure alignment among collaborators. A shared measurement system helps track progress toward goals and can alert actors if interventions are causing unexpected or negative consequences. Continuous communication between actors builds capacity, trust, and motivation, and helps actors better understand the system dynamics.

The CI model offers a structured, action-oriented framework with specific tools to help design, align, and launch multisectoral systems change interventions to impact childhood obesity. CI case studies demonstrate the possibilities of collective action and the model can be both an inspiration and a foundation for systems change [88].

**INNOVATING THROUGH DESIGN THINKING**

To optimize the potential of systems change in childhood obesity, creativity and innovation are key. Creativity and innovation come only when we operate in an environment where it is safe to fail—and fail frequently—so that lessons learned about what leads to failure can be rapidly parlayed into new solution ideas. Implementing a systems approach to childhood obesity must therefore be iterative and adaptable. Design thinking is a useful framework to facilitate this process [89]. The design-thinking approach embraces complexity and provides a way of thinking and a set of tools to help public health researchers and practitioners experience the needs of people and communities, empathize with the everyday challenges in weight prevention or management, and rapidly ideate, prototype, and test potential solutions [90]. Design thinking is nonlinear, provides a systematized way of engaging in community-based participatory research and practice [91], and can be embedded within a broader CI implementation framework. Though design thinking is a relatively new approach in public health, its concepts have been successfully applied to complex systems in other fields including business [90,92], engineering [93,94], and social services [95].

**CONCLUSIONS**

There is no debate that childhood obesity is a complex problem. The question is how to solve it. In this chapter, we summarized our thinking around what we call *translational systems science*—the idea that systems science is not only used to unravel complexity but to inform real-world solutions. In the traditional reductionist approach, the goal is to isolate “causes” that lead to obesity. In so doing, we lose sight of the bigger picture, including all the interconnections and dynamics across the elements, feedbacks, structures, and goals in the complex system in which childhood obesity occurs. A systems approach seeks to understand and manage such complexity with the hope that we can find sets of solutions that work in synergistic ways to ultimately shift the behavior of the system to favor healthy environments and healthy behaviors. Thinking in systems compels us to ask different questions and leads us to consider solutions that target system feedbacks, structures, and goals directly. Altering these systems dimensions is key to shifting the system paradigm. Tools exist outside the traditional public health field to facilitate systems change. CI and design thinking are two such tools that can help us put together a plan for implementation and evaluation in the real-world setting. Attempts at systems changes will inevitably lead to many failed starts, but not taking a systems approach is unlikely to lead to new solutions to effectively solve the childhood obesity epidemic.

**REFERENCES**


INTRODUCTION

Reversing the global obesity epidemic is one of the most serious public health challenges of the twenty-first century [1]. It is now widely accepted that obesity is a complex problem that needs to be addressed through comprehensive multisectoral action [2]. Over the last 15 years, the World Health Organization (WHO) and member states have collaborated to develop global strategies for the prevention and control of obesity and noncommunicable diseases (NCDs) [2–6] and to improve maternal and child health [7]. Reducing childhood obesity has been an important part of these comprehensive strategies. This is motivated by the need to protect children from harm, ensure their right to healthy food, and to reduce the global burden of diet-related NCDs, for which obesity is a major risk factor [2]. Most recently, in 2014, to better inform the development and implementation of comprehensive policy approaches, the WHO established the Commission on Ending Childhood Obesity [2]. As a result of these global efforts, there are now agreed high-level policies, strategies, and targets for addressing childhood obesity. However, translating these global recommendations into specific policy actions at the national level remains challenging [8]. No country has comprehensively adopted the recommended strategies [8]. Policy adoption is often characterized by the implementation of a few isolated interventions. These have mostly focused on the soft policy options of social marketing and education, rather than on comprehensive policy programs, including policies to create healthy food environments [8].
Given the complex nature of the obesity epidemic, the implementation of isolated policies is unlikely to be successful [8]. But moving toward comprehensive approaches will involve tackling several corporate, political, and societal barriers. While there are multiple macro challenges in reversing the obesity epidemic, this chapter focuses mainly on food policies and their implementation. Challenges in implementing policies aimed at increasing physical activity, such as active transport policies and urban design solutions, have been discussed in detail in the *Lancet* “Physical Activity” series.* The aims of this chapter are to

- Highlight the importance of reducing childhood obesity
- Provide a brief overview of the key global policy developments relating to the prevention of childhood obesity
- Discuss some of the main challenges related to the implementation of food policies to reduce childhood obesity: developing a shared narrative, rebalancing the power, and strengthening accountability of the main actors
- Identify priority strategies in moving from patchy progress to comprehensive policy approaches

**REDUCING CHILDHOOD OBESITY**

The simultaneous increases in obesity observed worldwide appear to be primarily driven by changes in the global food system [9]. These changes have led to mass production of increasingly processed, affordable, and effectively marketed food [9,10]. It is now widely recognized that children are growing up in increasingly obesogenic food environments, and unlike adult populations, bear little or no responsibility for their obesity and its health complications [2]. For this reason, efforts to prevent childhood obesity are often viewed as efforts to protect vulnerable children from social harm [2]. In addition, the prevention of unhealthy weight gain among children is a more achievable prospect than reducing the body weight of the large proportions of adults who are already overweight or obese. To tackle other NCD risk factors, such as smoking, high blood pressure, and high blood cholesterol, effective evidence-based interventions have been established and widely applied in adult populations to achieve reductions in the prevalence of those risk factors [9]. This is not the case, however, for obesity, where sustained weight gain among children is a more achievable prospect than reducing the body weight of the large proportions of adults who are already overweight or obese. To tackle other NCD risk factors, such as smoking, high blood pressure, and high blood cholesterol, effective evidence-based interventions have been established and widely applied in adult populations to achieve reductions in the prevalence of those risk factors [9]. This is not the case, however, for obesity, where sustained weight loss is a challenge even for motivated individuals, let alone across a population [9]. This has major implications for the time scale for reducing the prevalence of obesity-driven diseases, especially type 2 diabetes [9]. While the upswing of the obesity epidemic occurred at roughly the same rate in all age groups (the hallmark of an environmentally induced epidemic affecting the whole population), the scenario of the downswing of the obesity epidemic is unlikely to be the mirror image of the upswing, simply because the large proportion of people who are overweight or obese are unlikely to lose large amounts of weight en masse. A more likely scenario will be major cohort effects as childhood obesity reduces over time and those leaner childhood populations become leaner adult populations. Preventing and treating childhood obesity is thus likely to play a major role in reducing the global burden of NCDs, particularly type 2 diabetes.

**KEY POLICY DEVELOPMENTS**

Initially, the focus of global recommendations to address risk factors for obesity and diet-related NCDs was on adult populations. The first WHO document to focus entirely on obesity was the 2000 Technical Report 894, entitled “Obesity: Preventing and Managing the Global Epidemic” [3]. The release of this report put the prevention and control of obesity squarely on the global public health agenda. In the 15 years that have followed, significant other global policy milestones have been

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* See http://www.thelancet.com/series/physical-activity.
reached. While the recommended policies and strategies have grown in sophistication over time, global policy documents have consistently recommended a government-led, comprehensive, preventive approach that integrates prevention with policies aimed at helping populations lose weight and maintain healthy weights. They have also consistently specified that, while government is to take the lead, the success of prevention efforts depends equally on input from the private sector and civil society. The key global policy documents have been summarized in chronological order in Table 43.1. The table specifies whether policy recommendations have been aimed at children specifically or the general population. It also specifies whether the focus of each document is explicitly on obesity or on the prevention and control of NCDs.

The first WHO report to include specific recommendations for preventing and controlling obesity in children was Technical Report 916: “Diet, Nutrition and the Prevention of Chronic Diseases,” published in 2003 [12]. It was also the first report to include an analysis of environmental factors as determinants of the obesity epidemic and global dietary and physical activity recommendations. The implementation of these recommendations was outlined in the 2004 “Global Strategy on Diet,

<table>
<thead>
<tr>
<th>Year</th>
<th>Document</th>
<th>Target Population</th>
<th>Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Obesity: Preventing and managing the global epidemic [3].</td>
<td>General</td>
<td>Obesity</td>
</tr>
<tr>
<td>2003</td>
<td>Diet, nutrition and the prevention of chronic diseases [12].</td>
<td>General</td>
<td>NCDs</td>
</tr>
<tr>
<td>2004</td>
<td>Global strategy on diet, physical activity and health [13].</td>
<td>General</td>
<td>Nutrition and physical activity</td>
</tr>
<tr>
<td>2008</td>
<td>2008–2013 Action plan for the global strategy for the prevention and control of NCDs [14].</td>
<td>General</td>
<td>NCDs</td>
</tr>
<tr>
<td>2008</td>
<td>School policy framework: Implementation of the WHO global strategy on diet, physical activity and health [15].</td>
<td>Children</td>
<td>Diet and physical activity</td>
</tr>
<tr>
<td>2010</td>
<td>Set of recommendations on the marketing of food and nonalcoholic beverages to children [16].</td>
<td>Children</td>
<td>Marketing of unhealthy food</td>
</tr>
<tr>
<td>2011</td>
<td>Political declaration of the High-Level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases [17].</td>
<td>General</td>
<td>NCDs</td>
</tr>
<tr>
<td>2011</td>
<td>Global recommendations on physical activity for health: 5–17 years old [18].</td>
<td>Children</td>
<td>Physical activity</td>
</tr>
<tr>
<td>2012</td>
<td>Population-based approaches to childhood obesity prevention [1].</td>
<td>Children</td>
<td>Obesity</td>
</tr>
<tr>
<td>2012</td>
<td>Prioritizing areas for action in the field of population-based prevention of childhood obesity [19].</td>
<td>Children</td>
<td>Obesity</td>
</tr>
<tr>
<td>2013</td>
<td>Noncommunicable diseases global monitoring framework (includes target of 0% increase in adolescent obesity) [20].</td>
<td>General</td>
<td>NCDs</td>
</tr>
<tr>
<td>2013</td>
<td>Global action plan for the prevention and control of noncommunicable diseases 2013–2020 [21].</td>
<td>General</td>
<td>NCDs</td>
</tr>
<tr>
<td>2014</td>
<td>UN Food and Agriculture Organization, Second International Conference on Nutrition [22].</td>
<td>General</td>
<td>Nutrition and agricultural policy</td>
</tr>
<tr>
<td>2014</td>
<td>Comprehensive implementation plan on maternal, infant and young child nutrition (includes target of 0% increase in childhood obesity) [7].</td>
<td>Mothers and children</td>
<td>Maternal and child nutrition</td>
</tr>
</tbody>
</table>
Physical Activity and Health”; no strategies were aimed specifically at child populations [13]. The focus on childhood obesity sharpened between 2010 and 2015. In 2010, the 63rd World Health Assembly adopted resolution WHA63.23 on infant and young child nutrition [23], followed by the release of a comprehensive implementation plan on maternal, infant, and young child nutrition by the WHO in 2014 [7]. For the first time, the prevention of over- and undernutrition were explicitly linked [23]. The assembly also adopted WHA63.14, which outlined a set of recommendations on restricting junk food marketing to children [15]. The following year, the 2011 UN Declaration on the Prevention and Control of NCDs was adopted, representing a major political effort to seriously address the global NCD burden [17]. Following the declaration, “halting the rise in adult and adolescent obesity” was set as a target in the WHO NCD global monitoring framework [20].

Between 2011 and 2015, significant work was done by the WHO to develop specific tools and frameworks to translate global strategies into specific policy recommendations for childhood obesity. The comprehensive implementation plan on maternal, infant, and young child nutrition was the first document to set an obesity reduction target for children (no increase in childhood obesity) [7]. During this period, global recommendations for adolescent physical activity, recommendations for population-based approaches to childhood obesity prevention, guidelines for priority setting in childhood obesity prevention, and a framework for implementing the “Global Strategy on Diet, Physical Activity, and Health” in schools were also published by the WHO [1,15–18]. Furthermore, in 2014, the WHO established a high-level Commission on Ending Childhood Obesity (ECHO). The final report of the commission reaffirmed the message of earlier documents: that governments have the essential role in providing leadership in addressing childhood obesity [2]. The report identified the need for constructive relationships between government, the private sector, and civil society to move forward. Furthermore, it emphasized that policy implementation requires consideration of contextual differences and inequalities between and within countries. The report also highlighted the need for a monitoring and accountability framework at a national level to ensure effective policy implementation and action.

FEATURES OF A COMPREHENSIVE APPROACH TO PREVENT CHILDHOOD OBESITY

In “Population-Based Approaches to Childhood Obesity Prevention,” the WHO identified six key features that a comprehensive approach to preventing childhood obesity should include [1]

1. A mixture of government-driven, “top-down,” and community-based actions
2. A mixture of policy instruments, including legislative and fiscal tools, to ensure the availability and affordability of healthy foods and physical activity opportunities (see Box 43.2 for some examples of specific policies)
3. The integration of policies for childhood obesity prevention into existing structures to ensure sustainability of action
4. Interventions across a range of settings, including early child-care settings, schools, and community organizations
5. The establishment of cross-sectoral platforms and a multisectoral approach to childhood obesity
6. Strengthening structural components within government to support action on childhood obesity

In this document, the WHO further categorizes these policy instruments into three “components” of a comprehensive strategy: (1) supportive structures within government, (2) population-wide policies and initiatives, and (3) community-based interventions.
**INFRASTRUCTURE SUPPORT**

While supportive structures within government are often critical to intervention success, they are also frequently overlooked [1]. Strengthening these components is essential to support the implementation of more “direct” population-wide and community-based interventions [1,24]. The International Network for Food and Obesity/Non-communicable Diseases Research, Monitoring and Action Support (INFORMAS) framework for benchmarking and monitoring food environments identifies six key domains of infrastructure support that are derived from the WHO system’s building blocks [25]:

1. Leadership
2. Governance
3. Monitoring and intelligence
4. Funding and resources
5. Platforms for interaction
6. Health-in-all policies

Two examples of best-practice infrastructure support systems are described in Box 43.1.

**POPULATION-WIDE PREVENTION STRATEGIES**

There are a range of population-wide policy options recommended by the WHO and other organizations. Building on the work of these organizations, options have been categorized by the World Cancer Research Fund’s NOURISHING framework [4]. This framework classifies different food

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**BOX 43.1 INFRASTRUCTURE SYSTEMS WITHIN GOVERNMENT TO SUPPORT CHILDHOOD OBESITY PREVENTION POLICIES AND INTERVENTIONS**

**MONITORING AND INTELLIGENCE: ENGLAND’S NATIONAL CHILD MEASUREMENT PROGRAMME**

The National Child Measurement Programme was established in 2006 and aims to measure all children in England in the first (4–5) and last (10–11) years of primary school. In 2011–2012, 565,662 children were measured on beginning primary school and 491,118 children were measured in the last year of primary school. The large sample size allows for detailed data on prevalence and trends at a very local level and in particular subgroups of the population. [26]

**HEALTH-IN-ALL POLICIES: FINLAND’S HEALTH CARE ACT REFORM**

One recent example of positive change has been the Finnish city of Seinäjoki, where 6 years ago one in five 5-year-olds was obese. Through collaboration between the municipality’s health department and childcare, education, nutrition, recreation, and urban planning departments to ensure all day-care centers and schools provide the same quality of services, *this proportion has now halved*. This collaboration was facilitated by a reform of the Health Care Act in 2011 to mandate health promotion services and require municipalities to involve all sectors in their plans. Reform enabled many municipalities, including Seinäjoki, to provide free health-care counseling and health examinations of equal quality to all children and their families. Without reform, it is likely that many municipalities would have lacked the resources to hire additional public health staff to support their programs to improve child health. [27]
policies implemented around the world, providing a policy development tool for governments. The framework divides actions into the following 10 categories:

1. Nutrition label standards and regulations on the use of claims and implied claims on foods
2. Offer healthy foods and set standards in public institutions and other specific settings
3. Use economic tools to address food affordability and purchase incentives (such as taxes on unhealthy food)
4. Restrict food advertising and other forms of commercial promotion
5. Improve the quality of the whole food supply
6. Set incentives and rules to create a healthy retail and food service environment
7. Harness supply chain and actions across sectors to ensure coherence with health
8. Inform people about food and nutrition through public awareness
9. Nutrition advice and counseling in health-care settings
10. Give nutrition education and skills

Of these strategies, educational approaches and information campaigns have most frequently been used by governments. To date, over 20 jurisdictions have implemented some form of tax on unhealthy foods and beverages [28]. The implementation of a sugar-sweetened beverage (SSB) tax in Mexico provides an example of successful population-wide policy adoption and implementation. This is described further in Box 43.2.

COMMUNITY-BASED APPROACHES

Community-based approaches are those involving strong community engagement or participation [1]. Those that adopt a systems-based approach, addressing multiple components concurrently, are more likely to be achievable and sustainable at scale [1]. Other key factors that are likely to determine success include adapting the intervention to the local context, ensuring cultural and environmental appropriateness, using existing social and organizational structures of a community, and incorporating the ongoing involvement of all key community stakeholders [1]. One example of a large-scale systems-based approach is described in Box 43.3.

The Ensemble Prevenons l’besitë des Enfants (EPODE; Together let’s prevent childhood obesity) program is a coordinated, capacity-building approach for communities to implement effective and

BOX 43.2 POPULATION-WIDE STRATEGIES AND INITIATIVES

INTRODUCTION OF A SUGAR-SWEETENED BEVERAGE TAX IN MEXICO

In December 2013, Mexico passed two new taxes as part of their “National Strategy for the Prevention and Control of Overweight, Obesity and Diabetes,” which came into force in January 2014. One of these was a tax on SSBs, which applied an excise duty of 1 peso ($0.07) per liter to sugary drinks (defined as all drinks with added sugar, excluding milk or yoghurt). The revenue from the tax was to be invested in providing safe drinking water in schools. Initial price monitoring indicated that this increased the price of sugary drinks by around 10%, and all revenue was allocated to the general budget. A recent study conducted by the Mexican Institute of Public Health and the University of North Carolina suggests that, on average, the tax cut SSB sales by 6% in 2014, and by as much as 12% in the latter part of the year. While reductions occurred across all socioeconomic groups, they were higher among lower socioeconomic households, averaging a 9% decline over 2014 and up to a 17% decline by December 2014. There was also an increase of roughly 4% in purchases of untaxed beverages over 2014, mainly driven by an increase in purchased bottled plain water. [28,29]
Food Policy for Childhood Obesity Prevention

sustainable strategies to promote healthier lifestyles and prevent childhood obesity [1]. Although it has not incorporated a full systems approach, EPODE appears to be having some success in reducing childhood obesity [31].

CONSIDERATION OF NUTRITION IN AGRICULTURE AND TRADE

At a global level, there is a pressing need to make population nutrition goals a central consideration in the development of food and agricultural policies and international food and agricultural trade agreements, including food security initiatives. Policy work on “nutrition-sensitive agricultural policies” was progressed at the joint WHO/Food and Agricultural Organization’s Second International Conference on Nutrition in 2014 [22]. While this meeting recognized that many low- and middle-income countries are struggling with a double burden of under- and overnutrition, the final set of commitments from member states fell well short of what would be needed to truly reorient agricultural policies toward reducing the very high global burden of diet-related diseases [22].

Trade and foreign direct investment (FDI) agreements, such as the Trans-Pacific Partnership [10] and the Transatlantic Trade and Investment Partnership, present a threat to the nutritional health of populations, especially through the FDI clauses that allow transnational corporations to sue governments for loss of investment due to government policies that adversely affect their profits. Such suits are heard offshore in secret settlement tribunals (investor–state dispute settlements) [10]. The threats to population nutrition from trade and FDI agreements have been outlined by Friel et al. [10,32]. Some of the major threats identified by Friel et al. have been summarized as follows [10]:

- **Imports: Access to nutritious foods:** The reduction of tariff and nontariff barriers to trade through trade liberalization policies has resulted in disproportionately large increases in the import and domestic production of processed foods, creating an oversupply of highly processed foods that are calorie rich and nutrient poor.
- **Tax revenues and government spending:** Tariff reduction could affect nutrition through its potential to reduce the size of tax revenue available to fund health programs.
- **Increasing foreign direct investment and integrated food supply chains:** Many trade liberalization policies have facilitated greater foreign direct investment, which enables

**BOX 43.3 SYSTEMS-BASED COMMUNITY APPROACHES**

**HEALTHY TOGETHER VICTORIA (AUSTRALIA)**

Healthy Together Victoria was established in 2011 as part of a national effort to strengthen prevention [30]. It was led by the Victoria state government and worked through local government. It involved multiple players at the community level, including child-care centers, schools, workplaces, food outlets, sporting clubs, businesses, local governments, health professionals, and other stakeholders to create healthier environments. Taking a complex *whole of systems* approach to prevention, it used multiple strategies, policies, and initiatives at both state and local levels. Some strategies were aimed at the entire Victorian population, but most resources were concentrated at the community level in 12 Healthy Together Communities. These communities covered 1.3 million Victorians (25% of the Victorian population) through 520 schools, 938 early childhood services, and 4409 medium-to-large workplaces. The core driver creating system change was a dynamic and innovative workforce, both within the 12 Healthy Together Communities and more broadly across the state. Unfortunately, as the initiative was starting to achieve significant changes in community systems, the incoming federal and state governments defunded prevention, including Healthy Together Victoria.
transnational corporations to extend their supply chains. This has allowed for greater penetration of transnational food corporations into many developing countries, which has led to the global diffusion of highly processed, nutrient-poor food.

The annual “Global Nutrition Report,” which was launched in 2014, reports on progress toward nutrition goals, including reducing childhood underweight and overweight, globally and by country [33].

**REASONS FOR PATCHY PROGRESS ON REDUCING CHILDHOOD OBESITY**

Although there is global consensus on high-level strategies needed to comprehensively address childhood obesity, policy uptake has been low [8]. In the 2015 *Lancet* “Obesity” series, Roberto and colleagues described the implementation of the recommended strategies as being “patchy” at best, being limited to the implementation of isolated interventions [8]. However, there were some positive examples of policy implementation emerging globally, suggesting that there is reason to be optimistic about the future of obesity prevention. The series identified several reasons for the poor translation of global recommendations into national policies, including the power imbalance between the private sector and government/civil society, ineffective accountability mechanisms, and the need to improve the transfer of policy knowledge [8]. These are discussed further in the following sections.

**REBALANCING POWER AND DEVELOPING SHARED NARRATIVES**

Power to influence health-related policy decisions often rests disproportionately with commercial interests, an imbalance facilitated by the spread of neoliberal politics [34,35]. The idea that government intervention in health should be kept to a bare minimum has been a core narrative in the many countries that have adopted the economic and governance philosophies of neoliberalism [35]. The spread of these philosophies with their prioritization of free-market ideals has made deregulated markets the norm in many countries and privileged commercial interests in influencing policymaking [35]. The corporate political activity of Big Food and Big Soda in halting or slowing down efforts to introduce public health regulation of the food and beverage industry is clear [36]. Even in regions where pressure from civil society on government is strong, political lobbying by the food and beverage industry is stronger [37]. In some low- and middle-income countries, where civil society has successfully lobbied government to regulate the food and beverage industry, Big Food and Big Soda have still managed to intervene [37]. In Brazil, Chile, and Thailand, interference by Big Food and Big Soda has slowed or halted progress in industry regulation, even in the final stages of policymaking [37]. Thailand, for example, initiated a program to ban unhealthy beverages from schools [37]. However, the impact of the program has been slowed by the food industry’s financially remunerative contracts with schools to provide SSBs and junk food [37].

The power of commercial interests to influence public health grants them considerable sway over core narratives about obesity, its drivers, and its solutions [34–36]. In most countries, the obesity epidemic is viewed through two broad and distinct frames: for some, obesity is driven by environmental factors and can only be addressed through government-led action; for others, obesity is primarily caused by individual behavior and, therefore, is the responsibility of the individual not the government [35]. Roberto and colleagues identify the existence of such dichotomous narratives as a major obstacle for collaboration in preventing and reducing obesity [8]. Table 43.2 illustrates some of the dichotomies and their intersections in obesity narratives.

In most countries, the narratives in column A are predominant. However, as the second *Lancet* series on obesity highlighted, oversimplifying the issue into a series of dichotomies does not do justice to the understanding of the problems or solutions [8]. While the evidence suggests that both frames have some merit, it is often at the intersection of the dichotomy where key insights lie, as
TABLE 43.2
Dichotomies and Intersections in Obesity Narratives

<table>
<thead>
<tr>
<th>Issue</th>
<th>Narrative Dichotomies</th>
<th>Intersection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drivers of obesity</td>
<td>Individual choices</td>
<td>Environmental pressures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Commercial interests shape environments to exploit individual vulnerabilities, thus creating unhealthy preferences [8].</td>
</tr>
<tr>
<td>Consumption of unhealthy food</td>
<td>Demand driven</td>
<td>Supply driven</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The supply of unhealthy foods in early years creates preference for unhealthy foods, thus fueling the demand for unhealthy foods over the life course, sustaining a vicious cycle [2,8].</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Undernutrition</td>
<td>Overnutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Under- and overnutrition have some common drivers and solutions. Linking prevention of all forms of malnutrition could bring greater benefit [8,33].</td>
</tr>
<tr>
<td>Solutions</td>
<td>Treatment</td>
<td>Prevention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevention and treatment reinforce each other. Healthier food environments support people trying to lose weight; medical advocacy for prevention strategies and people trying to lose weight advocate for healthier food environments [8,12,21].</td>
</tr>
<tr>
<td>Regulation</td>
<td>Industry self-regulation</td>
<td>Government statutory regulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In reality, it may be that a combination (coregulation) and/or something in the middle (quasi-regulation) will be more feasible and effective [8,35].</td>
</tr>
<tr>
<td>Pressure for change</td>
<td>Bottom-up (consumer demand)</td>
<td>Top-down (regulation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Both approaches reinforce each other and combined approaches will be effective [8,38].</td>
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</tbody>
</table>

shown in the table. To work together effectively, government, the private sector, and civil society will need to come to a more integrated understanding of childhood obesity [2,8].

ENHANCING ACCOUNTABILITY FOR ACTION ON CHILDHOOD OBESITY

For multisectoral partnerships to be effective, they have to be supportive of population nutrition goals rather than corporate interests [38]. Governments need to ensure that power and accountability structures are aligned so that the influence of governments and civil society, acting on behalf of public interest, are not dominated by the commercial interests of the private sector [38]. At present, however, accountability mechanisms in most countries are weak and do not provide the necessary infrastructure to support effective partnerships [35]. In the second Lancet series on obesity, Swinburn and colleagues described effective accountability frameworks as those where (1) the principles of all parties are aligned, (2) a clear understanding of lines of accountability exists, and (3) sanctions are in place for noncompliance or poor performance [35]. They propose a four-step cycle of taking, sharing, holding, and ensuring a response to the account as follows [35] (Figure 43.1).

For obesity, taking the account must include regular monitoring of adult and childhood body mass index (BMI) as well as regular monitoring of food and physical activity policies and environments. Monitoring systems for food policies and environments have been developed and data are currently being collected by INFORMAS. INFORMAS data on food environments will complement the WHO NCD global monitoring framework, and the group will provide independent assessments of the policy efforts of government and the corporate activity of the food and beverage industry [35]. There is a need for an equivalent set of monitoring systems for physical activity environments.

Sharing the account will involve the wide dissemination of information collected through monitoring efforts. Holding [actors] to account will involve stakeholders acknowledging achievements and sanctioning poor performance of each other. This is currently the weakest step in the
accountability framework, especially when governments do not provide strong leadership of the accountability processes. The fourth step aims to ensure an active response to the account and will entail changes in policies and practices of governments, as well as in the food and beverage industry.

In this framework, government is responsible for holding the private sector to account, and civil society is responsible for holding both the private sector and government to account. It identifies six categories of accountability mechanisms that government and civil society actors have at their disposal—that is, legal, quasi-regulatory, political, market-based mechanisms, and the use of public and private communications. The strongest accountability lever available to governments is the use of legal mechanisms. However, while several countries now have regulatory accountability measures in place, enforcing sanctions remains the weakest component of the cycle [35]. In today’s globalized environment, national governance has become more and more complex as governments face the disjunction between soft obligations to implement WHO recommendations approved at the World Health Assembly and hard obligations to adhere to multinational trade and investment agreements [35]. In addition, global trade agreements can impose demanding evidentiary hurdles that must be crossed before public health regulations that may affect trade and foreign investment can be implemented [35].

In today’s political environment, where many countries have adopted neoliberal economic outlooks, it comes as no surprise that trade obligations are generally privileged over health obligations. However, while governments probably need to implement regulatory measures, the adoption of quasi-regulatory approaches is generally underutilized and could provide useful alternative pathways [35]. Although voluntary food industry commitments often lack transparency and are weakly

FIGURE 43.1 An accountability framework to promote healthy food environments. (Adapted from Kraak and colleagues, Cambridge University Press [license number 3695590621337]. With permission.)
enforced, governments can play a role in strengthening these frameworks [35]. Through establishing a clear policy framework and identifying measurable contributions that private stakeholders are expected to make, transparency and enforcement can be improved [35]. Furthermore, governments can take a legislative scaffolding approach, where they create a credible expectation that more direct forms of regulation will follow if the industry underperforms on its goals [35].

**STRENGTHENING CIVIL SOCIETY**

Civil society can also use a range of mechanisms to hold government and the private sector to account [35]. In most countries, however, civil society levers are relatively weak—even in countries with democratic political systems, independent media and judicial systems, and a low tolerance for corruption [35]. Government can strengthen civil society through improving participatory governance structures so that policymaking is weighted toward population nutrition goals rather than commercial interests [35]. In Brazil, for example, the Brazilian Food and Nutrition Council, which is responsible for translating nutrition conference recommendations into policy proposals, has two-thirds representation from civil society [35]. Private sector actors are included in the remaining third of its members, but only if they do not have substantial conflicts of interest with population nutrition goals.

Public health researchers and organizations can also play a role in strengthening the influence of civil society by mobilizing public support for action on obesity. “Bottom-up” or “grassroots” pressure for public health change has played a crucial role in the success of many public health campaigns [33]. Huang and colleagues identify several strategies that can be used to increase public support for action on obesity [38]. These include the refinement and streamlining of public information, the identification of obesity frames most effective for each population, improving media advocacy, the building of citizen protest and engagement, and developing a receptive political environment where change agents work across multiple organizations and sectors.

**IMPROVING THE IMPACT OF RESEARCH**

Learning from countries that have successfully implemented comprehensive approaches can help catalyze and improve policy implementation at the national level. The World Cancer Research Fund’s NOURISHING framework and corresponding policy database represents a major international effort in this area. Collecting data on international policy efforts will also help provide benchmarks from which to identify best-practice policies. However, in addition to improving data collection and monitoring, there is also a pressing need to improve the translation of research into policy and practice [39]. The concept of strategic science provides a conceptual framework for collaborations between researchers and change agents—those who can convert the knowledge into action [39]. The starting point is the cocreation of the research question by researchers and change agents. They may or may not collaborate in the actual data collection and analyses but certainly do so in the interpretation and communication of the findings. Research results should be communicated not only in academic publications, as with traditional science, but also in forms more relevant to policymakers. This collaboration creates a two-way policy “bridge” that ensures issues relevant to policy are addressed, and that research findings are communicated in real time to policymakers, who must often make decisions quickly.

**CONCLUSION**

It is clear that over the last 15 years, significant progress has been made in developing global strategies for the prevention and control of obesity and diet-related NCDs, including reducing childhood obesity. However, the translation of higher-level recommendations to the national level remains difficult. The disproportionate sway over public policymaking held by commercial interests, and their
influence over obesity narratives, have contributed significantly to the patchy progress observed at national levels. In this chapter, improving accountability mechanisms, mobilizing public support, and improving the collection and transfer of policy knowledge have been identified as key strategies in improving policy uptake and implementation of comprehensive policy approaches to prevent childhood obesity.

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