Adolescent Obesity and Puberty: The "Perfect Storm"

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Obesity is the most serious long-term health risk currently facing America's adolescents. Weight gain during adolescence carries a higher risk for adult obesity and the metabolic syndrome. This review highlights early adolescence as a particularly high-risk time for weight gain due to the synergy of naturally occurring metabolic changes along with increasing behavioral risk factors. One of the first potential health effects of abnormal weight gain during this period is earlier puberty, usually manifested as thelarche. The obesity epidemic is clearly implicated in the national trend toward earlier thelarche, although the data are not as strong in relation to menarche. Leptin activation of the hypothalamic-pituitary axis, combined with insulin resistance, and increased adiposity may result in the higher estrogen levels that are linked to breast development. Young adolescents also experience a sharp decline in their level of physical activity, worsening nutritional habits, and other important psychosocial and developmental risk factors that may contribute to obesity and estrogen-dependent disease in later life, including polycystic ovary syndrome and breast cancer. Unfortunately, the very psychosocial factors that contribute to abnormal weight gain during early adolescence make prevention and treatment in this population particularly challenging. Therefore, intervening prior to pubertal onset becomes even more important given the risk factors present once puberty begins.

Key words: **obesity; overweight; adolescent obesity; pediatric obesity; menstrual cycle; leptin, insulin; estrogen**

Introduction

Obesity and its co-morbidities constitute the preeminent health crisis facing America's children today. Physicians, parents, and policymakers alike are scrambling to find explanations and ultimately ways to treat and prevent this rapid rise in weight among children. For the first time in history, epidemiologists predict that life expectancy could level off or decline within next 50 years as a result of the obesity epidemic.[1] Between 1999 and 2003, the percentage of obese U.S. adolescents increased from 14.8% to 17.4%. The prevalence of obesity doubles between age 19 and 40, peaking at 36.8% among adults aged 40–59, suggesting that a large increase in weight occurs during young adulthood.[2] Minorities, especially Hispanic and African American youth, are at increased risk for obesity.[3]

This chapter explores why early adolescence is a particularly high-risk time for the development of obesity. In addition to the metabolic changes which occur during this interval, behavioral risk factors synergize to promote weight gain, putting adolescents at a much higher risk for weight gain and its complications. Although many of the adverse health consequences of obesity are not seen until adulthood, the relationship of obesity to the onset of puberty and menstrual dysfunction illustrates the metabolic and behavioral factors at work in adolescence. We first review the epidemiology of weight gain during adolescence, and then explore the data on the link between weight gain, thelarche, and menarche. We then discuss why younger adolescents are particularly vulnerable to obesity in terms of the metabolic and behavioral risk factors that occur around the time of puberty. Lastly, we highlight the challenges of obesity prevention and treatment in adolescence, in the context of these inciting factors.

Trends in Weight Gain in Early Adolescence

Obese children gain more weight in early adolescence, specifically ages 9–12, and then again in young adulthood. Although a certain level of physiologic weight gain is expected during this period, it appears that obesity and overweight occur at a higher rate as well. Kimm *et al.* analyzed data from the National

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Ann. N.Y. Acad. Sci. 1135: 265–279 (2008).
doi: 10.1196/annals.1429.009

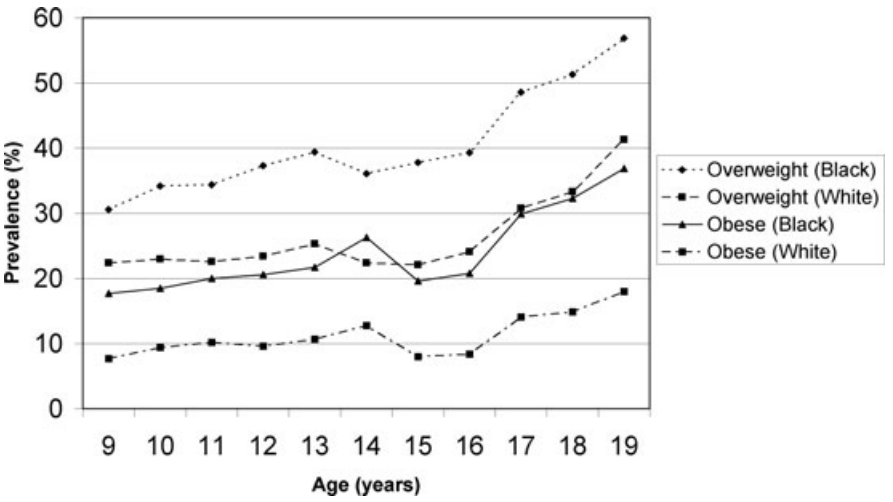

FIGURE 1. Prevalence of overweight and obesity among girls by age and race (NHLBI Growth and Health Study). (From Kimm *et al.*[4] Reproduced by permission.)

Heart, Lung, and Blood Institute (NHLBI) Growth and Health study (NGHS), and found that among girls age 9 to 10 years, the highest increase in skinfold thickness and BMI occurred between thelarche and menarche. BMI stabilized between ages 14 to 18 and then increased again.[3] FIGURE 1 shows an increase in the incidence of overweight/obesity during ages 9–12, relative stabilization during middle adolescence, and then a rapid increase in young adulthood among girls. They conclude that puberty and young adulthood are high-risk times for abnormal weight gain.

Weight gain during early adolescence carries with it higher-risk for adult morbidity. Thompson *et al.* followed the NGHS sample into adulthood and found that those with onset of obesity before age 12 were 11 to 30 times more likely to be obese in young adulthood. Furthermore, they found that childhood overweight was associated with adult hypertension, hypercholesterolemia, and the metabolic syndrome.[4] Wardle *et al.* conducted a study among boys and girls age 11–12 over five years and found that children who were overweight or obese at the start of the study were unlikely to have a decrease in BMI during adolescence, suggesting that weight gain during early adolescence is unlikely to change over time.[5] These data suggest that early adolescence is a vulnerable time for weight gain, and obesity during this time period predicts obesity in adulthood.

The medical complications of adolescent obesity are numerous and beyond the scope of this review. Diabetes, dyslipidemia, hypertension (clustered together as the metabolic syndrome), non-alcoholic steatohepatitis, cholelithiasis, obstructive sleep apnea, pseudotumor cerebri, and slipped capital femoral epiphysis are among the medical problems linked to obesity in adolescence.[6,7] Weiss *et al.* reported that the prevalence of the metabolic syndrome is as high as 50% in severely obese children.[8] Although none of these consequences are unique to adolescents, the earlier they manifest, the more medical and financial resources will be required in subsequent years.

In this review, we focus on one particular consequence of obesity on the health of adolescence: the timing and progression of puberty. Overweight and obesity are associated with an earlier onset of puberty. In addition to the health impacts of obesity reviewed above, earlier puberty is also associated with other important health outcomes: increased incidence of psychiatric disorders,[9,10] substance abuse, sexual risk-taking, and teen pregnancy.[11] A relatively younger age at menarche also increases the risk for breast cancer in adulthood.[12–14] Therefore, the impact of obesity during early adolescence not only relates to the medical complications of abnormal weight gain, but also earlier development itself.

Obesity and Earlier Pubertal Onset

The one impact of obesity on health unique to early adolescence is the trend toward earlier pubertal onset, as manifest by earlier thelarche.[15,16] There is also evidence of earlier menarche, but the evidence for this is less strong.[17] There are many theories regarding why the trend toward earlier puberty has occurred, ranging from environmental toxins to changes in socioeconomic status, but it is clear that nutritional status

plays an essential role in the timing and progression of puberty. What is not clear is whether the weight gain comes before the early puberty, if early puberty predisposes to abnormal weight gain, or both.

Several studies have documented a younger age for thelarche among all girls and the relatively earlier timing of puberty among African American girls. In 1997, Herman-Giddens *et al.* published the first major data showing an earlier onset of pubic hair and breast development using the Pediatric Research in Office Settings (PROS) data. They reported a mean age of breast development of 8.87 years in African American girls and 9.96 years in white girls with the same trend toward younger age for pubarche and menarche among African American girls.[16] The largest criticism of these data is the lack of a representative sample and using inspection for Tanner staging rather than palpation. Wu *et al.* in 2002, using NHANES III data, showed the same overall trend and racial differences, but in a nationally representative sample.[18]

The data supporting earlier age of menarche show a similar trend, but are less dramatic. Andersen *et al.* used NHANES data over 25 years to show that overall menarche had decreased by 2.5 months in 25 years.[19] The Bogalusa Heart Study, published by Freedman *et al.* in 2002, reported that the median age of menarche decreased by 2 months in white girls and 9.5 months in black girls.[15] Demerath *et al.*, using data from the 30 year Fels Longitudinal Study dataset, report a decrease of 4–6 months in age at menarche.[20] Most of the above-mentioned studies report earlier thelarche and menarche among African American girls. Perhaps the best data showing differences by race are from Biro *et al.*, using the NHLBI Growth and Health Study, a longitudinal study of girls starting at age 9 for ten years. They showed earlier onset of puberty (9.6 versus 10.2) and menarche (12 versus 12.6) for black girls.[21]

Given the consistent results among these studies, we can conclude that girls are maturing earlier and that there are racial differences in this trend. It seems that the results are more dramatic for thelarche versus menarche. The trend toward earlier pubertal onset may not indicate a new "normal," but instead may be a warning sign of health problems among young adolescents.[22] In fact, the release of these studies generated widespread speculation and investigation regarding the etiology of the trend. One theory posited has been the potential role of exposure to estrogenic chemicals and toxins in the environment.[17]

Given what we know about normal changes in insulin resistance, leptin, and estrogen metabolism that occur during puberty and their likely link to weight gain along with poor lifestyle (see the next section in this chapter), it is logical to ask whether obesity is also having an impact on pubertal timing and menstruation.[23] The impact of obesity on puberty in boys and girls seems to be different. Boys are more likely to have delayed pubertal onset and taller stature, whereas girls are more likely to have earlier thelarche.[24,25] The NHANES III analysis revealed a higher prevalence of obesity in girls who matured earlier, but the opposite trend in boys.[19,25] Leptin is an important factor in menstruation and onset of puberty in females, and the data show higher leptin levels in pubertal girls versus boys, so it is not surprising that obesity is associated with earlier pubertal onset in females.

There is a strong association between earlier thelarche and menarche with relative weight gain before and during puberty. Lee *et al.* using longitudinal data from 36 months through grade 6 reported that BMI at 36 months and velocity of BMI increase from 36 months through grade 1 are associated with earlier thelarche. However, they did not find a similar association for menarche.[26] The PROS group also found that increasing BMI was significantly associated with thelarche, but not menarche.[27] The NGHS data reveal that girls gain more weight around the time of pubarche and menarche and that participants with earlier thelarche gained more weight overall.[28] The Bogalusa Heart Study group report that the rate of early menarche among girls in the 75th percentile for weight was two times higher than for leaner girls.[15]

Studies also link earlier puberty with relative BMI increase *after* puberty. The Fels data show an association of earlier menarche with higher BMI in young adulthood, but no impact during adolescence.[29] The NGHS group also found a higher BMI among young adults who had early menarche, although this increase had been present throughout adolescence.[30] Only one study shows an association of earlier menarche with higher BMI in adulthood. Garn *et al.* reported that women with early menarche were 30% heavier than were late maturers.[31]

It is challenging to conclude from these studies that earlier thelarche and/or menarche are associated with obesity. First, none of the above studies commented specifically on obesity, but instead *relative* weight gain. Relative weight gain is likely physiologic to a certain extent. Second, many of the studies report cross-sectional data where it is hard to interpret causality. Third, it remains to be seen whether weight gain prior to, during, or after pubertal onset confers the largest risk for later obesity.

There are four studies that specifically comment on the link between earlier thelarche/menarche and overweight/obesity during adolescence. Davison *et al.* used

a longitudinal dataset to show that among 9-year-old girls with early thelarche, 59% were overweight and 30% were obese versus those with later development (21% and 8%).[32] Using the NHANES III, Wang *et al.* reported an odds ratio of 1.59 for overweight and 1.96 for obesity among 8–14-year-old girls with early thelarche.[25] Two studies report a similar association of overweight during adolescence with early menarche. Using the AddHealth dataset, Adair *et al.* report that earlier menarche was associated with a 1.98 times increase in overweight during high school for the entire sample, but the increase was 2.57 times higher for blacks.[33] Andersen *et al.*, using the NHANES dataset, found that girls who had reached menarche had a higher BMI z-score. They reported that for every two girls of the same age and race, with one at the 85th percentile for weight, the overweight girl would be 2.4 times more likely to have reached menarche.[19]

From these data we are able to conclude that obesity during adolescence is in fact associated with earlier thelarche and menarche. Using 30 years of follow-up data among a Massachusetts sample, Must *et al.* reported that being overweight *prior* to menarche has an odds-ratio of 4.3 for adult obesity, while early menarche alone (without associated weight gain) has an odds ratio of 0.87 for adult obesity.[34] These data hint that obesity prior to menarche, rather than earlier menarche alone, is a more accurate predictor for later-onset obesity. The earlier the weight gain, the more likely girls will have earlier puberty, and that the weight gain will persist.

An additional question is whether obesity has an impact on both the onset *and* the progression of puberty. Though the data associating relative weight gain and obesity with earlier thelarche are strong, there is not as much support for the association of weight gain and/or obesity and earlier menarche. Overweight girls are more likely to have thelarche as the initial sign of puberty versus pubarche.[35] Data from Biro *et al.* 2003 show that girls who have thelarche as the initial pubertal sign were more likely to have higher body fat proportions *prior* to the onset of puberty.[35] Given the weak data on an earlier age of menarche with obesity, it may be that overweight girls start earlier, but progress more slowly.[36]

The Biochemistry of Puberty and Attendant Weight Gain: Insulin, Leptin, and Estrogen

The mechanism behind the rapid weight gain seen during adolescence is linked to the normal physiologic changes seen during this time. Changes in the hormonal regulation of appetite, satiety, and fat distribution that occur during puberty may put adolescents at increased risk for additional weight gain. For girls, natural hormonal changes at this age lead to increased adiposity, which is age-appropriate. Weight gain during puberty is likely an obligate requirement to develop the physiologic capacity for reproduction.

As mentioned above, several epidemiologic studies demonstrate an association between relative weight gain at the onset of puberty as measured by thelarche, pubarche, and menarche,[27,28] but there is controversy regarding the mechanism and direction of this association.[37] Frisch *et al.* were the first to describe the "critical weight hypothesis" in the 1970s, which argued that a certain percentage of body fat was needed for menses to start.[38–40] Though an increased amount of body fat develops during puberty, the way in which the fat is distributed, along with complex hormonal regulatory factors (see below), also play an important part.[41,42] If children enter puberty already overweight or obese, these effects are compounded. Leptin and insulin are two hormones which play an important role in the timing of puberty and its progression, and have an impact on risk of obesity.

Leptin

Leptin is a hormone secreted by adipocytes in response to energy storage. The main role of leptin in humans is to communicate the status of energy availability to the hypothalamus and to allow for normal peripheral energy metabolism.[43] Leptin receptors have also been found in anterior pituitary, lymphocytes, bone, ovary, and endometrium, suggesting that it has an even more widespread impact.[44–46] Interestingly, girls exhibit a higher circulating leptin level than do boys, suggesting that leptin secretion may be a by-product of the increased adiposity among pubertal females.[47,48] Leptin also plays a major role in the initiation and progression of puberty.[49] Animal models have shown that genetic leptin deficiency is associated with a failure to undergo puberty and that replacement of leptin facilitates pubertal onset.[50] These findings have been replicated in human studies as well[51] Welt *et al.* administered leptin to women with hypothalamic amenorrhea and noted improved reproductive function in terms of resumption of menses, follicular development, and estradiol levels.[52] These results support the permissive role that leptin plays in normal reproductive function.

Given its role in signaling to the hypothalamus that adequate energy stores are present, leptin in effect serves as the "starvation" hormone. Low levels of

leptin indicate inadequacy of energy.[53] On the opposite end of the spectrum, higher serum leptin concentrations are associated with higher body fat content and earlier pubertal onset.[54] The proposed mechanism by which leptin affects pubertal onset is through permissive activation of the GnRH pulse generator by means of signaling of adequate energy stores.[55] Leptin activation of hypothalamic neurons normally results in an increase in sympathetic outflow, leading to increased muscle energy metabolism and adipose tissue lipolysis, resulting in increased energy expenditure.[56] To allow for the requisite weight gain during puberty, leptin sensitivity must in some way be attenuated during this interval. This is an important area for future study.

Insulin

The hormone insulin has numerous metabolic effects, but in terms of obesity, its effects on the adipocyte and hypothalamus are relevant. At the adipocyte, insulin facilitates glucose transport after a dietary glucose load, causes the uptake of plasma free fatty acids into the adipocyte for conversion to triglyceride, and finally inhibits lipolysis once the triglyceride is stored—all leading to increased energy storage.[57] At the hypothalamic level, insulin may interfere with leptin signaling, leading to leptin resistance and allowing for a greater fat mass before sympathetic efferents are activated, fomenting further weight gain.[53] Suppression of insulin release improves leptin sensitivity and promotes weight loss.[58]

Insulin resistance can be a consequence of obesity, but also may be associated with additional weight gain once present.[53,59,60] A normal increase in insulin secretion and resistance occurs at the onset of puberty in girls, and is thought to facilitate the physiologic increase in adiposity.[53,61–64] The development of insulin resistance during the process of puberty may drive further weight gain, in order to achieve reproductive competency. In obese patients with high circulating levels of insulin, persistent insulin resistance can develop, which is associated with multiple metabolic problems such as type 2 diabetes mellitus (T2DM).[65,66] Children who are already overweight or have poor diets, or those with low physical activity, may be at a much higher risk for additional weight gain beyond what is normal for this age in part due to insulin resistance, although the exact mechanism behind this has not been elucidated.

Many of the metabolic and cardiovascular complications of obesity are already evident during childhood, and are closely related to the development of insulin resistance. Hyperinsulinemia is one of the most common biochemical abnormalities seen in obesity. In its most extreme state, insulin resistance can result in further decompensation in glucose metabolism, dyslipidemia, and hypertension. Although an accelerated atherogenic process is present in obese children, thrombotic cardiovascular events do not usually appear until adulthood. The clustering of these manifestations is termed the "metabolic syndrome." In addition, nonalcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS) are related to the insulin resistance of obesity.[65]

Thus, it appears that insulin resistance and increased leptin levels are important factors in pubertal onset and the relative increase in fat mass that accompanies it, which is necessary for the activation of the GnRH pulse generator. In the context of obesity, these normal physiologic processes are exaggerated and may be linked to earlier puberty and menarche.

Estrogen

Estrogen also has an essential role in the initiation and progression of puberty, and estrogen levels are linked to excess adipose tissue. Estrone (E_1) and estradiol (E_2) are synthesized from androstenedione (AD) and testosterone (T), respectively, by the cytochrome P_{450}-dependent enzyme aromatase. Aromatases are located in the placenta, adrenal, skeletal muscle, and hypothalamus, but the main sources of estrogen biosynthesis in the adolescent are in the granulosa cell and adipocyte. Ovarian aromatase activity is regulated by follicle-stimulating hormone (FSH) secretion, whereas peripheral aromatase activity is dependent on total fat mass. Increases in estrogen are essential for normal progression of puberty, beginning with thelarche. As the GnRH pulse generator promotes early ovarian function, estrogen secretion leads to increases in growth hormone (GH) and insulin-like growth factor-1 (IGF-1) secretion.[67] These three all conspire to increase the degree of insulin resistance, promoting hyperinsulinemia, and energy deposition into adipose (see above).[68]

Thelarche is more likely to be initiated in obese girls earlier than in other girls, which may be related to the relationship between adiposity and estrogen.[35] Higher levels of circulating estrogen are also found in obese children. Increased adipose tissue mass leads to higher circulating levels of estrogen in multiple ways. First, peripheral E_1 and E_2 synthesis via aromatization occurs at the level of the adipocyte.[69] With excess fat stores, there is increased estrogen production. Second, a lower level of sex hormone–binding globulin (SHBG) in obesity leads to higher levels of free circulating estrogen and also androgen, which may be a harbinger of future PCOS.[70,71] Third, the advancement in timing of

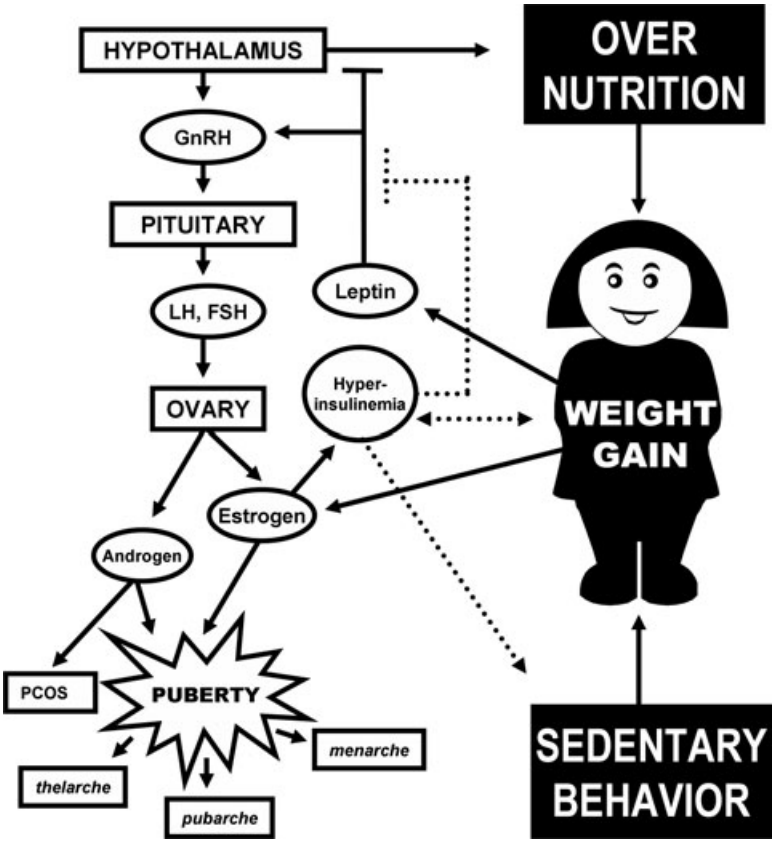

FIGURE 2. Metabolic risk, early puberty, and weight gain.

GnRH pulse generator activation due to the permissive action of higher leptin levels leads to higher estrogen levels at younger ages.[49] Fourth, estradiol metabolism can be modulated by environmental factors such as diet, with high-protein diets promoting hepatic estrogen inactivation, and high fat promoting the conversion to active estrogen metabolites.[72] Finally, decreased hepatic inactivation by estrogen-2-hydroxylation in the context of obesity leads to reduced estrogen clearance.[73] The result is higher levels of estrogen, which leads to earlier thelarche and pubertal progression.[32] Indeed, obese girls are more likely to exhibit earlier thelarche than other girls are, which may be related to the relationship between adiposity and estrogen.[35]

Thus, estrogen, insulin, and leptin are inexorably linked, in what becomes a positive feedback cycle. FIGURE 2 summarizes the hypothesized interaction of leptin, insulin, and estrogen during puberty. Once obesity is present, it leads to increased leptin, which is permissive for the GnRH pulse generator, leading to higher ovarian estrogen, which may help to foment insulin resistance, increased adipose tissue, and peripheral aromatization. Insulin may interfere with hypothalamic leptin signaling, potentially driving further weight gain and appetite, which leads to further estrogen formation.

Behavioral Risk and Attendant Weight Gain: Autonomy, Risk-Taking, and Stress

Metabolic changes during puberty only tell part of the story. Changes in diet, physical activity, family dynamics, and developmental factors during adolescence are equally important in the increase in weight experienced during early adolescence. Adolescence is a time of risk-taking behavior as children test their autonomy and assert independence. Healthy eating habits and levels of physical activity may break down as academic and social pressures become more demanding. More time spent in sedentary activities, such as TV, video games, and computer use, along with higher caloric intake and less physical activity are associated with increased weight gain during this time.[74,75] TABLE 1 summarizes the risk factors discussed below.

TABLE 1. Psychosocial and behavioral risk factors for weight gain in early adolescence

Risk Factor	Examples
Sedentary lifestyle	Reduced physical education activities
	Less sports participation
	Less unstructured "play time"
	Increase in television viewing, computer use, and video game time
Overnutrition	Reduction in fruit and vegetable consumption
	More fast food consumption
	Increase in sweetened beverages, less milk consumption
	Higher overall calories consumed
Disordered eating/obesogenic behavior	Skipping meals (e.g., breakfast)
	Fewer family meals
	Eating outside the home
	Dieting, binge eating, purging, taking laxatives/diuretics
Mental health	Being teased or bullied
	Depression and anxiety
	Increased stress
	Psychotropic medication use
Built environment	School lunch and vending machines
	Neighborhood safety concerns
	Lack of available parks/recreation
	Fewer organized sports activities, school physical education
Developmental factors	Transitional cognitive development
	Increasing autonomy, less parental supervision
	Increases in peer influence
	Clustering of risk behaviors

Aaron *et al.* showed a decline in physical activity of 26% in adolescents between the ages of 12 and 15 in a Pittsburgh sample.[76] Kimm *et al.* documented a decline in physical activity among pre-adolescent girls, with a steeper decline in African Americans, and an association with increasing BMI. By the age of 16.56% of the black girls and 31% of the white girls in their sample reported no regular physical activity.[77] The 2005 Youth Risk Behavior Surveillance (YRBS) data confirms these trends, showing that between grades 9 and 12, youth report an increase from 7.7% to 12% in "no physical activity in the last week." Unfortunately, the increase is higher in girls, going from 8.2% in grade 9 to 15.2% in 12th grade. By the time they reached their senior year, only one-third of respondents met current recommended levels of physical activity.[78] In adolescents, the main factors associated with higher levels of physical activity appear to be family and peer support, higher self-esteem and sense of self-efficacy, and fewer perceived time constraints.[79]

An increase in sedentary activities accompanies the decrease in physical activity during this period. A 1998 analysis of the National Health and Nutrition Examination Survey III by Andersen *et al.* documented that 26% of U.S. children watch 4 or more hours of television per day. They also showed that watching 4 or more hours of television each day is associated with a greater percentage of body fat and weight gain than was associated with watching less than 2 hours per day.[80] YRBS data actually show a slight decline in television viewing during high school, with the percentage of 3+ hours per day decreasing from 42% in grade 9 to 31% by grade 12. However, as was the case with changes in physical activity, African American youth had the highest rate of television viewing, with 64% reporting watching 3+ hours per day.[78] A recent analysis by Taveras *et al.* showed that a reduction in television viewing was not associated with increases in physical activity.[81] Given that we know that adolescents gain weight during this time, it seems likely that the lower rates of television viewing are not translating into higher levels of activity.

Many studies have demonstrated the association of lower levels of physical activity, a higher amount of sedentary time, and obesity.[75,80] From the adult literature, we know that dietary restriction alone can produce weight loss, but sustaining weight loss is much less likely without the addition of a moderate level of physical activity.[82] This is consistent with recent findings by Boutelle *et al.* which showed that successful weight loss among an NHANES sample of adolescents age 16–18 was associated with higher levels of physical activity and reduced sedentary time, but the effect size of sedentary time was modest.[83] A significant reduction in television viewing was achieved by Robinson *et al.* in their intervention targeting children, but this was not

associated with significant changes in BMI, physical activity, or dietary intake.[84] From these data we can glean that although sedentary activities such as television are important correlates for obesity in youth, the lack of physical activity is a far more important factor for both weight gain and weight loss.[85,86]

Also seen during adolescence are a rapid increase in the number of calories consumed, a reduction in the quality of nutritional intake, and an increase in "obesogenic" eating behaviors. Adolescents seem to develop a "calorie-rich, nutrient poor" diet which is widely considered to be one of the main causes of rapid weight gain during this time period. The 2005 YRBS data show that only 20% of high school students report consuming more than 5 fruits or vegetables per day.[78] The Growing Up Healthy Study showed an increase in consumption of fast food between the ages of 9–12 and 13–14 years, and fast food intake was associated with greater weight gain.[87] However, a higher consumption of fruits and vegetables does not have the expected protective effect on weight gain.[88]

Young adolescents also reduce their consumption of milk and increase the intake of soda and other sweetened beverages. The Growing Up Today Study (GUTS) showed that the consumption of milk significantly decreases and soda increases from ages 9 to 14 and that these changes are associated with weight gain, mostly due to the increase in total number of calories consumed.[89] A reduction in the consumption of sweetened beverages is one of the few interventions that has demonstrated a positive impact on obesity.[90] Especially for individuals with hyperinsulinemia, a reduction in the consumption of carbohydrates is associated with improved weight measures.[91]

In addition to the increased amount and poor quality of their diet, adolescents also develop unhealthy eating behaviors which are also associated with weight gain. Adolescents are more likely than younger children to eat outside the home, skip meals, and less likely to participate in family meals. Skipping meals, such as breakfast, has been associated with weight gain over time.[92] Fewer family meals, either because of eating in front of the television or eating outside the home, is another unhealthy eating behavior. Project EAT in Minnesota looked at rates of family meals and found that 25% of families reported eating together as a family 7 times in the past week. Boys, younger adolescents, and higher socioeconomic status were associated with more family meals. Family meals are associated with a higher intake of fruits and vegetables, calcium, and lower soft-drink consumption.[93,94] Although family meals are associated with a lower risk of being overweight at younger ages, they are not protective for weight gain later in adolescence.[95] They are, however, protective against other adolescent risk behaviors such as substance abuse, sexual risk-taking, and disordered eating.[96,97] The protective effect of family supervision also extends into after-school time, with a higher level of physical activity among adolescent girls with adult supervision in the afternoons.[98]

Perhaps one explanation for the association of weight gain with television viewing is the link between eating a significant number of calories during a relatively sedentary activity. The Planet Health study calculated that each hour of increased television viewing is associated with an additional 167 kcal/day and a reduction in fruit and vegetable consumption.[99,100] Robinson *et al.* reported that 18% of total energy intake among children is consumed while watching television. The same group also showed in a sample of African American girls that 50% of evening meals were eaten while watching TV.[101,102]

Unfortunately, many overweight adolescents engage in dangerous dieting behavior such as binge-eating, purging, food-restricting, and using laxatives/diuretics. Rather than reduce their sedentary behavior and poor diet, many teens, especially girls, resort to dieting to maintain or lose weight. YRBS data show that among all adolescents, these behaviors are very uncommon ($\sim$1% of the sample), but they do increase with age.[78] However, we know that these behaviors are more common in overweight versus normal-weight teens. One school-based sample reported that 18% of overweight girls engaged in weight control behaviors such as taking diet pills, using laxatives/diuretics, or vomiting.[103] Prior school-based studies have shown that disordered eating behaviors and extreme dieting and depression led to increased weight gain over time.[104,105] Field *et al.*, using data from the National Longitudinal Study of Adolescent Health, showed that dieting among girls was associated with increasing BMI over time.[106]

One of the often overlooked risk factors for the development of obesity, which also severely affects treatment outcomes, is problems with mental health. Children with a history of depression, anxiety, or more severe mental health disorders are at increased risk for weight gain.[107,108] The mechanism is likely a combination of poor lifestyle along with the increased appetite and weight gain accompanying many psychotropic medications. Many depressed adolescents are being placed on the atypical antipsychotics risperidone, olanzapine, quetiapine, clozepine aripriprazole, and ziprasidone to stabilize mood and/or behavior.[109] These medications induce insulin resistance, which foments persistent hyperphagia and weight gain, and increases risk for the metabolic syndrome.[109,110] Once the

adolescent is overweight, he or she is also at a uniquely high risk for developing depression, and even suicidal ideation, which can predispose to further weight gain.[111–113] Overweight children report higher rates of teasing, bullying, and poor self-esteem, factors that likely contribute to the high incidence of depression among overweight adolescents.[114–118]

In addition to the changes in diet and physical activity, family dynamics, and developmental factors, the "built environment" plays an important role in increasing the risk for weight gain among young teens. The built environment refers to the neighborhoods, schools, food sources, and communities in which children live. This environment has an effect on what children eat and their level of physical activity. Changes in the past 20 years in the built environment likely contribute to the obesity epidemic through the promotion of sedentary lifestyle and poor nutrition. What is unclear is whether changes in this environment could lead to lifestyle change. Various studies have considered the role of access to recreation and physical activity and obesity. For example, children with access to recreational programs near their homes are more active. Adolescents from a lower socioeconomic status and minority groups are less likely to live in areas with recreation facilities, and this is associated with decreased physical activity and obesity status.[119] A perception of living in an unsafe neighborhood has also been associated with higher rates of obesity.[120] School lunch programs are a common target for obesity interventions. While a school lunch program can be a large *source* of problems, this program is not unique to adolescents, as children have access to it for most of their school years. What is different is the availability of extra spending money and the freedom to purchase additional items both from vending machines and off-campus. Students with an open campus and access to vending machines are more likely to make less healthful choices.[121]

The final area unique to adolescents is their cognitive and social development. Adolescent development includes increasing independence, autonomy, greater peer affiliation, sexual awareness, formation of identity, and increasing cognitive ability to process complex information. In early adolescence, the peer group takes on a primary role and this is important as peer pressure is one of the major factors in the onset of risk-taking behavior.[122] Researchers are now grouping dieting and sedentary behavior with other adolescent risk-taking behavior such as sexual activity and substance abuse. There is some evidence that extreme dieting practices co-occur with other risky behaviors.[122,123]

It is a widely held belief that teens believe themselves to be immune from negative consequences, or that they are ignorant of the health implications of their actions. It is actually much more complicated than that. Research shows that teens are in fact concerned about their health,[124] and that they are able to identify health risks and do feel that they are vulnerable to poor health outcomes.[125] But although they accept the risk and acknowledge their vulnerability, they still engage in risky behavior. Halpern-Felsher and Millstein argue that instead of a poor perception of risk and the feeling of being "immune" to negative consequences, teens instead prioritize the benefits of the risky behavior over the consequences.[125]

In the case of obesity, adolescents may know that poor nutrition and sedentary behavior could lead to poor health outcomes and they correctly perceive themselves to be vulnerable to these effects, but they still engage in the behavior. When we begin to consider interventions around diet and physical activity in this age group, it is extremely important to consider adolescents' cognitive development and how they perceive health risk. Adolescent health interventions have started to focus more on resilience and youth development versus risk-based counseling, given how little impact education around consequences has had on behavior.[126]

The Challenge of Obesity Prevention and Treatment in Early Adolescence

The same behavioral and metabolic factors that predispose to weight gain during early adolescence also make prevention and treatment in this population challenging.[127] However, from the data reviewed above, it is very clear that early intervention will be essential to slow the progression of metabolic and behavioral risk factors for weight gain. Prevention and lifestyle-modification strategies in adolescence have been overwhelmingly disappointing. Our options for altering metabolic risk and counteracting changes in behavior in this age group are limited.

Medication is always initiated as an adjunct to standard lifestyle modification. The mechanism of action of pharmacotherapy for obesity treatment ranges from alteration of dietary intake (sibutramine), limitation of the availability or absorption of nutrients (orlistat), and insulin sensitization or suppression (metformin or octreotide, respectively).[128] There are many constraints to starting medication for the treatment of obesity. First, the youngest age for which there is an FDA-approved obesity pharmacotherapy is 10 years (orlistat). Second, medications are not always more efficacious than behavior modification. Third, the research

on pharmacotherapy in this population is limited. Finally (and likely most importantly), there are significant side-effects of pharmaceuticals which are not well tolerated at this age. As a last resort, bariatric surgery is being performed more regularly in adolescents, but the safety, efficacy, and financial feasibility of these procedures in this age group is still unknown.[129]

Given that pharmacologic and surgical options are limited, for the time being we are left with counseling for behavior change as the main option for intervention in adolescent obesity. Lifestyle interventions in this age group are fraught with complexity, given the rapidly changing cognitive development during this age range. Thus far, there is limited evidence that behavioral interventions can work for lifestyle change in children.[130] Some targeted interventions have found success with strategies such as television reduction, dance programs,[131] and reducing soda intake.[90] Only one intensive weight-loss program, the Stoplight Diet, has demonstrated sustained weight loss in children over a 10-year follow-up, and this was in a highly selected population with intensive patient contact.[132]

Lessons can be learned from the literature around risk prevention in the areas of reproductive health and substance use. This literature overwhelmingly shows that education alone is not sufficient to prevent high-risk behavior. Skills-based learning through peer education, role-playing, and practice are much more age-appropriate strategies than education alone. Other strategies include motivational interviewing and youth empowerment and development.[136,133] Programs with the most success are those that incorporate simple messages, have long-term follow-up, and include an approach that takes the developmental stage into account. In addition, if an adolescent has already developed significant self-esteem problems, disordered eating, and depression related to obesity, these can serve as huge barriers to lifestyle change.[134] Despite the lack of evidence that diet and physical activity counseling within the primary care office can lead to changes in behavior, most guidelines recommend it anyway as a "first do no harm" strategy.[135,136] However, adolescents do not present to the physician as often as younger children.

Postpubertal Impact of Obesity on Menstruation

As mentioned earlier, rapid weight gain is seen in early adolescence, then slows down, and then increases again in later adolescence. Exaggerated weight gain and obesity in the postpubertal female has specific detrimental effects on menstruation. Polycystic ovary syndrome (PCOS) results in amenorrhea and/or dysfunctional uterine bleeding in obese adolescents; this is discussed in detail in the chapter by Dr. Blank *et al.* in this volume. PCOS is particularly interesting as it is intimately intertwined with insulin resistance and the metabolic syndrome.[137] Obesity characterizes about 50% of women with classic PCOS, and it is even more common among adolescents.[138] Increased peripheral insulin resistance occurs in approximately 50% of patients with PCOS, and almost certainly plays a role in the pathogenesis of this condition. Insulin resistance is seen in girls with PCOS,[139] as are early markers of accelerated atherogenesis,[140] indicating that early intervention aimed at reducing cardiovascular risk may be beneficial.

Metabolic examination of patients with PCOS demonstrates hepatic and muscle resistance, but not ovarian insulin resistance, possibly accounting for insulin stimulation of theca cell androgen production. The correlation between insulin resistance and hyperandrogenism begs a unifying hypothesis as to their pathogenesis, which is proffered by the "serine phosphorylation hypothesis," which suggests that both P450*c*17 and the insulin receptor are aberrantly serine-phosphorylated; in the case of P450*c*17, this leads to excess activity and increased androgen production, and in the case of the insulin receptor, this leads to tissue-specific insulin resistance. However, this hypothesis remains to be proven.[141]

Other than PCOS, the impact of obesity on menstruation after puberty is not as well described. The hyperestrogenism state of obesity (discussed below) contributes to early thelarche, but may also be associated with amenorrhea in adult women. The increased production of estrogen through peripheral aromatization and reduced clearance in the liver produce higher estrogen levels. Over time, obesity may also lead to increased storage of organic compounds, such as atrazine and other toxins, which may both contribute to further obesity by inducing insulin resistance and also further estrogenic burden, further reducing GnRH secretion.[142] Higher estrogen levels can suppress GnRH secretion and lead to amenorrhea.[143,144] This effect is separate from the direct action of androgens and insulin resistance on ovarian function seen in PCOS. In addition, the increased peripheral aromatization to estrogen in obese postmenopausal women and their reduced hepatic estrogen clearance is associated with higher rates of breast cancer;[145] and this increased total lifetime estrogen burden may begin with the onset of puberty.[146]

Obesity may also have an impact on menstruation in the context of disordered eating. The amenorrhea that accompanies the malnutrition of anorexia nervosa and bulimia nervosa is well described.[147] The mechanism is likely a combination of hypothalamic-pituitary dysfunction brought on by stress and malnutrition, as administration of GnRH and leptin to malnourished patients results in resumption of ovarian function.[52,72] In binge eating, sufficient calories are being absorbed, so the menstrual cycle is unchanged. But binge eating and purging may have an effect on insulin release, resulting in hyperandrogenism and polycystic ovary syndrome.[148,149] Ingestion of amphetamines for weight control can cause an increase in prolactin levels, which can lead to menstrual dysfunction as well.[150]

Conclusion

Weight gain in early childhood and the physiology of puberty put adolescents at high risk for obesity. Obesity that is present before the onset of puberty is associated with worse health outcomes in adulthood. The relationship between obesity and the onset and progression of puberty and the occurrence of regular menses afterward illustrates the important interaction between metabolic and behavioral risk. Added to this are the changes in diet and physical activity that also occur at this age, and there is a "triple hit" for obesity. Indeed, adolescence is the "perfect storm" of inciting factors, which conspire to cause and promulgate the obese state. Girls are particularly susceptible because of increased insulin resistance from estrogenic exposure.

Important work has already been done in the area of documenting earlier pubertal onset, but several gaps in our knowledge remain. First, obesity researchers tend to focus on either the physiologic or behavioral aspects of weight gain. More cross-disciplinary research needs to occur to explore the interactions between the two. We are still in need of longitudinal studies that examine the association of overweight/obese status and pubertal progression. Although it is clear they are strongly linked, the data on obesity and pubertal progression thus far do not demonstrate causality. Although we know that weight gain promotes leptin release, more work needs to be done exploring the specific details of this interaction in terms of leptin sensitivity at the hypothalamic level.

Finally, as we look toward developing interventions and therapies that target early adolescents, we need creative approaches to behavior change in this group. We also need to fine-tune our screening strategies to triage adolescents to the intervention to which they may respond best. Given the significant psychosocial, mental health, and medical consequences that obesity carries for adolescents, early intervention is imperative. This is especially true given how hard it is to effect behavior change in adults. We must focus our prevention and treatment efforts on younger children, which will require developing screening tools to identify high-risk children and the creation of developmentally appropriate interventions.

Conflicts of Interest

The authors declare no conflicts of interest.

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