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Etiologies of Obesity in Children: Nature and Nurture

Joseph A. Skelton, MD, MS^{1,2,3}, Megan B. Irby, MS^{1,2}, Joseph Grzywacz, PhD⁴, and Gary Miller, PhD⁵

¹Department of Pediatrics, Wake Forest University School of Medicine, Winston-Salem, NC

²Brenner FIT Program, Brenner Children's Hospital, Winston-Salem, NC

³Department of Epidemiology and Prevention, Wake Forest University School of Medicine, Winston-Salem, NC

⁴Department of Family and Community Medicine, Wake Forest University School of Medicine, Winston-Salem, NC

⁵Department of Health and Exercise Science, Wake Forest University, Winston-Salem, NC

Synopsis

Childhood obesity is a profoundly complex problem and serves as an example of a biopsychosocial issue. Scientific inquiry has provided incredible insight into the complex etiology of weight gain, but must be viewed as an interaction between a human's propensity to conserve calories for survival in a world with an abundance of it. This chapter will provide a brief overview divided between biologic (Nature) and psychosocial and behavioral (Nurture) factors.

Keywords

etiology; obesity; pediatrics; genetics

INTRODUCTION

Scientific inquiry has provided incredible insight into the causes of and contributors to childhood obesity, a profoundly complex biopsychosocial issue. An ecological approach to understanding obesity best captures the overlapping factors involved (Figure 1)¹. In this chapter we will provide a brief overview divided between biologic (Nature) and psychosocial and behavioral (Nurture) factors. However, as with any complex condition, the line between the two can often be blurred.

NATURE

The genetic and biologic determinants of weight and obesity are intertwined. With the discovery of leptin in 1994², the understanding of energy regulation, appetite, and adiposity

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Address correspondence to: Joseph Skelton, MD, Department of Pediatrics, Wake Forest University School of Medicine, Medical Center Blvd., Winston-Salem, NC 27157, Tel: (336) 713-2348, Fax: (336) 716-9699, jskelton@wfubmc.edu.

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has exploded, and the field has become increasingly complex as a result. Continued discoveries implicate other contributors, from intestinal microbes to stress.

Neuroendocrine Control of Body Weight

In simplest terms, neuroendocrine control of weight is a balance between short- and long-term control of weight, overall energy intake, and energy expenditure. This balance can also be better understood when divided between the central nervous system (primarily the brain) and the body (primarily the gastrointestinal tract and adipose tissue).^{3–5}

Short-term control—Short-term control of body weight largely concerns control of energy intake.^{3, 5} Meal initiation is primarily influenced by environmental stimuli such as food, emotions, time of day, and peers⁶. However, once the meal begins, neuroendocrine factors exert significant influence, thereby effecting the size of the meal, the amount of energy ingested, and when the meal is terminated (Table 1)^{3, 5}. Some signals released in response to ingested or circulating nutrients coordinate the digestion and absorption of nutrients and feelings of satiety.⁷ Opposing signals, such as those initiated by ghrelin, act to stimulate appetite by increasing before a meal and decreasing after a meal is finished. In obese individuals, serum ghrelin levels are decreased, and alone, is unlikely to be a significant contributor to individual obesity status. However, ghrelin tends to increase during diet-induced weight-loss, and may explain increased levels of hunger with dieting⁸. Most of the short-term, gastrointestinal signals have local effects, such as slowing gastric emptying and overall proximal gastrointestinal (GI) motility⁷, but also act centrally, either directly or via vagal actions.^{3–5, 7}

Long-term control—Long-term control is divided between the brain and body through levels of adiposity. These “adiposity signals” from the body act to communicate energy storage levels centrally, which then act to adjust energy intake and expenditure. (Table 2)

The primary signals from the body are leptin and insulin, both of which exhibit long-term control of food intake and metabolism⁵. Leptin is secreted in proportion to fat content of adipocytes, and down regulates neurons that control food intake in the arcuate nucleus^{3–5}. Obese individuals may have relative “leptin resistance,” similar to insulin resistance, contributing to obesity^{9, 10}. As with leptin, serum insulin levels increase in proportion to body fat and act centrally to relay energy stores.

An important discovery in the understanding of weight control is the endocrine function of adipose tissue¹¹. Leptin has an important role in the long-term control of body weight¹², whereas other hormones and cytokines released from adipose tissue impact overall health. Adiponectin has an important anti-inflammatory function in the body and is generally viewed as a protective counter-mechanism to inflammatory processes originating in adipose¹³. Visceral adiposity, long known to be linked to the metabolic syndrome and cardiovascular disease, is detrimental to health through inflammatory mechanisms, primarily through adipokines¹¹. Interleukin-6, tumor necrosis factor- α , plasminogen activator inhibitor-1, and visfatin are adipose-derived signals involved in atherosclerosis, insulin resistance, and inflammation^{3–5}.

The brain’s principal region for energy balance is the arcuate nucleus, located in the hypothalamus, which controls energy intake (eating) and expenditure (metabolism)^{3–5}. In addition to direct influence by circulating nutrients indicating satiation (e.g. glucose, fatty acids and some amino acids), the arcuate nucleus receives signals from leptin and insulin, expressing receptors for most adiposity signals regulating long-term control of weight. Neurons controlling these processes are Agouti-related peptide/neuropeptide Y (AgRP/ NPY) and proopiomelanocortin/cocaine- and amphetamine-regulated transcript (POMC/

CART). AgRP/NPY neurons are anabolic in nature, stimulating appetite and reducing metabolism, while POMC/CART neurons are catabolic, inhibiting food intake via release of α -melanocyte stimulating hormone. Neurons of the arcuate nucleus project to many other areas of the brain, particularly the hypothalamic paraventricular nucleus and the lateral hypothalamus⁵. The paraventricular nucleus is a major determinant of energy expenditure, synthesizing anorexigenic factors corticotrophin releasing hormone (CRH) and oxytocin, thereby regulating the body's response to stress. The lateral hypothalamus is responsible for orexigenic peptides, melanin concentrating hormone (MCH) and orexin. Other areas of the brain key to control of body weight are also influenced by hypothalamic projections. The mesolimbic-dopamine system influences the body's hedonic and reward response to food. The autonomic centers of the brainstem exert influence in the GI tract. Figure 2 illustrates how short- and long-term control of weight across the body and brain are integrated.

The endocannabinoid system, involved in the control of appetite, is found in the central and peripheral nervous system, liver, muscle, gastrointestinal, and adipose tissue¹⁴. On exposure to palatable food, the system releases endocannabinoids that act on the cannabinoid-1 receptor, which affects satiety¹⁵. This action overrides satiation, resulting in continued eating. There is some evidence that endocannabinoids play a role in peripheral tissues, linked to ghrelin release and adipose tissue regulation¹⁶.

Genes and other contributors to obesity

Although many genetic contributors to obesity have been identified in the past few decades, only 176 known cases of obesity have been linked to single-gene mutations in humans¹⁷. However, an increasing number of mutated genes can be traced to obesity phenotypes. The 2005 Human Obesity Gene Map indicates that 253 quantitative trait loci are related to obesity phenotypes, with 127 candidate genes. Possible candidate genes have been identified on every chromosome except Y. A few genetic abnormalities have been identified, with only one having a treatment avenue presently^{12, 18} (Figure 2).

- Leptin deficiency has been described in a few small series of families of Pakistani origin, characterized by severe obesity, hyperphagia, and other abnormalities^{12, 18}. These rare cases are responsive to leptin therapy. Mutations in the leptin pathway, particularly the receptor gene, may account for up to 3–4% of cases of severe, early-onset obesity^{4, 12}. However, these genetic abnormalities are unlikely to respond to leptin therapy.
- Mutations in POMC have been described, resulting in a lack of central appetite signaling and therefore hyperphagia. Affected patients have red hair and adrenal insufficiency as well¹⁹. Mutations in an enzyme that cleaves POMC have also been identified; these individuals are characterized by hypoglycemia, hypogonadotropic hypogonadism, and intestinal malabsorption.
- The melanocortin 3 (MC3R) and melanocortin 4 (MC4R) receptors are key in feeding behaviors. MC3R abnormalities may have a role in body weight regulation in African-American children. MC4R mutations are found in upwards of 3% of early onset severe obesity in children^{4, 12, 19}. Heterozygous and homozygous mutations appear to cause obesity, hyperphagia, and hyperinsulinism, as well as tall stature.
- Brain derived neurotrophic factor (BDNF) is thought to play a role downstream in the leptin pathway, and may be linked to early onset obesity in patients with WAGR syndrome⁴.
- Albright's hereditary osteodystrophy (AHO) is associated with pseudohypoparathyroidism, and also involves the leptin pathway⁴. Individuals with

AHO also have short stature, developmental delays and mental retardation, brachydactyly, and ectopic ossifications.

While the connection between a particular single nucleotide polymorphism (SNP) and obesity is not always clear, large genome-wide association studies hint at possible links, such as the fat mass and obesity associated gene (FTO) and reduced satiety, or perilipin A gene and resistance to weight loss⁴. Advances in genomics are rapidly identifying important areas of exploration.

There are numerous genetic syndromes associated with obesity, and for many the link is not clear. Syndromes may result in behavioral and health issues that lead to increased energy intake or decreased activity, or may have disruptions in the central control of appetite that result in hyperphagia. Typically, obesity is not the presenting sign of the syndrome, but is important in the clinical care of the child. For instance, Prader-Willi syndrome (short stature, hypotonia, developmental delay) involves significant hyperphagia, as do Bardet-Biedl (short stature, developmental delay, retinitis pigmentosa, polydactyly) and Alstrom (blindness or vision loss, hearing loss, hyperinsulinemia) syndromes⁴. Many other syndromes are associated with obesity, including Cohen syndrome, Fragile X, Sotos syndrome, Turner syndrome, and Beckwith-Wiedemann syndrome.

Infectious etiologies—A form of adenovirus (AD36) that results in increased adipose tissue in animal models^{20–22}. Laboratory studies using human adipose tissue demonstrates increased adipocyte formation²³, and individuals with higher obesity levels are more likely to have antibodies to AD36^{24, 25}. While it is unlikely the obesity epidemic is a result of widespread adenovirus infection, there appears to be some link between the two.

Gut microbiota—Similar to adenovirus, the predominance of particular strains of colonic bacteria have been associated with higher levels of obesity in animal models, with increasing evidence of an association in humans^{26, 27}. Theories linking obesity and gut microbes revolve around the bowel flora's use of energy from ingested foods, bacterial fermentation of foods into readily absorbable fatty acids, and influences on metabolism in peripheral organs.

Stress—Chronic stress impacts weight status through dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in altered cortisol metabolism²⁸. Stress can result from multiple causes, e.g. sleep deprivation, malnutrition, depression, and environmental stressors such as poverty. These factors may be related to obesity risk, even in the prenatal period^{29, 30}.

Medications

Many medications, particularly antipsychotics, cause weight gain³¹. High dose inhaled glucocorticoids, oral glucocorticoids, anti-psychotics (risperidone, olanzapine, clozapine), mood stabilizers (lithium), anti-depressants (tricyclics), anti-convulsants (valproate, carbamazepine), oral contraceptives, and insulin and insulin secretagogues are the more commonly reported ones, but there is a lack of studies in children³². Some anti-hypertensives, such as propranolol, nifedipine, and clonidine, can also lead to weight gain, as do many chemotherapy agents⁴. It is unclear what mechanisms are involved. With antipsychotics, for example, a complex interplay of hunger disruption, metabolic effects, and unknown mechanisms have been reported³³.

Endocrinologic conditions

Of children referred for evaluation of obesity, endocrinologic causes are only found in 2–3% of cases³⁴. Table 3 lists the most common disorders seen. Cushing Syndrome has a prevalence of approximately 1 in a million, while insulinomas are even more rare^{4, 35}. Hypothalamic obesity usually results from damage to the hypothalamus; these cases tend to occur in pediatric patients associated with surgery or radiation therapy. An example is children treated for craniopharyngiomas, which has high rates of obesity development post-treatment^{36, 37}.

In summary, whereas pure genetic contributors to obesity, such as the mythical “fat gene”, are quite rare, there are many genetically linked causes that can increase a child’s risk of obesity. There is evidence for the existence of a thrifty genotype and phenotype^{38, 39}. The protection of energy stores through famine and hunting/gathering societies has produced a human with a fine-tuned system of weight control described above. However, these factors are largely absent for most humans in industrialized nations today.

NURTURE

While there have been great discoveries in the biologic determinants of obesity in children, the rapid rise in obesity prevalence almost certainly points to environmental changes having the greater impact. External influences on obesity vary by life stage, circumstance, and genetic predisposition. Changes in the nutritional and activity environments of children and families over the past several decades have likely had the greatest impact on the present epidemic.

Obesity and the Life Cycle: Prenatal

Antenatal and In-Utero Environment—The antenatal environment influences fetal development. Fetal growth may be determined by cell counts, maternal brain centers that control satiety and appetite, and endocrine function even prior to conception⁴⁰. Antenatal stress or placental insufficiency may also influence altered pancreatic function and insulin sensitivity. These effects can persist into adulthood, increasing the risk for obesity-related conditions, such as metabolic syndrome⁴¹.

Maternal Malnutrition and Famine—Nutrient restriction from maternal malnutrition in the first two trimesters of the pregnancy is strongly linked to birth weight and an increased risk of obesity in young children⁴¹. In a historical cohort study of boys with intrauterine exposure to famine within the first two trimesters of development (the “Dutch Hunger Winter” during World War II), a 94% increase in risk of developing childhood obesity was found⁴². This may be attributable to structural and functional abnormalities of the endocrine system caused by nutrient restriction and disturbance in insulin and glucose homeostasis^{43, 44}.

Maternal Diabetes—Many studies have investigated prenatal exposure to diabetes in utero, indicating an increased prevalence of childhood overweight or obesity if the mother was diabetic during pregnancy⁴⁵. Mechanisms potentially responsible for this increased prevalence include fetal hyperglycemia and hyperinsulinemia, caused by the diabetic mother’s poor glycemic control^{46, 47}. Insulin levels in third-trimester amniotic fluid have also been linked to childhood obesity and the development of insulin resistance and systolic hypertension⁴⁸.

Maternal Smoking During Pregnancy—Children exposed to prenatal cigarette smoke are more likely to exceed the 90th percentile for BMI during adolescence⁴⁹. In one

longitudinal study, 14% of 6-year-olds exposed to maternal smoking in the womb were obese, compared to 8% in those who were unexposed⁵⁰. Additional studies confirm these findings⁵¹, even after adjusting for multiple maternal confounders⁵². Proposed mechanisms for this association include nicotinic effects on leptin⁵³ and maternal appetite, and impaired fetal oxidative metabolism due to carbon monoxide and cyanide compounds found in cigarette smoke⁵².

Maternal Weight and Pregnancy—Maternal weight both before and during pregnancy, and the magnitude of weight gain during pregnancy, are linked to increased risk of overweight or obesity in offspring⁴⁸. Maternal obesity, especially in the first trimester, markedly increases the risk that a child will be obese by 4 years old^{52, 54}. Maternal weight gain during pregnancy is also associated with higher likelihood of childhood obesity^{55, 56}, and the odds of having a child with a BMI above the 95th percentile at age 7 increases by 3% for every kilogram of weight gained during pregnancy⁵⁷.

Obesity and the Life Cycle: Post-natal

Breastfeeding—Breastfeeding versus formula feeding is an important nutritional decision that may impact childhood obesity risk. In some studies, breastfeeding was protective against child^{50, 58–61} and adolescent^{62–64} obesity, while others have found little effect^{65–67}. The evidence suggests that breastfeeding reduces risk for pediatric weight gain; formula-fed children have an obesity prevalence of 4.5% compared to 2.8% in breastfed children⁶⁸. More recent investigations indicate that breastfeeding for 6 months or more has a modest protective effect against adolescent obesity, but not overweight⁶⁹. In one report, breastfeeding more than 6 months was associated with the lowest risk of overweight and obesity in 5-year-olds⁸.

Early Postnatal Years—As with breastfeeding, over-nutrition and early childhood feeding practices are major contributors to childhood obesity, influencing leptin concentrations and adiposity later in life⁷⁰. The rate at which an infant gains weight during their first few months, and the type of infant feeding (formula or breast milk), is linked to weight status in later childhood, as well as adult cardiovascular disease risk⁶¹. Independent of birth weight and weight at one year old, rapid weight gain even within the first 4 months of life is associated with an increased risk of overweight at age 7⁷¹.

Early Childhood Feeding and Parenting—Home and social environments, parenting styles, and family feeding practices are the primary influences on early childhood nutrition behaviors^{72, 73–76}. Nearly two-thirds of all meals consumed by children come from the home, despite the prevalence of fast food restaurants and convenient dining establishments⁷⁷. Thus, the home environment and family feeding behaviors are crucial components in the development of childhood nutritional habits, and have an undeniable influence on childhood weight status^{78, 79}.

Authoritarian parenting styles, characterized by restriction, pressures to eat certain foods, and over-monitoring, are most consistently linked to pediatric weight gain^{80, 81}. However, children raised by authoritative parents who promote responsibility, monitoring, and modeling⁸⁰, are more likely to have healthier nutrition and lower BMIs⁸². Child-centered feeding practices⁷⁴, positive nutrition encouragement, and parents' intake of fruits and vegetables are also positively associated with fruit and vegetable consumption in their children⁷⁵. These data support the notion that family factors are crucial components in the prevention and treatment of pediatric obesity.

Early introduction of solid foods may have a contribution to the development of obesity. There is some evidence that rapid weight gain in infancy can predict later obesity⁸³, with infants already being exposed to unhealthy dietary patterns⁸⁴. Most studies have tracking obesity development to infancy have not accounted for age of first solid food introduction⁸⁵. An Australian study found that delayed introduction of solids did significantly reduce the odds of overweight and obesity at age 10 years⁸⁶, and a prevention study appeared to lower risk of obesity development by delaying introduction of solids as part of a multicomponent intervention⁸⁷. One review of the literature did not find an association between age of solid food introduction and obesity development⁸⁸, but available evidence has not answered this question sufficiently.

Adiposity rebound—Adiposity rebound – when a child reaches a BMI nadir before body fat increases – typically occurs between 5 and 6 years old. Normal weight children with at least one overweight parent at the time of adiposity rebound are nearly 5 times as likely to be obese as an adult. If both parents are obese, children before the adiposity rebound have a 13-fold risk of being obese adults⁸⁹. Risk for adult obesity increases with earlier onset of childhood obesity. Children who reach adiposity rebound earlier are five times more likely to develop adult obesity, and those who are already overweight at the time of adiposity rebound have six times the risk for adult obesity⁸⁹.

Changes in the Family

It is intuitive that changes in family structure affect nutrition and physical activity habits of families. Family meals, fast food, early childhood feeding practices, sleep routines, parenting style, media use, family-based physical activity, adult obesity levels, socio-economic status, and interaction with health services are key factors associated with childhood obesity, and are most likely moderated by changes in the family. Families in the United States have experienced substantial changes as the child obesity epidemic has developed. In 1970, approximately 85% of children lived with two married parents, by 2010 this estimate dropped to 66%⁹⁰, and most of the change occurred between 1970 and 1990 (Table 4). During the same period, children living in a mother-only household increased from 11% to 23%, with significant differences across racial groups⁹⁰. This is important, as children from mother-only households are at substantially increased risk for living in poverty⁹¹, a major risk factor for childhood obesity and poor health outcomes^{92, 93}. During this same time period, there was a substantial growth in women's labor force participation, increasing from 43% in 1970 to 66% by 2009⁹⁴. However, there is little direct evidence linking these changes in the family to obesity risk in children.

Lifestyle and Environment

Diet—Among dietary factors linked with obesity, high-fat and sugar-containing foods have been the most studied. While overconsumption of some foods leads to excessive weight gain and obesity, other patterns (e.g. consuming a diet high in fruits and vegetables) are thought to protect against obesity. Fruits and vegetables have high water and dietary fiber contents, making them low in energy density. While the mechanism(s) for their action remain unclear, eating a diet high in fruits and vegetables may help reduce body weight and fat by displacing energy-dense foods from the diet^{95, 96}. Fiber in fruits and vegetables helps reduce total energy intake by initiating satiety^{97, 98} and altering postprandial hormones through a reduction in glycemic load^{99, 100}. Yet in a recent review of studies about fruit and vegetable intake and adiposity levels in children¹⁰¹, only 1 of 5 observed the expected inverse relationship between fruit and vegetable intake and adiposity¹⁰². In a cross-sectional analysis, the lifestyle behavioral pattern of eating dinner, cooked meals, and vegetables was inversely related with obesity in children¹⁰³. There are limitations to these studies, with others drawing different conclusions on the link between fruits, vegetables, and obesity¹⁰⁴.

However, no studies show a worsening of weight status with increased vegetable and fruit consumption.

America's eating patterns have changed drastically in the past three decades. In children ages 2–18 years, energy density and portion sizes of key foods, including salty snacks, fruit drinks, french fries, hamburgers, cheeseburgers, pizzas, and Mexican fast foods all increased from 1977 to 2006¹⁰⁵. McConhay and colleagues showed that nearly 20% of variance in daily energy intake can be attributed to portion size¹⁰⁶. Similarly, portion size, but not energy density, of snacks was the primary determinant of energy intake¹⁰⁷. At the same time, portion sizes of foods in the American diet have increased in the last several decades^{108, 109}.

In one study, doubling the portion size of foods offered to preschool age children during a 24-hour period increased energy intake by 12%⁹⁶, but only in certain foods. However, there was no compensatory reduction in other foods, leading to a higher daily energy intake. In contrast, an earlier study suggested young children can self-regulate energy intake up to 30 hours following a meal¹¹⁰. In general, increasing portion sizes and energy density of foods and meals raises meal consumption from ~10–40% and daily energy intake by 12%^{96, 111–114}. But there is a dearth of well-designed studies on how portion size and energy density affect energy intake in children.

Rising rates of obesity coincide with the increased consumption of added sugars¹¹⁵. For 2 to 18-year olds, nearly 20% of total energy intake is from added sugars in foods and beverages¹¹⁶. Recent systematic reviews ranged from finding no evidence to strong evidence that sugar-sweetened beverages make a significant contribution to BMI in children^{117, 118}. Cross-sectional studies in children showed positive associations (at least in sub-group analyses) between the use of sugar-sweetened beverages and measures of obesity (weight, BMI, body fat)^{119–125}, although others showed either weak or no association between these variables^{126–130}. In a study of over 10,000 children and adolescents, overweight people consumed a higher proportion of their total intake from soft drinks than did normal weight individuals¹³¹. Observational follow-up studies reported positive associations between intake of sugar-sweetened beverages and overweight/obesity^{120, 132–134}.

Activity—Arguments that the obesity epidemic is caused largely by reduced physical activity and not energy intake are based on national survey data indicating that daily energy intake is unchanged or reduced in the last several decades. Not only is daily energy expenditure decreasing, sedentary activities are increasing^{135–137}. In one report, children who watched over 4 hours of television daily had the highest BMIs, and those who watched less than 1 hour daily had the lowest BMIs¹³⁵. In a separate study in Mexico City, the odds ratio of obesity was 1.12 for each hour of television watched per day and 0.9 for each hour of moderate-to-vigorous physical activity per day¹³⁶. They found no such effect for time playing videogames.

In an early meta-analysis looking at the relationships between sedentary behaviors and obesity in children and youth, a statistically significant association was observed between television viewing and body fatness in children¹³⁸. However, in one study, television viewing only explained ~1% of the variance in body fatness, whereas video and computer game use showed no effect with body fatness. Studies have also failed to find correlations between television viewing and BMI¹³⁹. While there is biologic plausibility linking television viewing to body fatness, most of the evidence is from cross-sectional studies, which many demonstrate fairly small responses. In a randomized controlled trial, an intervention specifically geared to reduce television viewing and video game use in 8–9 year

old children, produced an improvement in body fatness over a 6-month follow-up¹⁴⁰. Other intervention studies that did not specifically intervene on these sedentary behaviors reported decreases in television viewing and body fatness, but were not necessarily causal^{141, 142}. Currently we lack empirical data to support claims that television viewing, playing video games, or using computers lead to obesity or interfere with physical activity. A possible confounder to these analyses is consumption of energy-dense snacks while participating in the sedentary behaviors. As Proctor et al.¹⁴³ found, children who watched the most television and had a fat intake of more than 34% of their daily kcal consumption, gained the most body fat from 4 to 11 years.

Overall, low levels of physical activity, defined by not meeting recommended levels, are problematic, and mirrors increased sedentary activity^{144, 145}. This disruption in energy balance can explain much of the rise in pediatric obesity.

Sleep—The link between pediatric obesity, higher body fat, and sleep duration has been widely demonstrated in the literature, and was recently reviewed in this journal¹⁴⁶. Although trials are ongoing, no interventions have reported on the manipulation of sleep patterns and the influence on weight gain in children. In adults, however, studies have shown that chronic sleep deprivation may lead to weight gain, which can be attributed to the influence of sleep on hormonal secretions¹⁴⁷. Restricted sleep is associated with increased food intake, including both meals and snacks^{148, 149}, thereby increasing obesity risk. Lack of sleep can also lead to reduced physical activity and increased sedentary behaviors^{150, 151}.

Although causation cannot be established, epidemiologic studies in children have indicated a definitive association between reduced sleep duration at night and increased weight status. A number of reviews and meta-analyses agree that children who sleep less have an increased risk for obesity between 56% and 89%^{152, 153}. Increased BMI in children is associated with reduced sleep duration, which is most likely due to an increase in adipose tissue deposits¹⁵⁴.

Industrialization and Obesity

Obesity and associated health issues are a world-wide health concern. Increased consumption of a more “Western” diet means that eating sugar and fat-laden, highly processed energy-dense foods occurs globally. Popkin describes nutrition transition as existing in several stages, with urbanization, economic growth, and technological changes for work, leisure, and food processing leading the changes in stages¹⁵⁵. Obesity is evident in Stage 4, or the degenerative disease period, characterized by increased intake of fat, sugar, and processed foods, and a more prominent presence of technology in work and leisure.

Although urbanization, a demographic factor, improves growth patterns in children, it also increases the proportion of children above the 95th percentile for weight-for-age. Major social and economic changes in communities, such as transitioning from physical to mechanized transportation, introduction of processed foods and supermarkets, and television access, also change obesity and overweight prevalence in children. For example, the proportion of children (5–12 year age group) above the 85th percentile for BMI increased from under 15% to nearly 50% in less over 20 years in the White Mountain Apache reservation¹⁵⁶.

The Built Environment

The built environment is a likely explanation for disparities in several health indicators, including the prevalence of obesity. There is substantial evidence showing that alterations in built environments regarding physical activity and eating is a factor in childhood obesity¹⁵⁷. For example, neighborhood differences in food access influence levels of obesity^{158–161}. In

adolescents and adults, better availability to healthful food products leads to healthier food intake, including more fruits and vegetables, less dietary fat, and improved diet quality^{162–166}. Consequently, lower risks for obesity in children and adolescents are associated with better access to a supermarket^{158, 159, 161, 167}.

Schools play a prominent role in a child's nutrition, since most children eat at least 1 meal per day at school and spend ~6 hours per day in this setting. The presence of fast-food establishments within 0.1 mile from a school was associated with a 5% increase in obesity rates, whereas further distances had no effect on obesity rates in the school¹⁶⁸.

Urban sprawl is also associated with adult obesity, while walkable neighborhoods and communities with sidewalks, safe intersections, accessible destinations, appealing green spaces, and public transit have improved activity levels and health¹⁶⁹. For each additional hour spent in a car per day, there is a 6% increase in the likelihood of obesity; for each additional kilometer walked, a nearly 5% drop in obesity is present¹⁷⁰. A policy statement from the American Academy of Pediatrics has called for a multidisciplinary approach to building communities that promote active lifestyles in children¹⁷¹.

SUMMARY

Childhood obesity is a complex medical issue, representing the interplay of physical and environmental factors. The neuroendocrine control of weight contains multiple situations where genetic variation can influence a person's weight status. Unfortunately, the unhealthy evolution of food and activity environments has placed children at a higher risk for obesity and associated weight problems than they ever have been before.

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Figure 1.

AgRP	Agouti-Related Peptide
ARC	Arcuate Nucleus
CART	Cocaine-Amphetamine-Regulated Transcript Neurons
CCK	Cholecystokinin
Ghr	Ghrelin
GLP-1	Glucagon-Like Peptide 1
In	Insulin
Lep	Leptin
α-MSH	α-Melanocyte-Stimulating Hormone
NPY	Neuropeptide Y
OR	Orexin
Oxm	Oxyntomodulin
POMC	Pro-opiomelanocortin
PP	Pancreatic Polypeptide
PVC	Periventricular Nucleus
PYY ₃₋₃₆	Peptide YY

Figure 2.
Signals involved in the control of energy intake and expenditure

Table 1

Signals involved in the short-term control of body weight

Name	Origin	Action and affect
Amylin	Pancreas (β -cells); co- secreted with insulin	Reduces meal size via brainstem mechanisms
Cholecystokinin (CCK)	Intestine (I-cells)	Controls meals size by slowing gastric emptying; stimulates gallbladder contractions; likely activates vagal receptors to terminate meal
Ghrelin	Stomach	Potent appetite stimulation, likely via central nervous system mechanism
Glucagon-Like Peptide 1 (GLP-1)	Intestines (L-cells)	Stimulates insulin release; reduces appetite
Oxyntomodulin	Colon	Reduces appetite
Pancreatic Polypeptide	Pancreas	Reduces appetite, likely by inhibiting pancreatic, gallbladder, and GI tract activity.
Peptide YY (PYY ₃₋₃₆)	Intestines (Ileum/colon); co-secreted with GLP-1	Reduces appetite. Slows gastric emptying

Table 2

Signals involved in the long-term control of body weight

Name	Origin	Action and effect
Adiponectin	Adipose tissue	Enhances insulin sensitivity, decreases inflammation
Agouti-Related Peptide	Arcuate Nucleus (hypothalamus)	Increases appetite; decreases metabolism
Arcuate Nucleus	Hypothalamus	Area of energy regulation; location of CART, POMC, AgRP, NPY
Cocaine-Amphetamine-Regulated Transcript Neurons	Arcuate Nucleus (hypothalamus)	Reduces energy intake
Insulin	Pancreas	Reduces energy intake
Leptin	Adipose tissue	Reduces energy intake
α -Melanocyte-Stimulating Hormone	POMC (ARC, hypothalamus)	Reduces energy intake
Neuropeptide Y	Arcuate Nucleus	Increases appetite; decreases metabolism
Orexin	Hypothalamus	Increases appetite
Oxymodulin	Colon	Reduces appetite
Pro-opiomelanocortin	Arcuate Nucleus (hypothalamus)	Releases α -MSH; reduces energy intake
Periventricular Nucleus	Hypothalamus	Appetite and autonomic regulation

Table 3

Endocrinologic causes of childhood obesity

Condition	Significant signs and symptoms
Hypothyroidism	Short stature and obesity but weight below 95 th percentile for age
Growth hormone deficiency	Decreased linear growth velocity with increasing weight gain; increased central adiposity
Cushing Syndrome	Decreased linear growth velocity; increased central adiposity; abdominal striae; insulin resistance
Insulinoma	Increased food intake to counteract low blood sugars
Hypothalamic obesity	Hyperphagia; other endocrine disorders;
Pseudohypoparathyroidism Type 1A	Multiple other endocrine deficiencies

Table 4

Percentage of children living in major family structures by decade between 1970 and 2010

	Living w/Two Married Parents	Living w/Mother Only	Living w/Father Only	Living w/no Parent
1970	85.0	10.9	1.1	3.0
1980	76.6	18.0	1.7	3.7
1990	72.5	21.6	3.1	2.8
2000	69.1	22.4	4.2	4.1
2010	65.7	23.1	3.4	4.1
Decade change				
1970–1980	–10.4	+65.1	+54.5	+23.3
1980–1990	–5.4	+20.0	+82.4	–24.3
1990–2000	–4.7	+3.7	+35.5	+46.4
2000–2010	–4.9	+3.1	+19.0	0.0

Source: Child Trends (2011)