Endotext

SPECIAL CONSIDERATIONS RELEVANT TO PEDIATRIC OBESITY

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ABSTRACT

In most humans, body fatness is a quantitative trait reflecting the interactions of environment, genotype, and development. The metabolic predisposition to obesity and its co-morbidities in adulthood begins in the intrauterine environment, extends into early childhood, and is further impacted by puberty. An understanding of the pathogenesis of obesity in children, and its implications for the risk of obesity in adulthood, has the potential to inform healthcare providers about early identification and use of precision medicine approaches towards both prevention and treatment. This chapter begins with a review of the epidemiology and definition of pediatric obesity followed by a discussion of risk factors for adult obesity from genetics to the prenatal environment (epigenetics) through childhood. The next section emphasizes that while some adiposity-related problems are unique to the pediatric population, multi-system co-morbidities of adult obesity are increasingly prevalent in children. The chapter concludes with a discussion of recommendations for intervention(s) and an invitation for providers to engage federal and local governments in discussions of ways to unite families, schools, and communities in the battle against the costliest nutritional problem for children in the United States.

INTRODUCTION

Obesity and its co-morbidities currently account for over $250 billion per year in health care costs (~25% of total U.S. health care budget (1)) and is projected to increase to over $900 billion by the year 2030 (2). Obesity is a complex disease reflecting interactions of an increasingly permissive environment on a background of genetic predisposition and developmental programming (3-7). Results from 2017-March 2020 National Health and Nutrition Examination Survey (NHANES, Figure 1A) indicate that an estimated 21.5% of U.S. children and adolescents aged 2-19 years have obesity (Body mass index [BMI] > 95th percentile for age and sex), an increase of 25% over the last decade, and 6.1% have severe obesity (BMI > 125% of 95th percentile for age and sex) (6,8,9). The prevalence of obesity is significantly higher in non-Hispanic Black and Hispanic children (Figure 1B**)**. By adolescence, the prevalence increases to two-fold and nearly three-fold in these groups respectively compared to their non-Hispanic White or Asian counterparts.

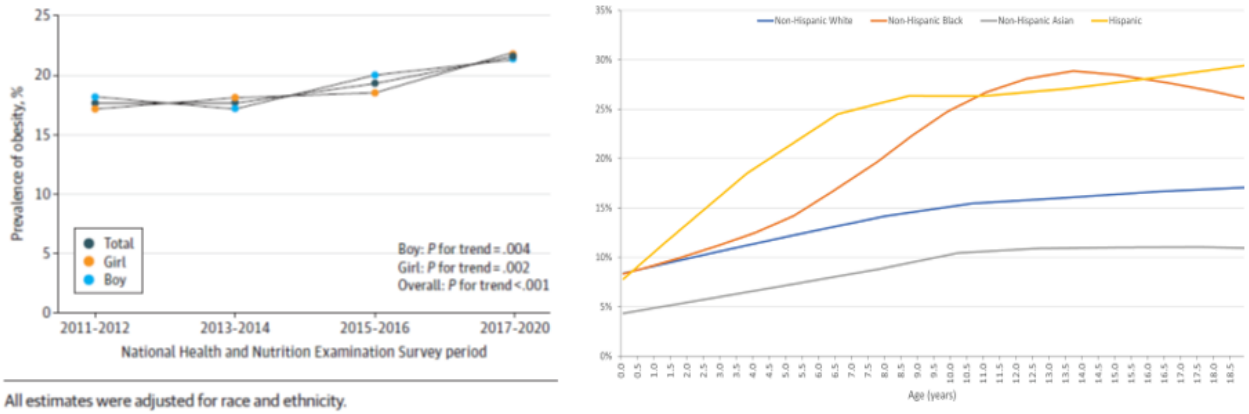

Figure 1. Prevalence of obesity in youth. A. Trends in prevalence of obesity by age group in the past decade years (281). B. Obesity prevalence in youth by age, race, and Hispanic origin in United States, generated using data from National health and nutrition examination survey 2015-2018 (n=6710). Obesity was defined as BMI ≥ 95th percentile for youth 2-20 years of age using CDC 2000 growth charts and weight-for-height ≥ 97.7th percentile from birth to 2 years using WHO growth charts (282).

The prevalence of pediatric obesity and its co-morbidities, such as type 2 diabetes mellitus (T2DM), have been increasing in parallel. Pediatric obesity tracks into adulthood, especially if present in the peri-pubertal period (over 20-fold increased risk adult obesity) and if one or both parents have obesity (10). These problems disproportionately affect Black, Hispanic, and Native American communities (8,11,12). It is also worth considering that although a higher percentage of adults have obesity, the fractional magnitude of obesity prevalence among youth is growing faster. From 1971-2018 the prevalence of adults with obesity increased by about 2.8 fold (from about 15% to 42%) whereas the percentage of children with obesity increased by 3.8 fold (from about 5% to 19.7%) (8). Recent CDC reports using data from comprehensive electronic health records indicate that the monthly rate of BMI increase in children aged 2-19 years nearly doubled during the COVID pandemic period (0.100 versus 0.052 kg/m^2/month; ratio = 1.93) and the prevalence of obesity increased from 19.3% in August of 2019 (pre-pandemic) to 22.4% in August of 2020. Children with higher BMI z-scores and between the ages of 6 and 11 years were most affected. (13).

Adults entering non-surgical weight loss treatment will typically lose weight for approximately 6-8 months followed by inexorable weight regain. Overall, only about 15% of adults with obesity are able to lose and sustain a greater than 10% weight loss, even with intensive lifestyle or pharmacological interventions. This number has not changed in over 20 years despite multiple new pharmacological and other treatment options (14-17). A key question is whether or not children are more responsive to interventions to treat, or to prevent, obesity.

Reviews of large lifestyle weight loss intervention studies indicate that children are more successful than adults in sustaining weight loss (usually defined by BMI z-score) provided that they remain involved in the intervention (see treatment discussions below) and that earlier intervention is more effective. Reinehr et al (18), performed retrospective quality assessments of 129 pediatric obesity programs at 6, 12, and 24 months and found that reduction of overweight was achieved by 83% of the children after 6 months, by 82% after 12 months, and by 76% after 24 months. The mean change of SDS-BMI was −0.20 ± 0.32 at 6 months, −0.19 ± 0.40 at 12 months, and −0.20 ± 0.54 at 24 months indicating an average of about 8% sustained reduction in adiposity. In adults with T2DM and overweight or obesity enrolled in the prospective LookAHEAD trial (15), the 1 year weight loss in the intensive lifestyle intervention group was 8.6± 0.1%

(similar to children) but by year 2 it had fallen to 6.4±0.2% and by year 4 to 4.7±0.2% despite continued intervention.

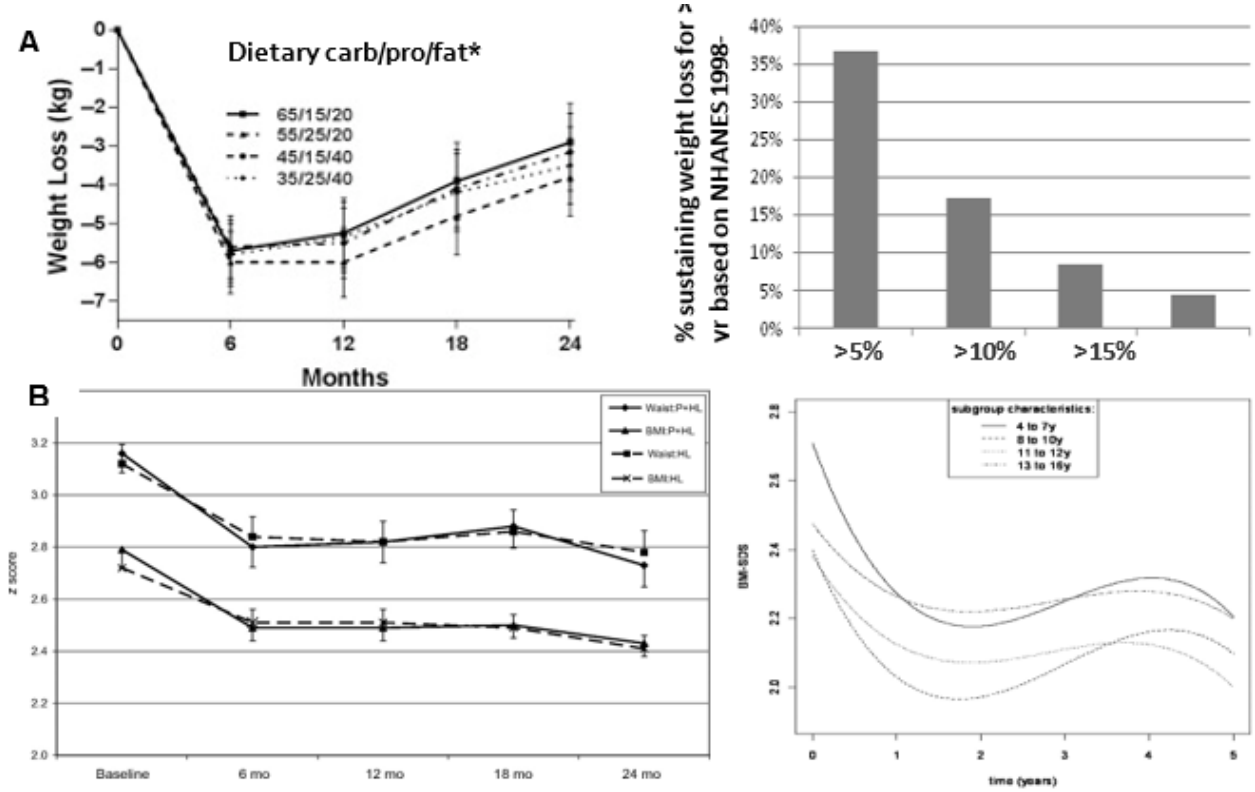

Figure 2. Patterns of weight loss and regain in children and adults. A. On average, adults will lose weight for only about 6-9 months during lifestyle intervention to treat obesity. After this, most will then begin to regain weight (283-286). B. In contrast, children tend to lose more fatness (expressed as BMI z-score) and sustain their weight loss longer following a lifestyle intervention (61,62). This is especially true for younger children. *Based on DeJonge et al (286). †Based on Kraschnewski et al (16).

Meta-analyses of pediatric weight loss lifestyle interventions have generally noted reductions in BMI, BMI z score and weight that are influenced by both the type and duration of the intervention (19,20) and exceed results seen with lifestyle interventions in adults especially if intervention is initiated early. Figure 2 illustrates examples of patterns of weight loss followed by weight regain seen after lifestyle interventions in adults (Figure 2A) and children (Figure 2B). It is clear that most adults will lose a smaller fraction of total body fat and are less likely to sustain that loss than are children, and that younger children are more likely to reduce body fatness and keep it off than older children or adults. Similar patterns of weight loss and weight regain are seen in pharmacological interventions to treat adults with obesity.

These data indicate that there is a greater likelihood of successful treatment of obesity and reduced weight maintenance in children than adults but must be interpreted caution. Adult studies, such as LookAHEAD involve a continuous active intervention that may include medication while pediatric studies, such as Obeldisks (11) (Figure 2) are only single year interventions with intermittent follow-up. Prospective pediatric studies such as Obeldisks may have a much higher attrition rate (about 70%) than adult studies such as LookAHEAD (about 10%), perhaps due to

less contact with participants and type of intervention, as well as participant retention resulting in a smaller and less diverse study population of pediatric completers.

DEFINITION AND EPIDEMIOLOGY

The ideal diagnostic criteria for pediatric obesity would include some assessment of adiposity-related co-morbidity, the risk of persistence of the obesity into adulthood, as well as the risk of future morbidities that would be worsened by excess weight.

Several basic principles are pertinent to such an assessment:

- During the first year of life there is an increase in weight for height followed by a decline and a second increase at about 6 years of age (designated as "adiposity rebound"). Early adiposity rebound, prior to 5 years of age, is associated with a higher risk of adult obesity (21,22).
- The risk of persistence of pediatric obesity into adulthood increases with age, independent of the length of time that the child has been obese (3,23).
- Growth patterns are familial and may be predictive of adult adiposity. A mildly overweight adolescent with a family history of adult obesity may be at greater risk for subsequent obesity than a severely overweight youth with a negative family history (3,23).
- The risk of adiposity-related morbidity is strongly influenced by family history, regardless of obesity in the affected family members, and varies between racial/ethnic groups (3,23,24).

BMI is often used as a "surrogate" for body fatness. Although it does not measure body fat, it correlates with direct measures of body fatness within a population (25,26). In adults, obesity is frequently divided into categories– Class 1: BMI of 30-35 kg/m^2; Class 2: BMI of 35-40 kg/m^2; and Class 3: BMI ≥ 40 kg/m^2. Class 3 is also categorized as "severe" obesity. These definitions cannot be used in children because normative values for BMI are age- and sex-dependent (27). In 2007, the AAP Expert Committee recommended that children between the ages of 2-19 years with BMI > 95th percentile are classified as "obese" and those with a BMI between the 85th and 95th percentile are classified as "overweight" (28) using the 2000 Centers for Disease Control (CDC) growth charts. These charts were constructed from data collected between 1963-1980, that included lambda-mu-sigma (LMS) parameters to calculate ten smoothed percentiles between 3rd and 97th percentile (28). However, extreme percentiles for heavier children extrapolated using CDC LMS parameters did not match well to the empirical data for the 99th percentile obtained in the later years. Instead, a better fit to the empirical data was obtained by using 120% of the smoothed 95th percentiles (29). This modification gave rise to the extended BMI growth charts that provides a flexible approach to describe and track children with obesity. (30). The American Health Association recommended classification of BMI ≥ 120% of 95th percentile as severe (equivalent to Class 2) obesity (31). Subsequent publications have defined overweight as BMI between 85-95th percentile, Class 1 obesity as BMI between 95th- 120% of 95th percentile, Class 2 between 120% -140% of 95th percentile and Class 3 as ≥ 140% of 95th percentile, making the classification similar to that used in adults (32-34) (Figure 3). For children less than two years of age weight/recumbent length ≥ 97.7th percentile based on the World Health Organization (WHO) charts is currently used to define obesity (24,35).

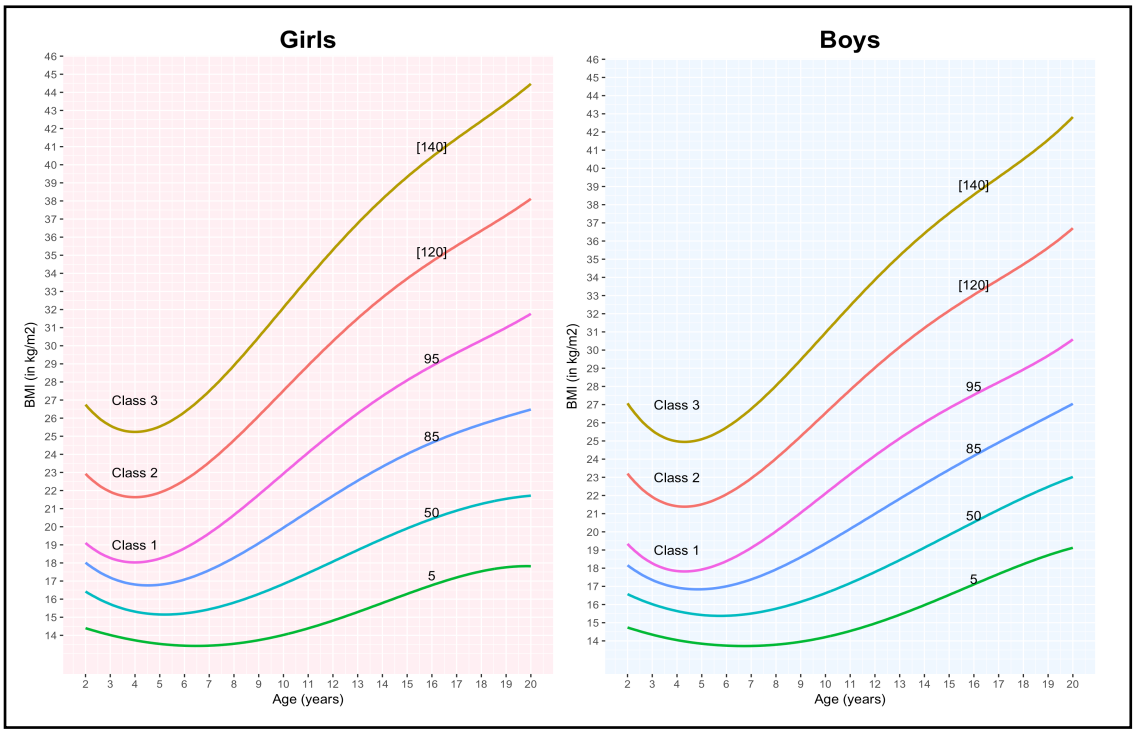

Figure 3. Normative BMI growth curves for boys and girls. Extended BMI curves for youth aged 2-20 years of age based on Gulati et al (30). Class 1 obesity defined as BMI between 95th- 120% of 95th percentile; Class 2 between 120%-140% of 9th percentile; Class 3 ≥ 140% of 95th percentiles (287).

Normative data have also been established for waist circumference during childhood (Figure 4). Waist circumference is measured at the level of the upper border of the right superior iliac crest with horizontal alignment of the measuring tape, parallel to the floor, lying snug, but not compressing the skin. These data are most helpful in identifying children at risk for insulin resistance, type 2 diabetes, and dyslipidemia. The limitation of waist circumference is in the difficulty in properly locating anatomic landmarks such as the umbilicus and superior iliac crest, especially in individuals with severe obesity and/or a large volume of subcutaneous adipose tissue.

As noted above, BMI does not directly measure body fat. Individuals at either extreme (low or high) of percent body fat may be incorrectly labeled solely based on BMI. In such cases, if the clinician is uncertain, further evaluation may require more precise methods of assessing body fat such as bioelectrical spectroscopy (BIS), air displacement plethysmography (BOD POD), dual-energy X-ray absorptiometry (DEXA) scanning, or Quantitative Magnetic Resonance (QMR) (36,37).

Obesity in childhood and adolescence predisposes to obesity in adulthood. In a meta-analysis of 200,777 subjects derived from fifteen prospective studies, Simmonds et al showed that youth with obesity were five times more likely to have obesity in adulthood. Over half of the individuals with obesity in childhood will have obesity in adolescence and nearly 80% of adolescents with obesity will continue to have obesity in adulthood (38). In a separate meta-analysis of thirty-seven studies, the same group showed that high childhood BMI was associated with an increased incidence of adult diabetes (OR 1.70, 95% CI 1.30-2.22), coronary heart disease (OR 1.20, 95% CI 1.10-1.31), and a range of obesity associated cancers (39). It should be noted that while childhood obesity persists when present, not all adults with obesity or its associated co-morbidities had obesity in childhood, re-emphasizing that obesity is a result of complex

interaction between familial predisposition, likely from genetics, and the environment.

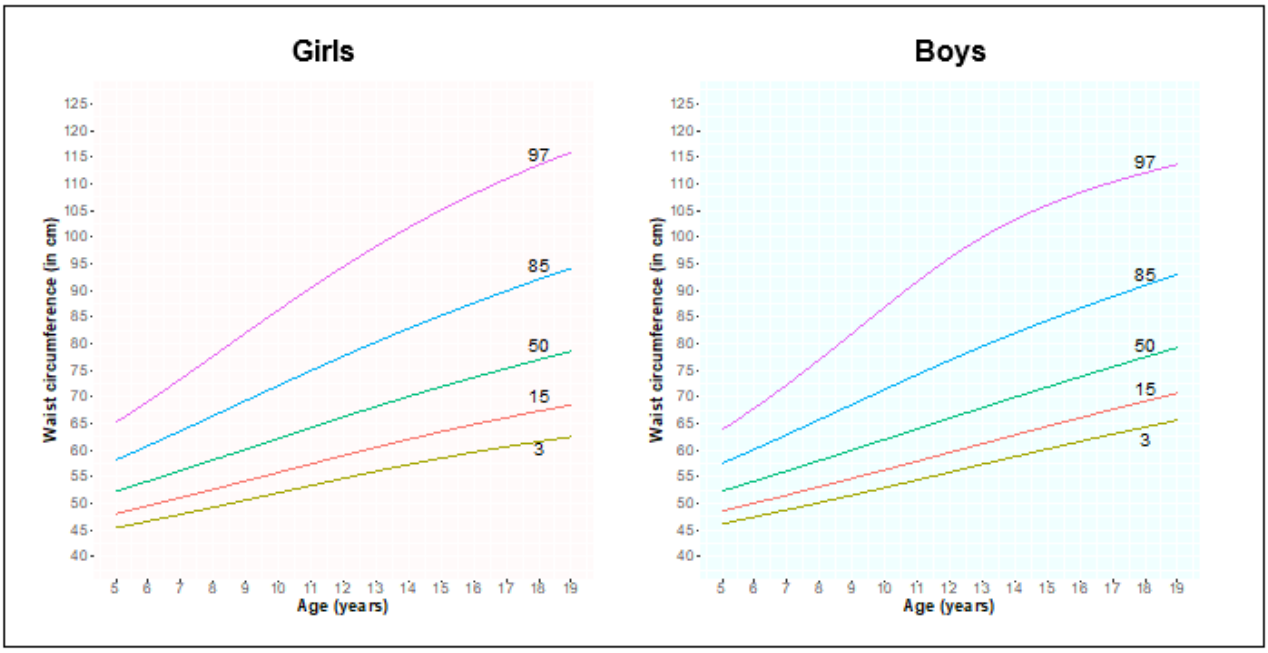

Figure 4. Waist circumference (measured at the iliac crest while subjects stood and placed their hands on opposite shoulders) curves for North American Children age 5-19 years derived from NHANES III data (196) by the Canadian Pediatric Endocrine Group (https://cpeg-gcep.net/content/waist-circumference-and-waist-height-ratio-charts). Charted indices for these variables at extreme of body fatness are currently not available.

In addition to initiating therapy in childhood when it is more likely to be effective, it is also important to identify the child who is "at-risk" of becoming an obese adult. The risk of adult obesity is higher in children with a first degree relative with obesity and also increases as the child approaches puberty. Whitaker et al (23), examined health records from 854 subjects born at a health maintenance organization in Washington State between 1965 and 1971 and tracked them into early adulthood (age 21-29 years). The odds ratio for a child with obesity (defined as BMI > 85%ile for age and sex) becoming an adult with obesity rose steadily from 1.3 at age 1-2 years, to 22.3 at age 10-14 years, and 17.5 at age 15 to 17 years of age. In contrast, the effects of parental obesity on odds ratio decreased with age from 3.2 at age 1-2 years to 2.2 at age 15-17 years. More studies like this using larger populations will be informative regarding predictors of having obesity in adulthood.

ENERGY HOMEOSTASIS

The first law of thermodynamics dictates that the accumulation of stored energy (fat) must be due to caloric intake more than energy expenditure. A sustained small excess of energy intake relative to expenditure will, over time, lead to a substantial increase in body weight. For example, a 50 kg individual who increases their daily caloric intake by 150 kcal (8 ounces of whole milk) above their usual daily energy expenditure (~1800 kcal/day) would gain approximately 8 pounds before sufficient fat-free mass (FFM) was reached to result in a new equilibrium between energy intake and expenditure (assuming approximately 30% of weight gain is FFM). This assumes, however, that there were no metabolic adaptations to maintain body energy stores in the face of overnutrition (40,41). In fact, adults maintain a

relatively constant body weight, and most children tend to grow steadily along their respective weight percentile isobars for age, with little conscious effort to regulate energy intake or expenditure, despite the potentially large effects of small imbalances in energy intake versus expenditure.

The high rate of recidivism to previous levels of fatness by reduced-obese children and adults (42-47), and the tendency for individuals to maintain a relatively stable body weight over long periods of time despite variations in caloric intake (48), provide empirical evidence that body weight is regulated. It is now known that energy intake and expenditure are responsive to complex interlocking control mechanisms in which numerous afferent signals from the gastrointestinal, endocrine, central and peripheral nervous system, and adipose organs are 'sensed' by central nervous system tracts whose efferent systems affect energy intake and expenditure so as to maintain (or restore) weight (40,49). Adding to the complexity of this system's interactions, the amount of energy stored in the body as fat also exerts potent effects on growth, pubescence, fertility, autonomic nervous system activity, and thyroid function, suggesting that humoral "signals" reflecting adipose tissue mass interact directly or indirectly with many neuroendocrine systems (40,50-54). Weight loss and maintenance of a reduced body weight are accompanied by changes in autonomic nervous system function (increased parasympathetic and decreased sympathetic nervous system tone), circulating concentrations of thyroid hormones (decreased triiodothyronine and thyroxine without a compensatory increase in TSH) (55-58), and appetite (increased hunger, reduced sense of fullness) (59) that are consistent with a homeostatic resistance to altered body weight, acting, in part, through effectors that mediate energy expenditure and intake.

Such a neurohumoral system to protect body energy stores would convey clear evolutionary advantages. During periods of undernutrition, the perceived reduction in energy stores would result in hyperphagia, hypometabolism, and decreased fertility (protecting females from the increased metabolic demands of pregnancy and lactation and the delivery of progeny into inhospitable environments). While carefully controlled studies of the effects of weight loss on energy expenditure in children are not yet available, the higher success rates in sustained fatness reduction in younger children versus adults discussed above suggests that these same systems appear to be more malleable in children prior to puberty (60-62).

MOLECULAR GENETICS OF BODY FATNESS

Heritability of Body Fatness

The storage of excess calories as fat would have been highly advantageous to our progenitors by increasing survival during periods of prolonged caloric restriction and conferring a reproductive advantage. The opportunities for our distant forebears to consume calories to the point of becoming morbidly obese and the likelihood of their survival to an age at which such co-morbidities as T2DM, hypertension, or hyperlipidemia were both low. Thus, it is likely through natural selection that the human genome would be enriched with genes favoring the storage of calories as adipose tissue (63,64). Conversely, there would be few, if any, evolutionary pressures to discourage obesity and 'defend' body thinness.

With the possible exceptions of the rare cases of obesity due to single gene mutations (see below) or specific anatomic/endocrine lesions (see above), body fatness is a quantitative trait reflecting the interaction of development and environment with genotype. Twin and adoption studies indicate that the heritability of body fatness and of body fat distribution in adulthood is 50 to 80%, [approximately equal to the heritability of height and greater than the heritability of schizophrenia (68%) or breast cancer (45%)] (65) (66). Studies have also identified significant genetic influences (heritability greater than 30%)

on resting metabolic rate, feeding behavior, food preferences, and on changes in energy expenditure that occur in response to overfeeding (67-75). Genetic influences on resting energy expenditure (REE) are evidenced by studies demonstrating that African-American children tend to have lower REE than Caucasian-American children, even when adjusted for body composition, gender, age, and pubertal status (76).

The calculation of heritability in twin studies assumes that each member of a monozygotic or dizygotic pair is reared in the same environment, and that the degree to which body fatness is more similar within mono- than dizygotic twin pairs is due to the greater genetic similarity of identical vs. non-identical twins. Studies comparing adopted children with their adoptive and their biological parents assume that each child shares little or none of the immediate environment with each biological parent, and that the degree to which body fatness is more similar between children and their biologic vs. adoptive parents is due to the 50% of their genotype that each child shares with each biological parent. Based on twin studies, the heritability of body fatness appear to increase with age (77), illustrating the complex interactions of many obesity-risk allelic variants with the environment.

Common Single Gene Mutations Associated with Obesity

The pivotal role of genetics in the control of body weight is confirmed by the existence of rare single gene variants producing extreme obesity phenotype (e.g., Prader Willi, Bardet-Biedl, Alström, and Cohen syndromes). The most common monogenic cause of obesity – variants in *MC4R* – does not cause syndromic features, while others cause obesity in association with other distinctive dysmorphic phenotypes (67,78) (Table 1). The fact that mutations in different genes can produce obesity suggests that these genes may be part of a control system for the regulation of body weight, i.e., that feeding behavior and energy expenditure are integrated in a system with complex control mechanisms which can be disrupted at many loci. Further, the impact of a genetic change may not be a direct increase in weight – as an example – recent studies of Prader Willi Syndrome have demonstrated that the endocrine phenotype is due to a deficiency in prohormone convertase, an enzyme that has also been identified as a single gene mutation cause of obesity (79,80).

Table 1. Common Single Gene Mutations Associated with Obesity (67)

Syndrome/Gene	Chromosome	Phenotype
Alström syndrome/ *ALMS1*	2p14-p13 (Recessive)	Childhood blindness due to retinal degeneration, nerve deafness, acanthosis nigricans, chronic nephropathy, primary hypogonadism in males only, type II diabetes mellitus, infantile obesity which may diminish in adulthood.
Bardet-Biedl syndrome (22 different genes)	16q21 15q22-q23	Retinitis pigmentosa, mental retardation, polydactyly, hypothalamic hypogonadism, rarely glucose intolerance, deafness, or renal disease
Beckwith-Wiedemann syndrome	11p15.5 (Recessive)	Hyperinsulinemia, hypoglycemia, neonatal hemihypertrophy (Beckwith-Wiedemann Syndrome), intolerance of fasting

Börjeson-Forssmann-Lehman syndrome/ *PHF6*	X-linked	Intellectual disability, epilepsy, microcephaly, short stature, gynecomastia, hypogonadism, obesity, tapering fingers and short toes, multiple ophthalmological problems, coarse facial features, ptosis, large and long ears, supraorbital ridge
Carpenter /*RAB23* and *MEGF8*	Unknown (Recessive)	Mental retardation, acrocephaly, poly- or syndactyly, hypogonadism (males only)
Cohen /*COH1*	8q22-q23 (Recessive)	Mental retardation, microcephaly, short stature, dysmorphic facies
LEPTIN DEFICIENCY / *LEP*	7q31.3 (Recessive)	Hypometabolic rate, hyperphagia, pubertal delay, infertility, impaired glucose tolerance due to leptin deficiency.
Leptin Receptor / *LEPR*	1p31-p32 (Recessive)	Hypometabolic rate, hyperphagia, pubertal delay due to deranged leptin signal transduction.
Melanocortin 4 Receptor /*MC4R*	18q22 (Dominant)	Obesity – early onset hyperphagia, increased bone density
Neisidioblastosis	11p15.1 (Recessive or Dominant)	Hyperinsulinemia, hypoglycemia, intolerance of fasting
Prader Willi syndrome	15q11-q12 (Uniparental Maternal Disomy)	Short stature, small hands and feet, mental retardation, neonatal hypotonia, failure to thrive, cryptorchidism, almond-shaped eyes and fish-mouth
Pro-opiomelanocortin / *POMC*	2p23.3 (Recessive)	Red hair and hyperphagia due to low POMC production of alpha-MSH in hair follicles and the hypothalamus, respectively; adrenal insufficiency due to impaired POMC production of ACTH.
Prohormone Convertase/ *PCSK1*	5q15-q21 (Recessive)	Abnormal glucose homeostasis, hypogonadotropic hypogonadism, hypocortisolism, and elevated plasma proinsulin and POMC
Pseudohypo-parathyroidism (type IA, aka Albright's) / *GNAS*	20q13.2 (Dominant)	Mental retardation, short stature, short metacarpals and metatarsals, short thick neck, round facies, subcutaneous calcifications, increased frequency of other endocrinopathies (hypothyroidism, hypogonadism)

Genome-Wide Association Studies (GWAS) of the Obesity Phenotype

The single gene mutations in humans listed in Table 1 are invariably associated with distinct phenotypes and marked (if not extreme) obesity. On the other hand, polygenic obesity may be phenotypically less extreme and with a more variable and subtle phenotype without any other syndromic features. GWAS of large populations have identified over 100 genetic loci as unequivocally associated with obesity-related traits (81-83) and over 500 loci associated with obesity-susceptibility (84), these allelic variants generally have been shown to exert only a small, but cumulative, effect on BMI (85).

In 2007, Frayling et al (86) reported a link between a SNP in the first intron of the *FTO* gene (rs9939609) and obesity in a GWAS of approximately 500,000 individuals with type 2 diabetes. Individuals

homozygous for this SNP (AA) were approximately three kilograms heavier and at a 1.7-fold increased risk of obesity than those who were homozygous unaffected (TT). Since then numerous other FTO-related SNP's have been identified that are associated with BMI (87,88). These SNP's are especially relevant to the study of childhood obesity because of their frequency (14-18% AA; 39-50% AT; and 30-35% TT (89)) and the fact that the behavioral phenotype is evident in early childhood before obesity is manifest. Cecil et al. (90) used a three-pronged preload model to quantify energy intake in 4 to 10 year-old subjects genotyped with AA, AT, and TT alleles and found that the presence of an A allele was associated with increased energy intake and caloric density (kcal/gm) of foods chosen without any effect on energy expenditure (doubly labeled water method) or compensation index for increasing preload. Wardle et al. (89) reported that 4 to 5 year-old children who were homozygous (n=24) or heterozygous (n=66) for the *FTO*/*FTM* allele (AA or AT) and had eaten a meal to satiety, ate significantly more than control subjects (n=43, TT) when offered additional food, even when corrected for body fatness. The choice of snack was limited in this latter study and, thus, the authors were unable to comment on preference for calorically dense foods. Two separate studies of large cohorts (totaling over 36,000 individuals) reported no association of *FTO* genotype with increased BMI prior to the age of seven (86,91). There appears to be no effect of the A allele on energy output (88,92). Thus, behaviors that are premonitory of subsequent weight are evident and measurable in pre-obese children with allelic variants of *FTO*. These abnormal feeding patterns associated with increased energy intake (93) including decreased dietary restraint following a caloric preload (94,95), and ratings of hunger prior to or satiety after a meal (96) are not seen in already-overweight adults. These data emphasize the importance of studying eating behavior in subjects "at risk" for weight gain to understand the dynamics of food intake that favor the development of obesity.

More recently, use of polygenic risk scores (combination of the risk estimate apportioned by each common variant) using as many as 2.1 million common variants has enhanced the ability to quantify the susceptibility of obesity. Khera et al(4) used such a polygenic risk score in the 7,861 participants in the Avon Longitudinal Study of Parents and Children, a birth cohort recruited between 1991-92 and longitudinally followed to 18 years of age. The birth weight of the individuals in the top decile of the polygenic risk score was 0.06 kg (p=.02) higher compared to the bottom decile. By 8 years of age, the difference increased to 3.5 kg ($p < .0001$) and by 18 years, the difference in weight was 12.3 kg ($p < .0001$). The authors postulate that the aggregation of risk for obesity that can be conferred by having many common variants approaches the susceptibility equivalent to rare monogenic mutations in *MC4R*.

ENVIRONMENTAL FACTORS AFFECTING PEDIATRIC RISK OF OBESITY AND ADIPOSITY-RELATED MORBIDITIES

Epigenetics

The term "epigenetics" was first coined in 1942 by the British developmental biologist C.H. Waddington to refer to how gene regulation modulates development. In 1990, the molecular biologist Dr. Robin Holliday re-defined the term "epigenetics" as "the study of the mechanisms of temporal and spatial control of gene activity during the development of complex organisms." More recently this has been understood simply as the study of changes that affect the expression or "potency" of genes without necessarily affecting the nucleotide sequences of the genes themselves (97,98).

Epigenetics is extremely relevant to obesity in that it has allowed examination of the effects of the intrauterine environment, primarily in the form of factors affecting DNA methylation, histone acetylation, and expression of micro RNA's, on gene expression relevant to obesity and its co-morbidities. Increased DNA methylation decreases the transcription of

relevant genes and is affected by parental obesity, maternal diet (e.g., nutrition, folic acid content and other methyl donors), gestational diabetes (see below), and maternal medications (antibiotics and antipsychotics), smoking or exposure to chemicals such as bisphenol (99,100). Histones are proteins that "package" DNA into nucleosomes and post-translational modifications in the tails of histone affect the accessibility of DNA for methylation and translation. Loss of histone demethylase leads to obesity via decreased expression of *PPAR*α and *UCP1*, and de-acetylation of the *GLUT4* histone tail leads to impaired glucose transport (101,102). The human genome has been suggested to contain over 1000 micro (non-coding) RNAs (miRNAs), which may influence expression of more than 60% of mammalian genes by regulating gene expression. Each miRNA can interact with expression of multiple genes, including many involved in adipogenesis (103), that play pivotal roles in the development of obesity and its co-morbidities.

Major intrauterine environmental influences on the risk of subsequent obesity via these processes and others include maternal adiposity and gestational weight gain, under- and over- nutrition, gestational diabetes, maternal stress, and various chemicals, pharmaceuticals etc., to which the mother and fetus may be exposed during pregnancy.

- *Maternal weight* impacts the fetus at multiple levels beyond those due to obesity risk alleles that may be inherited from either parent. This is exemplified by studies of offspring of mothers before and after bariatric surgery. The genotype of the mother is unchanged yet the fatness, blood pressure, circulating concentrations of insulin and gene expression relevant to diabetes, autoimmune disease, and vascular disease risk are all reduced in children who develop in the post-bariatric surgery intrauterine environment (104). Weight gain during pregnancy has a strong positive correlation with the incidence of large for gestational age babies and subsequent childhood obesity (105) augmented 2-5 fold in mothers with pre-partum obesity compared to those who were neither overweight nor obese prior to pregnancy.

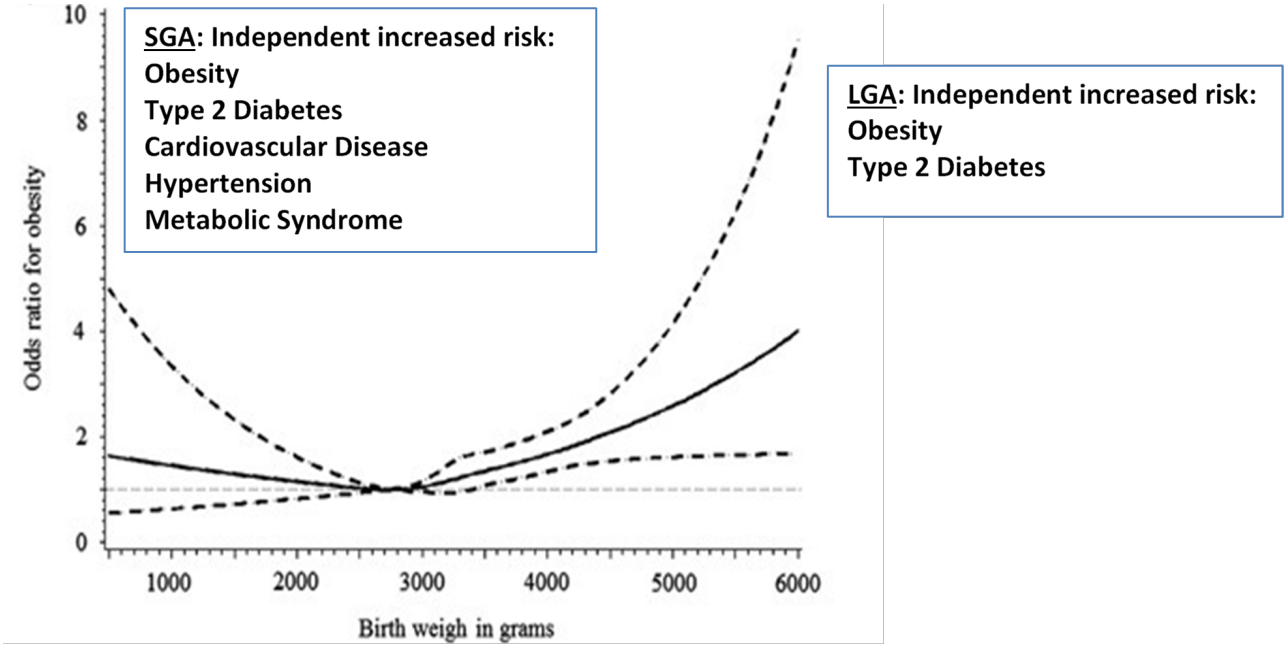

Figure 5. U-shaped curve of odds risk for obesity at age 9-11 years based on birth weight. Curve is corrected for gestational diabets, gestional age, childs age, breast or formula feeding, highest level of parental education, sleep time, moderately vigorous physical acitivvity time (MVPA), sendentary time and healthy/unhealthy diet scores (288) weight Dashed lines identify 95% confidence intervals. Inserted

text boxes indicate independent effects of small for gestational age (SGA) and large for gestational age (LGA) on various health parameters in adults.

- *Pre-Natal undernutrition* (see Figure 5) reflects maternal undernutrition or compromised fuel delivery to the fetus–the latter usually due to placental dysfunction. Studies that have examined the prevalence of obesity in children conceived during periods of natural or man-made famine such as the Nazi-imposed Dutch famine of 1944-45 (the "Winter Hunger") (106) report a small but statistically significant increase in the prevalence of obesity (defined as weight for height greater than 120% of WHO standards for 1948) in 19 year-old male military recruits whose mothers were malnourished only during the first trimester of pregnancy (2.77% prevalence if mother was in famine area vs. 1.45% if mother was outside of famine area during pregnancy) and a decrease in the prevalence of obesity among recruits whose mothers were malnourished during the child's immediate post-natal period (0.82 % if mother was in famine area vs. 1.32% if mother was outside of famine area during pregnancy). It has been hypothesized that early intrauterine malnutrition might affect hypothalamic ("appetite center") development while the anti-obesity effects of early post-natal malnutrition might be due to suppression of adipocyte formation.

  Long-term tracking studies of children who are small for gestational age, possibly due to prenatal undernutrition, have reported that, even when corrected for adult adiposity, birthweight is negatively correlated with the incidence of adiposity-related morbidities, including T2DM, hypertension, stroke, and cardiovascular disease, in adulthood (107-112). This association implies an interaction between the prenatal environment and development/function of pancreatic beta-cells and other organs such as the hypothalamus, liver, and kidneys that are involved in the regulation of adult energy homeostasis and cardiovascular function. As hypothesized by Barker (113-115), the metabolic, cardiovascular, and endocrine basis for adult adiposity-related morbidities may originate through adaptations that the fetus makes in response to undernourishment, especially when availability of calories in the environment that baby is born into is no longer limited. Therefore, the small-for-gestational-age baby should be considered to be at increased risk for adult morbidities that are exacerbated by increased adiposity (63).

- *Pre-Natal over* nutrition (see Figure 5) is exemplified by the infant of a mother with gestational diabetes mellitus (GDM). The high ambient glucose concentrations of the prenatal environment stimulate fetal hyperinsulinemia, increased lipogenesis, and macrosomia. Since women with gestational diabetes are often overweight or obese, it is difficult to separate the metabolic effects of gestational diabetes on subsequent adiposity of offspring of mothers with GDM from the possibility that the mother has transmitted a genetic tendency towards obesity. Yet several studies have shown that GDM is associated with an increased risk of obesity in the offspring, independent of the degree of maternal obesity (116-119).

- *Maternal stress,* which can be metabolic (e.g., obesity, diabetes, undernutrition, illness), psychiatric (e.g., depression, anxiety, bereavement), or pharmacological (e.g., steroids, antidepressants, antibiotics) have all been associated with increased risk of offspring obesity. These stressors affect developing neural systems regulating energy homeostasis, endocrine systems affecting risk of diabetes–including increased activity of the hypothalamic-pituitary-adrenal (HPA) axis, immune system alterations resulting in increased circulating concentrations of pro-inflammatory cytokines, decreased concentrations of adiponectin relative to fat mass, and increased risk of hypertension (120,121).

- *Cocaine and marijuana:* Exposure of the fetus to cocaine or marijuana during pregnancy has been reported to increase the likelihood of obesity in childhood and increase risk factors for T2DM (122-124). The mechanisms have yet to be ascertained.

Early Feeding Practices

For reasons discussed above, accurate assessment of the effects of early infant feeding practices on subsequent adiposity must control for possible effects of maternal adiposity as well as socioeconomic status and other factors that may affect the ability to breastfeed (125). Meta-analyses have shown that predominantly breastfeeding for at least 3-6 months is associated with significant reductions in the prevalence of obesity of their offspring through young adulthood (126-128), even when controlled for other adiposity-risk variables.

In addition to any benefits of the dietary macronutrient content on subsequent adiposity, observations suggest that the institution of a well-balanced diet in childhood may form the basis for long-term healthy dietary habits that will significantly lower adult cardiovascular disease risk even if the diet composition does not substantially affect weight (129). Studies have also identified positive correlations between the consumption of sugar-sweetened beverages, caloric density of snacks, fast food intake, the portion size of meals, and the hours of television watched (see below) with weight gain in children (129-135).

Early Life BMI Trajectories

A prospective longitudinal study of 7,738 U.S. children starting kindergarten in 1998-1999 showed that children with overweight and obesity at 5 years of age were four times as likely as their normal-weight counterparts to have obesity at 10-year follow-up. Among children who became obese between the ages of 5 and 14 years, nearly half had been overweight and 75% had been above the 70th percentile for BMI at baseline, indicating that incident obesity for these children had occurred at younger ages (136). Many studies have examined the association of rapid weight, or weight/length or BMI trajectories in the first three years of life and noted association with overweight, obesity or severe obesity at 6 years to adolescence (137-141). One study simulated growth trajectories across life course using pooled data from nearly 42,000 children and adults representative of U.S. population in 2016 adjusting for secular trends. They estimated that a 2-year-old with obesity will continue a trajectory of rapid weight gain and has a 74.9% (95% CI 67.3 to 81.5) probability of being obese at age 35 years. These risks are higher for those with severe obesity.

Social Determinants of Health

Social determinants of health are the conditions in which people are born, grow, live, work, and age. These include the family, physical and social environment, each of which influences obesity either directly through children's nutrition and activity or indirectly via added stress. Analysis of NHANES data has demonstrated a higher prevalence of obesity and severe obesity with greater age and lower education of the household head (142). This same study noted an association of severe obesity in youth residing in non-metropolitan statistical areas with more difficult access to large supermarkets. In a study of national sample of 3,748 children from US households receiving Supplemental Nutrition Assistance Program (SNAP) compared to those without, Gorski Findling et al noted higher odds of obesity amongst those receiving the SNAP program (OR 1.14 [95% CI 1.05-1.24]) and with access to a combination grocery/other store, compared to those with access to supermarkets with greater variety of fresh food. They also noted that in convenience stores, 26.1% of the average child's total household food spending was on sugary beverages (SNAP 29.8% vs non-SNAP 15.5%) (143). In a study of households in New York City, Elbel et al noted that living farther than 0.025 mile (about half a city block) from the nearest fast-food restaurant was

associated with lower rates of overweight and obesity, along with lower BMIz scores (144). The built and natural environments play a critical role in the access to physical activity (PA) for children. Street connectivity, defined as the directness of links and density of connection in street networks provides better access to outdoor PA such as walking, playing and cycling. Studies with perceived street connectivity by children, frequently near school, had higher odds of PA (OR 1.13, 95% CI 1.04-1.24). Similarly, higher odds of moderate to vigorous PA (OR 1.33, 95% CI 1.17-1.52) was noted with higher levels of street connectivity. No significant associations were identified with BMI or BMI z-scores (145). The same authors also conducted a metanalysis of natural environment with levels of PA in children. Ambient temperature was identified as the most consequential predictor associated with PA. An increase of 10 °F heating and cooling was associated with reduction in moderate to vigorous PA by 5 and 17 min respectively. No associations were reported with air quality (146).

Thus, a complex array of determinants contributes towards the risk of obesity and severe obesity in youth and will require a multipronged approach for intervention. (147-157)

Physical Activity, Sedentary Behavior, and Sleep

Behaviors related to PA and sedentary established in childhood have been shown to track well into adulthood (150,151) and are independent correlates of BMI and adiposity (158,159) (160,161). Meta-analyses of cross-sectional studies show negative associations of PA and positive associations of sedentary behavior (SB) with adiposity in children (162-164), that are further evident with direct objective (e.g., calorimetry) rather than subjective (self-reported) assessments (163). The implications of these findings for early intervention to treat and prevent pediatric obesity are discussed below.

MORBIDITIES ASSOCIATED WITH OBESITY IN CHILDREN

As in adulthood, obesity in childhood adversely affects every organ system (Table 2). Adiposity-related morbidities, such as hyperlipidemia, track well into adulthood (165) and pediatric obesity may be considered an independent risk factor for adult adiposity-related morbidities, even if the obesity does not persist (166). Certain morbidities, such as slipped capital femoral epiphyses, are the consequence of the biomechanical stresses associated with excess weight while others, especially cardiovascular morbidities, appear to be more closely related to central body fat distribution rather than absolute fat mass. The psychological stress of social stigmatization imposed on children with obesity may be just as damaging to some as the medical morbidities, resulting in significant body dissatisfaction, social anxiety, loneliness, and, especially in girls, somatic symptoms (167,168). These negative images of the obese are so strong that growth failure and pubertal delay have been reported in children due to self-imposed caloric restriction arising from fears of becoming obese (169).

Table 2. Pediatric Adiposity-Related Morbidities (165,167-173)

Cardiovascular	Hypertension, ↑ total cholesterol, ↑ low density lipoproteins, ↓ high density lipoproteins, metabolic syndrome
Respiratory	Abnormal respiratory muscle function and central respiratory regulation, difficulty with ventilation during surgery, lower arterial oxygenation, obstructive sleep apnea, asthma, more frequent and severe upper respiratory infections
Gastrointestinal	Nonalcoholic fatty liver disease, gallstones, gastroesophageal reflux disease
Endocrine	Type 2 diabetes, precocious puberty, polycystic ovarian syndrome, Vitamin D deficiency
Orthopedic	Coxa vara, slipped capital femoral epiphyses, Blount's disease, Legg-Calve-Perthe's disease, degenerative arthritis.
Dermatologic	Intertrigo, furunculosis, acanthosis nigricans (HAIR-AN Syndrome)
Immunologic	Impaired cell-mediated immunity, polymorphonuclear leukocyte killing capacity, lymphocyte generation of migration inhibiting factor, and maturation rates of monocytes into macrophages
Psychologic	Low self-esteem, anxiety, somatization, depression, eating disorders
Lymphatic	Obesity associated lymphedema of the lower legs
Malignancy	Higher lifetime risk of obesity related cancers

Pediatric Obesity and Cardiovascular Risk Factors

Obesity, hyperlipidemia, hypertension, and other risk factors for cardiovascular disease in children track well into adulthood (23,165,170-173). In long-term follow-up studies, adolescent fatness was a powerful predictor of mortality, cardiovascular disease, colorectal cancer, gout, and arthritis, irrespective of body fatness at the time that the morbidity was diagnosed (166,172). Therefore, it is possible that the metabolic groundwork for the chronic diseases of adulthood is laid down in childhood and the overweight youth must be assessed for both current adiposity-related morbidities and their future risk.

Pediatric Obesity and Type 2 Diabetes Mellitus

The incidence of youth-onset prediabetes and T2DM is increasing parallel with the rise in obesity in the US (174,175). Between 2001 and 2017, there was a 95.3% (95% CI 77.0-115.4%) relative increase in the prevalence of T2DM in youth < 19 years of age. The greatest absolute increase were observed among non-Hispanic Black and Hispanic youth (174). In the past 2 years of COVID-19 pandemic, the burden of youth onset T2DM has increased dramatically. In a review of two U.S. medical claims databases (~500,000 individuals), persons aged < 18 years with COVID-19 infection were more likely to receive a new diagnosis of diabetes (both Type 1 and Type 2) > 30 days after infection compared to those without or those with pre-pandemic acute respiratory illness (HR = 2,66 [95% CI 1.98-3.56]) (176). The underlying causes for this increase are yet to be identified.

Pathologic processes associated with diabetes, including the development of insulin resistance and deterioration of beta-cell function, progress more rapidly in youth-onset T2DM than in adult-onset disease. These factors result in worse glycemic control and an increased risk of early diabetes-related complications (177-179). In the 10-year follow-up of 500 youth with new-onset T2DM enrolled in the Treatment Options for Type 2 Diabetes and Adolescents and Youth (TODAY) clinical trial, the cumulative incidence of hypertension was 67.5%, dyslipidemia 51.6%, diabetic kidney disease 54.8%, nerve disease 32.4% and retinal disease 51.0%. At least one complication occurred in 60.1% of the participants, and at least two in 28.4%. Risk factors for the development of complications included minority

race or ethnic group, hyperglycemia, hypertension, and dyslipidemia (180).

The pathophysiology of T2DM is discussed in the *Endotext* Diabetes section (181). Like obesity, T2DM is a complex metabolic disorder(182). In studies of adults and children with a strong family history of T2DM, it appears that impaired pancreatic islet-cell function is the first identifiable metabolic abnormality in some subjects who subsequently develop T2DM, while in other populations, insulin resistance is the first identifiable phenotype (183,184). These data, along with the observation that subjects may be insulin-resistant but not meet clinical definition for diabetes, and that many individuals with impaired β-cell function may not go on to develop T2DM (185,186), suggest that T2DM is due to a combination of insulin-resistance and an impaired β-cell ability to respond to that state of insulin-resistance. In this sense, a state of relative insulin resistance, or the expression of an underlying tendency towards conditions associated with insulin resistance, the major causes of which in adolescence would be pubertal hormonal changes and/or obesity, may act to "unmask" a pre-diabetic state of impaired insulin secretion in some individuals. Consistent with this, available evidence suggests that the incidence of T2DM in children peaks around puberty, as do the ethnic differences in the prevalence of pediatric obesity (187,188), coincidentally with the known decline in insulin-sensitivity and increase in adiposity in the peri-pubertal period (189-191).

Central body fat distribution, usually defined on the basis of waist circumference or the ratio of waist-to-hip circumference, is an independent predictor of adiposity-related insulin resistance in adolescents and adults (191-193) as well as other co-morbidity risk factors (194-196). There appear to be effects of ethnicity on the relative impact of body fat distribution on insulin sensitivity. In Caucasian-American children, increasing visceral adiposity is the best correlate of increased fasting insulin levels and insulin secretion during OGTT, and of glucose disposal during hyperinsulinemic-euglycemic clamp studies (191). In African American (but not Caucasian) pre-pubertal children, intra-abdominal adipose tissue volume was significantly correlated with fasting insulin concentrations and with insulin sensitivity as measured by area under the curve (AUC) during oral glucose tolerance testing (197-199). Other studies of African-American prepubertal girls have found that elevated fasting insulin concentrations and reduced insulin sensitivity are significantly correlated with greater subcutaneous, but not visceral, adipose tissue volumes (200). Because of the increasing frequency of T2DM among adolescents with obesity, and the worsening of diabetes-related morbidities that may result from delayed diagnosis, the clinician should be alert to the possible of T2DM in all adolescents with generalized and central obesity, and especially those with strong family histories of early-onset (< 40 years of age, one or more parent affected) T2DM (201).

ENDOCRINE CHANGES ASSOCIATED WITH OBESITY IN CHILDREN

The most common endocrine disorders associated with obesity are secondary to excess body fat and will correct with weight loss (Table 3).

Table 3. Endocrine Changes Associated with Obesity in Children (202-206)	
Somatotroph	↓ basal and stimulated growth hormone release, normal concentration of insulin-like growth factor-I, accelerated linear growth and bone age
Lactotroph	↑ basal serum prolactin but ↓ prolactin release in response to provocative stimuli
Gonadotroph	Early entrance into puberty with normal circulating gonadotropin concentrations may be due to earlier priming of the hypothalamic-pituitary-gonadal axis by estrogens created by aromatization of androgens in adipose

	tissue and/or by increased circulating concentrations of leptin associated with higher adipose tissue mass.
Thyroid	Normal serum T_4 and reverse T_3, normal or ↑serum T_3, ↓ TSH-stimulated T_4 release resulting in ↑ TSH levels
Adrenal	Normal serum cortisol but ↑ cortisol production and excretion, early adrenarche, ↑ adrenal androgens and DHEA, normal serum catecholamines and 24-hour urinary catecholamine excretion
Gonad	↓ circulating gonadal androgens due to ↓ sex-hormone binding globulin, dysmenorrhea, dysfunctional uterine bleeding, polycystic ovarian syndrome
Pancreas	↑ fasting plasma insulin, ↑ insulin and glucagon release, ↑ resistance to insulin-mediated glucose transport

There are, however, several endocrine or genetic syndromes in which obesity is part of a distinct symptom complex that often includes poor statural growth (e.g., hypercortisolism, hypothyroidism) (Table 4) and/or very distinct heritable phenotypes (e.g., Prader Willi; Bardet-Biedl syndromes) (Table 1). Assessment of skeletal maturation by bone age, and physical examination for age-appropriate secondary sexual characteristics as well as syndrome-specific morphology or symptomatology (e.g., hypotension, constipation in hypothyroidism, centripetal distribution of fat in hypercortisolism) can usually rule out these syndromes as causes of obesity.

Table 4. Other Diseases, Injuries, and Medications Associated with Obesity (67,206)

Disease	Structural/Biochemical Lesion	Clinical Features
Acquired hypothalamic lesions	Infectious (sarcoid, tuberculosis, arachnoiditis, encephalitis), vascular malformations, neoplasms, trauma, post-surgical	Adipocyte hypotrophy with little hyperplasia, headache and visual disturbance, hyperphagia, hypodipsia, hypersomnolence, convulsions, central hypogonadism-hypothyroidism-hypoadrenalism, diabetes insipidus, hyperprolactinemia, hyperinsulinism, type IV hyperlipidemia
Cushing's Disease / Syndrome	Hypercortisolism	Moon facies, central obesity, ↓ lean body mass, glucose intolerance, short stature

Hypothyroidism	Hypothalamic, pituitary, or thyroidal	Hypometabolic state (constipation, anemia, hypotension, bradycardia, cold intolerance), cretinism (if congenital)
ROHHAD or ROHHADNET syndrome*	Hypothalamic	Hyperphagia, obesity, hypoventilation, adipsic hypernatremia, thermal dysregulation, GH deficiency, hyperprolactinemia,
Medications	Tricyclic antidepressants, Glucocorticoids, Antipsychotic drugs, Antiepileptic drugs, Sulfonylureas	

*ROHHAD - rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; ROHHADNET - rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation with neural crest tumors.

WEIGHT STIGMATIZATION (FAT SHAMING)

Weight stigmatization (devaluation and denigration of a person because of obesity) includes explicit and implicit weight bias and perpetuates the view that obesity and the difficulty in weight loss are the fault of the individual's poor diet and exercise choices (207). Weight stigmatization is so common across age, gender, race, and ethnicity that it must be considered as a co-morbidity of overweight and obesity; is prevalent in children and adolescents regardless of their socioeconomic and demographic characteristics. Between 25% and 50% of children have been bullied and/or have been discriminated against based on their weight (167,168). Weight bias is reported among peers, families, teachers, health professionals, and multiple media outlets (207-209) and has been shown to precipitate unhealthy eating habits, psychosocial stress, and additional weight gain in children (209-211).

PREVENTION AND TREATMENT OF OBESITY: CLINICAL APPROACH TO THE PEDIATRIC PATIENT

Prenatal Care

Prevention of obesity in childhood includes early, including prenatal, identification of the child at risk for subsequent obesity and application of effective interventions to reduce that risk. Ideally, this process includes health professions involved in obstetrics, maternal-fetal medicine, and pediatrics.

Pregnancy-related modifiable risk factors for maternal under- and over- nutrition, SGA, LGA, pre- and post-natal rapid weight gain as well as childhood overweight and obesity include higher maternal pregravid adiposity, excessive gestational weight gain, gestational diabetes and hypertension, and smoking during pregnancy (212). Addressing any of these risk factors is beneficial to the health of the mother as well as the fetus. The likelihood of modifying these risk factors is variable. The Institute of Medicine (USA) recommends different ranges of weight gain for women who are underweight (12.5-18.0 kg if BMI < 18.5 kg/m^2), have a BMI within the normal range (11.5-16.0 kg if BMI 18.5-24.9 kg/m^2), are overweight (7.0-11.5 kg if BMI 25.0-29.9 kg/m^2) or are obese (5.0-9.0 kg for BMI $\geq$30 kg/m^2) (213). As discussed above, there are clear offspring-health benefits of maternal bariatric surgery (104). However, it is difficult to implement non-surgical weight loss plans in preparation for pregnancy and the health benefits of lifestyle interventions both before and during pregnancy on childhood adiposity and co-morbidities smaller and less sustained than observed with bariatric surgery (212,214). Benefits of better control of gestational diabetes are more substantial and persistent (215).

Initial Evaluation

Pediatric obesity is a persistent worldwide problem, and preventing pediatric obesity and its comorbidities is of paramount importance. The authors posit that every youth with overweight, obesity, and severe obesity should have an opportunity for medical management shared with the individual, the family, and the medical home. The 2017 Endocrine Society guidelines for pediatric obesity assessment, treatment, and prevention provide an excellent framework towards this goal (24) (Figure 6). A thorough medical and family history is crucial as in any chronic condition.

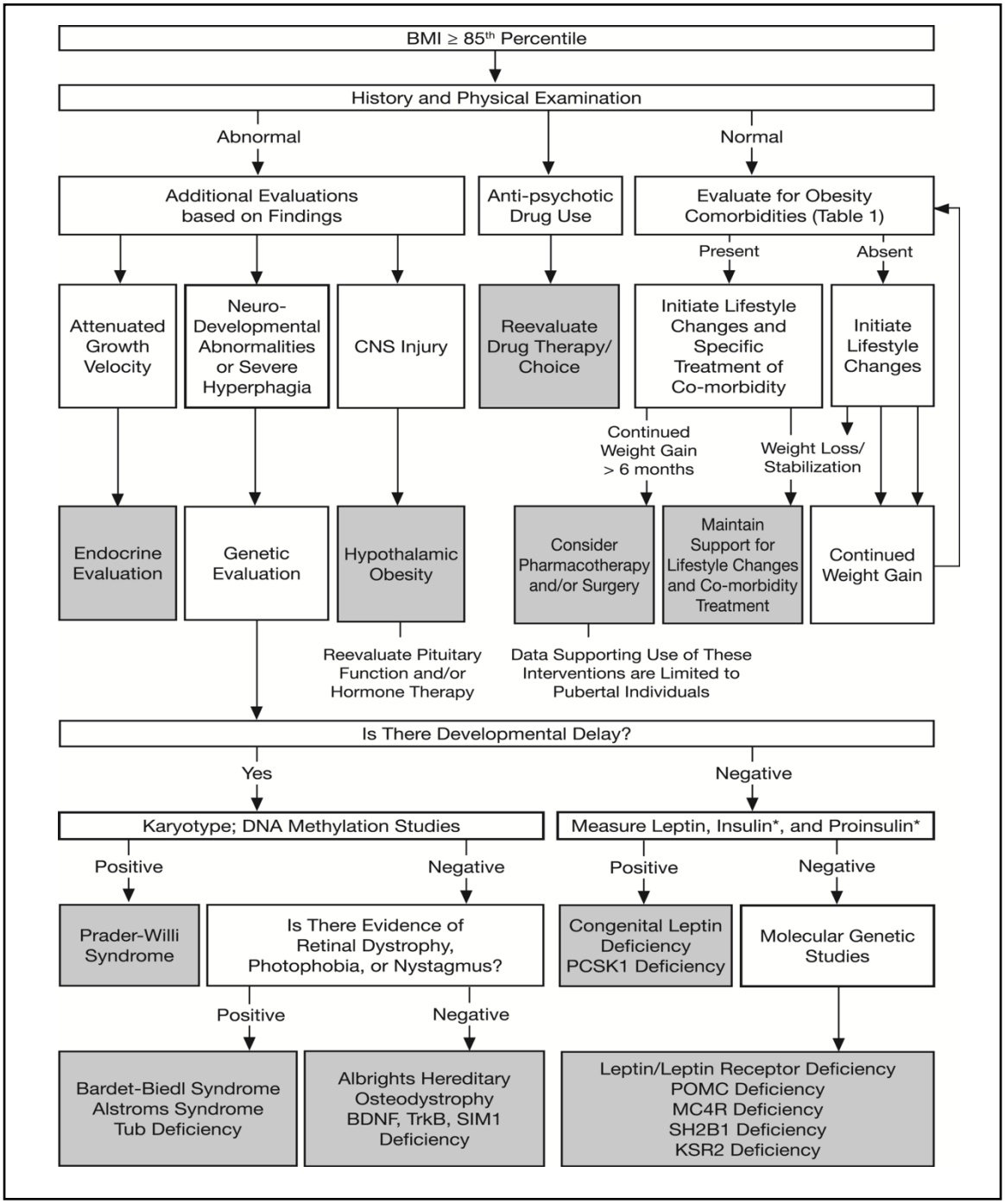

Figure 6. Algorithm for implementing the 2017 Endocrine Society guidelines on management of children and adolescents with obesity (24).

Initial, and subsequent, evaluations should include a dietary history of the child's and family's typical eating habits (including snacks and the frequency with which they consume sugar-added beverages and foods prepared outside of the home). A physical activity history should also be obtained, including school physical education, after-school activities, and activities of daily living (such as walking to school), family activities, and sedentary activities (such as television watching). The family history should encompass obesity, bariatric surgery, T2DM, gestational diabetes, and other comorbidities of obesity including sleep apnea and use of continuous positive airway pressure (CPAP).

A detailed physical examination focused on identifying possible causes of unwanted weight gain (e.g., enlarged thyroid gland, cushingoid body habitus) and weight–related co-morbidities (acanthosis nigricans, hypertension, etc. see Tables 2-4) should be performed. Laboratory studies should be guided by history and physical examination and at minimum include fasting measurements of glucose, lipids, hemoglobin A1c, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and vitamin D to screen for diabetes, dyslipidemia, fatty liver disease, and hypovitaminosis D. Because of the increased risk of polycystic ovarian syndrome (PCOS) in adolescents with obesity, total and free testosterone, as well as sex hormone binding globulin (SHBG), should be measured in girls with signs of hyperandrogenism, oligomenorrhea, or other symptoms suggestive of this disorder (216). Routine evaluation for endocrine etiologies of pediatric obesity are not recommended by the Endocrine Society (24) except if statural growth is compromised. The authors suggest amending this to include a broader list of phenotypes that may be related to thyroid disease. These should include any possible indices of hypothyroidism in the first 3 years of life to avoid the deleterious effects of early thyroid disease on subsequent development (217). They should also include screening for symptoms of acquired hypothyroidism, especially autoimmune thyroiditis and especially in adolescent females, with later onset weight gain or autoimmune disease (218).

Children under 5 years of age who are extremely obese, especially if they have concurrent adiposity-related morbidities, evidence of developmental delay, or other phenotypic features associated with the rare obesity syndromes (such as Prader Willi or Bardet Biedl syndrome) discussed above (Table 1), can be referred to a physician who specializes in the treatment and genetic evaluation of pediatric obesity (219). Targeted therapies are available for some of these conditions.

Health care providers are often confronted by the difficulty in deciding whether or not to attempt intervention in a child who is not obese but is overweight or has a growth trajectory that may be premonitory of obesity. Assessment of the risk of progression to obesity should be based on family history of growth patterns and of adiposity-related co-morbidities, any evidence of co-morbidity in the child, and familial readiness to engage in early intervention to prevent obesity. Parents of a child who is clearly "at-risk" maybe more reluctant to begin lifestyle or other therapies since the child is not obese. If parents are amenable then the same therapies used to treat obesity can be initiated. If the parents are not amenable then the health care provider should monitor growth of the child and co-morbidity risk and keep parents involved in the discussion of progression towards obesity and/or its co-morbidities.

Family based interventions are most effective for management of pediatric obesity (219-221). Efforts spent in assessing the home environment are critical to success of management. Factors such as parental and sibling adiposity, education, and the quality of the relationship between the primary caregiver and the child have all been identified as significant determinants of the likelihood of a successful pediatric weight loss intervention (222). The logical extension of these findings is that optimal therapeutic interventions

must include support for the child's family, regardless of the level of obesity of the family members (223).

The clinician should begin assessment of family therapeutic readiness by asking the entire family how concerned they are about the patient's overweight, in a supportive manner designed to elicit cooperation from the family and patient. Examples might include asking, "Do you feel that weight is a problem?" or "What do you think that you could change to help you lose weight?" rather than, "Why can't you control what you eat?" The discussion should emphasize the potential benefits of therapeutic intervention, including the importance of cooperation of all caregivers, the increased likelihood of diminishing adult body fatness with early adoption of consistent and long-term lifestyle intervention.

Treatment of the child with overweight or obesity must be individualized and the clinician should remain sensitive to issues such as ability of the parents to prepare meals for the patient, neighborhood safety or availability of adult supervision, which may impact on the availability of physical activity after school, and remain culturally sensitive in making dietary recommendations.

Therapeutic Intervention

The approach to management of a child with overweight or obesity is in many ways more complex than the same choice in an adult because of additional concerns regarding growth if negative energy balance is excessive. The major goal of management should be to diminish morbidity rather than to achieve a "cosmetically endorsed" body weight. While imperfect, BMI is clinically the most readily accessible parameter to assess the level of obesity. The "severity" of obesity should initially be assessed based on the BMI references provided above, presence of current morbidities such as T2DM, and risk of future adiposity-related morbidity (based on family history) (219). This increased risk of treatment-associated impairment of statural or brain growth is higher in younger children and caloric restriction to reduce weight should not be used in infants less than 2 years of age. Beginning therapy with the assumption that obesity is a choice and can be "fixed" easily by moving more and eating less is outdated and inaccurate in the current science of obesity and promotes weight stigmatization and "fat shaming". Excessive emphasis on behavior and self-sufficiency may precipitate eating disorders, as well as other psychological disorders such as low self-esteem, anxiety, and depression – especially if long-term weight loss is unsuccessful, especially in the peri-pubertal stages (167). It is important to tailor the management for individual child and their family. Program adherence, defined as the number of contacts with the weight-management program, is a primary factor in successful weight loss for overweight children and adolescents (224). Maximizing adherence is like to include program modification over time in a given child. As more data accumulate regarding precision medicine approaches to identify genetic and other predictors of responses to different interventions, adherence and success are likely to improve. Clinicians can prescribe intensive, age-appropriate, culturally sensitive, family-centered lifestyle modifications (dietary, physical activity, behavioral) to promote a decrease in BMI (rather than weight). When weight is maintained at a constant level or weight gain is proportionally slower than height gain, BMI can reduce with increase in linear growth. In the otherwise healthy child with obesity with no evidence of co- morbidity, such modifications may be sufficient to maintain long-term health. In contrast, in a youth with severe obesity (BMI ≥ 120% of 95th percentile of BMI) or presence of co-morbidity such as T2DM or hypertension, such management can be augmented with pharmacotherapy and/or bariatric surgery, as deemed suitable (225,226).

DIETARY RECOMMENDATIONS

The Dietary Guidelines for Americans, 2020-2025 can be used as a reference for dietary counseling (227). These guidelines emphasize following a healthy dietary pattern at every life stage with a focus on meeting food group needs with nutrient (and not

calorie)-dense foods and beverages and stay within the appropriate calorie limits. Hence, the entire family can be engaged in culturally appropriate dietary modifications. Studies suggest that the long-term sustenance of such intervention is most successful with a supportive family. It is also important to convey to the family on the need for sustenance of such changes for long-term favorable outcomes. Encouragement can be provided by examining growth and growth velocity curves with patients and their families to illustrate progress. If appropriate, the significance of any evident reduction in morbidity (e.g., lowering of blood pressure or cholesterol) can be reinforced. Reasonable goals in the form of a "target" body weight at the next visit should be set at each office visit so that the patient and parents are aware of what is expected. These goals should be modest and attainable even if patients are only moderately compliant with their diet and exercise regimens since achievement of an interval “target weight" will also encourage the patient.

The caloric need of a person varies maintain, gain, or lose weight are dependent upon age, sex, height, weight and level of physical activity. The Dietary Guidelines provide estimated amounts of calories needed to maintain energy balance of various age and sex groups at three different levels of physical activity from toddlers to age 2 years, as well as ages 2 and older (227). These estimates are based on the Estimated Energy Requirements (EER) equations, using average reference height and weight by age and sex. These are a useful starting point to tailor the needs to that of the patient. It is useful to get an assessment of the current caloric intake from the families. However, self-reported caloric intake is often inaccurate. For direct assessment, the child's *ad libitum* diet can be observed and recorded by the parents for a minimum of five consecutive days. A diet diminished to 300 to 400 kcal/day below weight-maintenance requirements as assessed by dietary history or as calculated based upon formula relating anthropometry to energy expenditure, e.g., the Harris-Benedict Equation (228) should result in weight loss of approximately one pound per week. Note that since weight reduction *per se* causes decreased energy expenditure (both from decreased metabolic mass and whatever hypometabolic state is invoked by losing weight (40,49,67) and during weight loss, periodic downward adjustments of energy intake will be necessary to sustain ongoing weight reduction. The family should be instructed in long-term monitoring of caloric intake within, and outside of, the home and cautioned not to become overly critical or punitive towards the child if weight loss is slow or compliance is suboptimal.

The core elements of Dietary Guidelines for Americans sorted by food group are listed below:

- Vegetables: Increased relative consumption of vegetables of all types – dark green; red and orange; beans, peas, and lentils; starchy; and other vegetables.
- Fruits: Consumption of whole fruits rather than juices.
- Grains: At least half of the consumed grains should be whole grains.
- Dairy: Dairy intake should be focused on fat-free or low-fat milk, yogurt, and cheese, and/or lactose-free versions and fortified soy beverages and yoghurt as alternatives.
- Protein: Protein intake should focus on lean meats, poultry, and eggs; seafood; beans, peas, and lentils; and nuts, seeds, and soy products.
- Fats: Children need fats – both saturated fats and cholesterol for normal growth and brain development. On the other hand, trans fats, such as those from fried foods are unhealthy. Eggs, butter, whole dairy products and oils, including vegetable oils and those in seafood and nuts are recommended.

The guidelines also recommend limiting foods and beverages higher in added sugars (including those with high fructose corn syrup), saturated fat, and sodium. Less than 10% of calories per day should be derived from added sugars starting at age 2 years, and families should be advised to avoid beverages with any added sugars. In the US, 57-61% children derive

> 10% of their energy from added sugars, 88% consume > 10% saturated fat and nearly 95% consume foods containing greater than the recommended sodium amount.(229-234) Simply reducing the consumption of these types of foods should in and of itself result in a net negative energy balance most likely by reducing hedonic "eating in the absence of hunger" (235,236) and other aspects of energy intake which have been found to be correlated with subsequent weight gain in children .

Ultra-processed (UPF) are defined as "Industrial formulations typically with 5 or more and usually many ingredients. Besides salt, sugar, oils, and fats, ingredients of UPF include food substances not commonly used in culinary preparations, such as hydrolyzed protein, modified starches, and hydrogenated or intensified oils, and additives who purpose is to imitate sensorial qualities of unprocessed or minimally processed foods and their culinary preparations or to disguise undesirable qualities of the final product, such as colorants, flavorings, non-sugar sweeteners, emulsifiers, humectants, sequestrants, bulking, de-foaming, anticaking, and glazing agents" (237,238). These "ready to eat" or "ready to heat" preparations are typically high in added sugar, *trans*-fat, sodium, and refined starch and low in fiber, protein, vitamins, and minerals. The consumption of UPF has increased by 20-50% per decade 2000-2015 in the USA, and to an even greater degree in low- and middle- income countries (239). Diets high in UPF is associated with adverse health outcomes including obesity, hypertension, dyslipidemia, diabetes and pre-diabetes in adults (240-243,244) and, more recently, in children (7); (245,246). Though the Dietary Guidelines for Americans has yet to issue recommendations regarding UPF consumption, we believe that the evidence that UPF's promote obesity and many of its co-morbidities in children is more than sufficiently compelling to recommend avoiding them.

A helpful brochure to recommend healthy eating for children including Nutrition conversation starters can be obtained from https://www.dietaryguidelines.gov/professional-resources.

The composition of the diet should contain at least the minimal recommend amounts of protein, essential fatty acids, vitamins, and minerals. The 2017 consensus from the Endocrine Society (24) recommended the following basic principles of dietary intervention to achieve negative energy balance, which it should be noted would likely be beneficial to everyone regardless of adiposity:

- Replace all sugary drinks (including juices, sodas, and whole milk) with water, noncaloric beverages, and low-fat or skim milk.
- Create a balanced diet including vegetables, fruits, whole grains, nuts, fiber, lean meat, fish, and low-fat dairy products. Specifically encourage consumption of at least five servings of fruits and vegetables daily.
- Reduce intake of calorie dense foods such as saturated fats, salty snacks, and high glycemic foods including candy, white bread, processed white rice, pasta, and potatoes.
- Minimize consumption of foods outside of the home. Fast foods in particular.
- Eat breakfast daily.

Based on available data it appears that dietary macronutrient composition in childhood does not significantly affect later adiposity (247) and that diets consisting of drastically altered proportions of nutrients may be dangerous and yield no better results than a limited intake of a nutritionally balanced diet (248,249). It should be noted that the results of these studies vary substantially and may be age-dependent. For example, in a retrospective study Davis et al (250) reported that synergistic effects between the duration of breastfeeding and low sugar-sweetened beverage intake in reducing the odds of obesity in toddlers who were Hispanic. In contrast, a recent study comparing the effects of the low fat versus low glycemic index diet in the treatment of obesity in a population of Hispanic

American adolescents found no differences between groups based on dietary macronutrient composition (251) and a recent meta-analysis by Hall and Guo (252) found that low fat diets promoted greater fat loss than low carbohydrate diets in adults.

As noted above, nutritional counseling should encourage decreasing the use of calorically dense (high fat or high glycemic index) foods and adding more fruits and vegetables to the daily diet. The substitution of water for non-nutritious high calorie sugar containing drinks (juices, iced teas and soda pop) may be very helpful (225), at least transiently (253). In some cases, reductions in calorically dense foods and sugar-containing drinks through substitution and/or elimination alone can decrease calories and weight without changing the general pattern of food consumption in the family. When families eat at restaurants and fast-food vendors, they have less control over food choices than they do at home. Thus, reduction in the number of meals prepared outside the home may also be an effective weight-loss strategy. Parents and adult caregivers should understand the important role they play in the development of proper eating habits in their young children. The parents' food preferences, the quantities and variety of foods in the home, the parents' eating behavior and physical activity patterns all determine how supportive the home environment is to the child with obesity.

THERAPEUTIC EXERCISE

Physical activity may promote a slightly increased muscle mass, thereby raising total metabolic rate, and the putative effects of exercise to reduce visceral adipose tissue mass independently lower the risk of hyperlipidemia and diabetes mellitus (254-256). However, the energy cost of even vigorous exercise is low when compared to the caloric content of many "fast foods" or other "snacks", and exercise should not be viewed as a "license to eat". For example, walking at three miles per hour for one hour consumes about 200 kilocalories, about the same number of calories contained in a 1¾ ounce bag of potato chips. Use of "treats", such as ice cream, potato chips, etc., as incentives to exercise negates its impact. As with all interventions to reduce pediatric adiposity, increasing physical activity and decreasing sedentary behavior is most likely to be effective, sustained, and benefit the entire family if the entire family participates.

Combining the 2017 Endocrine Society statement on pediatric obesity (24) with other recommendations for physical activity in children (147), the following guidelines are suggested which again could be applied to the entire family, regardless of their adiposity:

- Exercise should be fun, age-appropriate, and tailored to the child's fitness level and ability and should involve large muscle groups (e.g., quadriceps) to increase energy expenditure. Exercise frequency, duration, and intensity should increase over time.
- Moderate-to-vigorous physical activity should, on the average, encompass 90-120 minutes of the day in preschoolers and toddlers (usually unstructured physical activity) and at least 1 hour of the day in children 6 years or older (usually structured physical activity such as after school sports).
- Improve sleep hygiene (10-13 hours per night for preschoolers and 8-10 hours per night for adolescents) in response to numerous studies demonstrating associations of decreased sleep duration and weight gain (257-259).
- In order to address the issue of increased sedentary behavior due to screen time, the American Academy of Pediatrics provides a downloadable Family Media Plan in English and Spanish (**www.healthychildren.org/MediaUsePlan**) (260). This plan is for all children and can be personalized for every family depending on the children's age(s), family priorities, time of the year (e.g., academic year versus vacation), etc., and includes elements such as screen free zones, screen free times, choosing good content, using

medial together and digital privacy and safety. In its 2017 recommendations specifically for children with obesity, the Endocrine Society suggested that nonacademic screen time should be reduced to 1-2 hours per day and that other sedentary behaviors, such as digital activities, should be decreased (24).

While no specific aspect of the sedentary lifestyle has been shown to directly cause obesity, behaviors such as television viewing, reading, working at a computer, driving a car or commuting do exert effects on health. Television viewing appears to be directly associated with the incidence of obesity, and inversely associated with the remission of obesity. The impact of television viewing on obesity seems to be due to both displacing more vigorous activities and its effect on diet. Not only is television viewing a sedentary behavior, but food has also constituted the most heavily advertised product on children's television in the United States. In Mexican-American children, adiposity was significantly correlated with time spent watching television but not with time spent watching videos (261), suggesting that the bulk of the positive association of television watching and adiposity is due to the approximately 60% of advertising that is devoted to food (134). Children and adolescents should be encouraged to view as little television as possible. Limitation of television, video games, and internet viewing will encourage greater participation in physical activity. Clinicians should encourage children to participate in organized or individual sports (participate, not watch from the bench) and advocate for better community- and school-based- activity programs.

If the patient is unable to lose weight and/or co-morbid conditions persist, consideration should be given to referral of the child to a physician specializing in the treatment of pediatric obesity. Weight-loss programs, weight-reduction camps, etc. are often not covered by medical insurance and should be considered for the child who is morbidly obese with some caution. Enrollment in a highly supervised environment may demonstrate to an overweight child that weight loss is possible and encourage them to continue. However, rapid weight loss may precipitate cholelithiasis (262) or eating disorders. A child may become overly pre-occupied with his/her weight and, even if a moderate degree of weight-loss is achieved, lose self-esteem. Obsession with weight on the part of the child or their family may lead to serious deterioration of intra-family relationships.

Digital Interventions

Technology based interventions provide a novel tool to add to the armamentarium for weight management in youth. Technologies can include information and communication technology, web-based interventions, mobile phone applications and smart-phone based interventions, text-messaging, and wearable technology. In a systematic review of 8 studies (n=582 youth) of technology-based interventions with or without wearable devices with a spread of intervention ranging from behavioral counseling via telehealth to text-message based reminders and family-based therapies, significant differences in BMI were reported by 5 of the 8 studies. Pooled analysis showed standardized mean difference of -0.61 (95% CI -1.10, -0.13, p <.01), albeit with significant heterogeneity. Interestingly, as is seen with in-person interventions, the effect was lower in the sub-group with parental involvement (263). Similarly, in a separate meta-analysis of 12 randomized controlled trials (3227 youth), use of wearable devices, such as pedometers or wristband activity trackers, had statistically significant reduction in BMI, BMI z-score and body fat, but not in waist circumference. The impact was higher in individuals with obesity compared to those with normal weight (for prevention of obesity) (264). Where accessible, such technologies can provide an additional tool for weight management in youth.

Pharmacological and Surgical Interventions

For youth with severe obesity or those with concomitant co-morbidity, both pharmacotherapy and surgical interventions can augment intensive lifestyle

management prescribed above. Several pharmacological therapies have been approved by FDA for use in youth ≥ 12 years of age in the past 5 years and clinical trials with additional medications are ongoing at the time of this publication. Professional associations such as The Obesity Society, Pediatric Endocrine Society as well as other experts have provided guidelines for clinical considerations on the use of obesity pharmacotherapy(265-267). Figure 7 provides a mechanistic overview of pharmacotherapies.

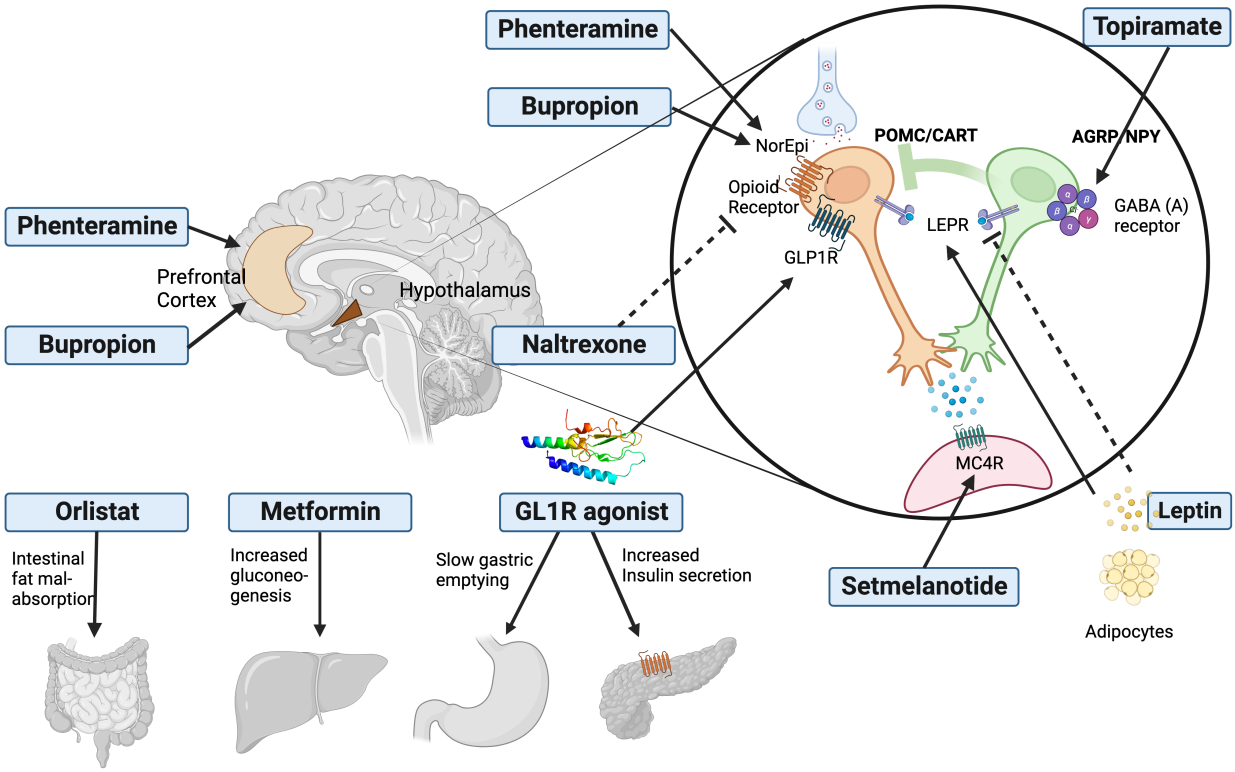

Figure 7. Mechanism of action of the available medications. Many of the currently used medications for obesity impact the centers for weight regulation in the brain including hypothalamus and the prefrontal cortex, as well as other organs. Abbreviations: NorEpi: norepinephrine; POMC: pro-opiomelanocortin; CART: cocaine- and amphetamine regulated transcript; AGRP: agouti-related polypetide; NPY: neuropeptide Y; GLP1R: glucagon like polypeptide receptor 1; LEPR: leptin receptor; GABA: gamma amino butyric acid; MC4R: melanocyte 4 receptor. Bupropion and Naltrexone are not approved for use in pediatrics for weight loss. The therapeutic preparation of leptin is called metreleptin. Figure created using biorender.com

Both the indications for pharmacotherapy and the available approved pharmacological interventions are different in children than in adults. General recommendations for use of pharmacotherapy include: a) availability of a multidisciplinary team including at least one pediatric specialist; b) severe obesity (BMI ≥ 120% of 95th percentile or BMI ≥ 35 kg/m^2) or presence of a co-morbidity with BMI ≥ 95th percentile (or BMI ≥ 30 kg/m^2); c) concomitant lifestyle intervention; d) continuation of medication(s) if there is ≥ 5% BMI reduction from baseline at 12 weeks on the optimal dose or arrest or slowing of weight gain; e) discontinuation if not tolerated or if dangerous side effects occur or persist despite dose adjustment (265). A list of available therapies and evidence for pediatric

use are listed below with guidance on administration is provided in figure 8.

Medication	Status	Side effects	Contraindication	Pediatric data
Orlistat $	FDA approved for obesity ≥ 12 years	GI symptoms, abdominal pain; oily stools and spotting; fecal urgency; flatus; Fat soluble vitamin	Chronic malabsorption, cholestasis, pregnancy	-2.61 kg placebo-subtracted weight loss at 1 yr
Phentermine $	FDA approved for conditions other than obesity	Irritability, insomnia, dry mouth, dizziness, tremor, headache, HR/BP elevation, GI symptoms	Cardiovascular disease, hyperthyroidism, glaucoma, concomittant MAO inhibitor	3.2 kg weight decrease, 4.1% reduction in BMI at 6 months with lifestyle intervention
Topiramate $	FDA approved for conditions other than obesity	Cognitive dysfunction, paraesthesia, nephrolithiasis, metabolic acidosis	Pregnancy (teratogen), acute myopia and secondary angle closure	2-4.9% reduction with 75 mg x 6 months
Topiramate/ Phentermine $$	FDA approved for obesity ≥ 12 years	Headache/dizziness, GI symptoms, cognitive dysfunction	Both of above	10.4 % reduction of BMI at 56 weeks. Oral
GLP-1RA. Liraglutide Semaglutide - ongoing pediatric trial $$$	Liraglutide FDA approved for obesity ≥ 12 years; Semaglutide for diabetes	GI symptoms, Hypoglycemia if on insulinogenic meds, small risk of pancreatitis/cholelithiasis	Pregnancy, Personal or family h/o medullary thyroid cancer or MEN2	Upto 10.8% BMI reduction. Injectable. Ongoing trials for oral Semaglutide in youth
Metformin $	FDA approved for obesity ≥ 10 years	GI symptoms, bloating, flatus, diarrhea, usually well tolerated	Severe hepatic/renal disease	BMIz reduction of 0.1 - 0.86 BMI
Lis - dexamphetamine $	FDA approved for conditions other than obesity	GI symptoms, dizziness, dry mouth, irritability, insomnia, nausea, HR/BP issues	Cardiovascular diseases; psychiatric adverse reactions, Serotonin	BMIz -0.24 to -0.51
Recombinant leptin (metreleptin) $$	Special approval needed	Headache, abdominal pain	Neutralizing antibodies develop; T-cell lymphoma in lipodystrophy.	Only useful in LEP deficiency
Setmelanotide $$$$	FDA approved for genetic causes of obesity ≥ 6 years	Hyperpigmentation; priapism; injection site reactions, GI symptoms,	Pregnancy, Age < 6 years	POMC/PCSK1/LEPR deficiency BBS syndrome 20-25% loss of BMI/BMIz

Figure 8. Pharmacotherapy for youth with obesity, approval status and available pediatric data.

Bariatric surgery is only approved in adolescents and, although the frequency of adolescent bariatric surgery is increasing, it still accounts for only about 1% of total U.S. bariatric surgery cases (268). Outcome studies of adolescent bariatric surgery have shown significant improvements in weight, cardiometabolic co-morbidity risk, and quality of life tempered a high incidence (57%) of hypoferritinemia and need for additional abdominal procedures (13%) (269). The American Society for Metabolic and Bariatric Surgery recommends the following selection criteria for adolescents eligible for bariatric surgery:

- Body mass index ≥ 35 kg/m^2 and a severe comorbidity, with significant comorbidity with short-term effects on health or BMI 40 kg/m^2 or above with more minor comorbidities.
- *Physical maturity*, defined as completing 95% of predicted adult stature based on bone age or reaching Tanner stage IV. This criterion is based on theoretical concerns that rapid weight loss might inhibit statural growth if an adolescent has not reached near adult height.
- History of lifestyle efforts to lose weight through changes in diet and physical activity.
- Ability and motivation of the patient and family to adhere to recommended treatments pre- and postoperatively, including vitamin and mineral supplementation.
- Appropriate understanding of the risks and benefits of surgery on behalf of the adolescents
- Supportive but not coercive family.

Contraindications to bariatric surgery include:

- Medically correctable cause of obesity
- An ongoing substance abuse problem (within the preceding year).

- A medical, psychiatric, psychosocial, or cognitive condition that prevents adherence to postoperative dietary and medication regimens or impairs decisional capacity.
- Current or planned pregnancy within 12 to 18 months of the procedure.
- Inability on the part of the patient or parent to comprehend the risks and benefits of the surgical procedure.

Both the American Society for Metabolic and Bariatric Surgery and the Endocrine Society have recommended that a multidisciplinary team consisting of a bariatric surgeon, a pediatrician specializing in obesity, a nutritionist, a mental health professional, an exercise physiologist, and a health care coordinator should be established to evaluate optimal therapy for a child who is a candidate for bariatric surgery based on the presence of co-morbidities and failure of other interventions.

ADDRESSING WEIGHT STIGMATIZATION

Health care providers have an opportunity to improve the quality of life and intervention outcomes for children with obesity by addressing weight bias (209). Recent specific recommendations include:

- Avoid oversimplification: Recognize the multifactorial nature of obesity as a disease that may require long-term, or even lifelong, attention and challenge stereotypes that obesity, or the difficulty in losing weight, is a lifestyle choice rather than a biological issue.
- Avoid weight bias: When speaking with the patient or their family focus on the chief complaint (even if it is not weight-related), feel free to discuss implicit and explicit weight bias with families, and support evidence-based care including medication or surgery.
- Encourage a collaborative relationship: Ask if it is okay with the patient and family to discuss weight during an appointment, use person-first language ("having obesity" rather than "is obese"), acquaint them with the multifactorial complex nature of weight management, and explore alternative factors that contribute to higher BMI.

OTHER INTERVENTIONS

There are new types of intervention that are only recently being vetted in pediatric randomized clinical trials. Prebiotics, probiotics, and other manipulations of the gut microbiome have been suggested as possible means of treating or preventing pediatric obesity with some initial promising results in relatively small studies (270-272). There is a wide variability in the efficacy of school-based interventions but with more attention to the methodological differences between those that are more successful and those that are not, it may be possible to create a cost-effective practical means of addressing the burgeoning problem of pediatric obesity (273).

There are also a number of bills languishing in Washington that have been left in committee and not allowed to be aired for public debate. The Sugar-sweetened beverage excise task (SWEET) act, the Stop Subsidizing Childhood Obesity Act, and establishment of nutrition standards for all foods served and sold in schools have all been projected to return between 4 and 35 times the number of dollars invested in health care cost savings over the next 10 years (274). The failure of the SWEET Act, and other legislation that might affect childhood obesity rates, to get into open debate suggests that health care professionals dealing with the problem of pediatric obesity could be more vocal regardless of whether they support the legislation. Implementation of the improved school meals endorsed by the Healthy, Hunger-free Kids Act has been shown to result in significant improvement in school-meals and to be increasingly acceptable to students, with improvement in participation in school-based breakfast programs since its implementation (275,276). Any efforts to remove funding from the Healthy, Hunger-free, Kids Act (277) or the Supplemental Nutrition Assistance Program (SNAP), in particular SNAP-Ed, will potentially promote poor dietary habits and food

insecurity (278-280) and should provoke a similar level of discussion by health professionals in public forums. These are important issues and commentary from those most familiar with the problem should be helpful in their evaluation.

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