SPECIAL CONSIDERATIONS RELEVANT TO PEDIATRIC OBESITY

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ABSTRACT

In most humans, body fatness is a continuous quantitative trait reflecting the interactions of environment, genotype and development. Attempts to elucidate mechanisms of weight gain by comparing obese and non-obese individuals as adults, i.e., once the genotype is fully expressed and subjects are weight stable, are less likely to be fruitful than studies of children who are at-risk for adult obesity based on family history, current adiposity, or other risk factors for subsequent weight gain, provide a unique window into those factors that lead to adult obesity. The potential opportunities to prevent adult obesity through early intercession are evident in the relatively poor long-term success rate of non-surgical adult obesity treatments compared to both successful weight loss and reduced weight maintenance following pediatric intervention. 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) and onward through childhood. The next section emphasizes that the same multi-system co-morbidities traditionally associated with adult obesity are becoming more and more prevalent in children, along with a number of other problems that are more unique to the pediatric population. This chapter concludes with a discussion of new recommendations regarding interventions to reduce co-morbidity and adult-obesity risk and an invitation for physicians 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

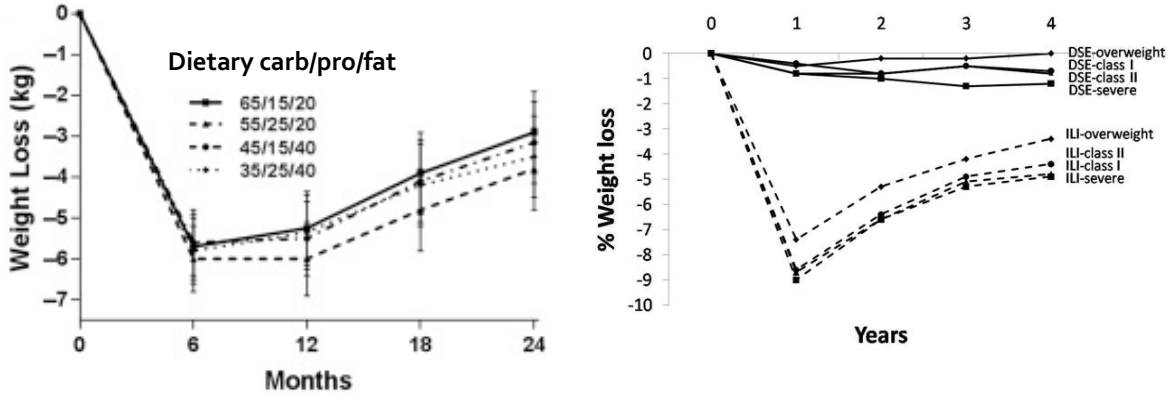
Care for obesity and its co-morbidities currently accounts for over $200 billion per year in health care costs (21% of total U.S. health care budget) in the United States and is projected to increase to over $900 billion by the year 2030 (1). Obesity is a complex disease reflecting interactions of an increasingly permissive environment (more calorically dense food and sedentary lifestyle availabilities) with multiple known obesity-risk allelic variants (2, 3). In the United States, 18.5% of children are obese (defined as a body mass index (BMI) > 95th percentile) and 16.2% are overweight (95th percentile > BMI > 85th percentile) (4, 5). The prevalence of pediatric obesity and its co-morbidities, formerly thought of as “adult-onset” diseases such as type 2 diabetes mellitus (T2DM), have been increasing in parallel. These problems disproportionately affect African, Asian, Hispanic, and Native Americans (2). Pediatric obesity tracks well into adulthood, especially if present in the peri-pubertal period (over 20-fold increased risk adult obesity) and if one or both parents are obese (6). It is also worth considering that although a higher percentage of adults than children are obese, the fractional relative magnitude of obesity prevalence among children is growing faster. From 1972-2014 the prevalence of adults with obesity increased by about 2.5 fold (from about 15% to 37%) whereas the percentage of children with obesity increased by 3.4 fold (from about 5% to 17%) (7). This suggests that the age of onset of obesity for those genetically or otherwise “at-risk” is getting younger and younger.

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 30 years, despite multiple new pharmacological and other treatment options (8, 9).

Figure 1 illustrates the typical patterns of weight loss followed by weight regain seen after lifestyle interventions in adults (**Figure 1A, B**) and children (**Figure 1C, D**) over years. 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 lose weight 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. *The greater likelihood of successful treatment of obesity and maintenance of weight reduction in children suggests that reducing the risk of a child who is overweight or with obesity becoming an adult with obesity, is a more cost- and treatment-effective means to reduce the prevalence of adult obesity than waiting to treat that at-risk child when they have entered adulthood.*

Figure 1. 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 (10-12). **B.** In contrast, children tend to lose more fatness (expressed as BMI z-score) and sustain their weight loss longer following a lifestyle intervention (13, 14). This is especially true for younger children DSE – Diabetes Support and Education; ILI – Intensive Lifestyle Intervention. Classes refer to severity of obesity in adults.

A.



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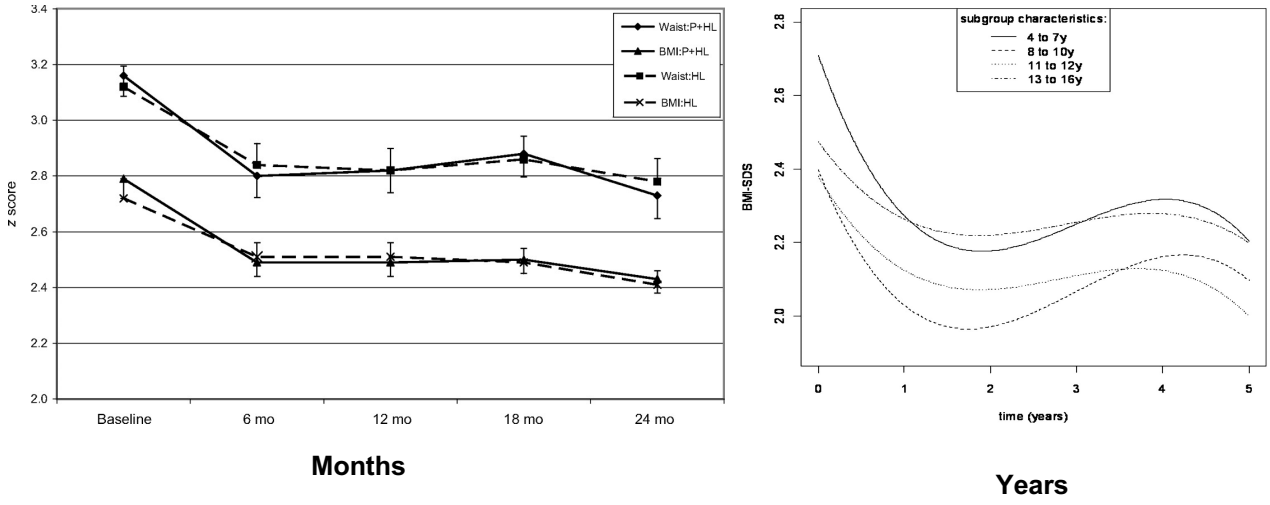


DEFINITION AND EPIDEMIOLOGY:

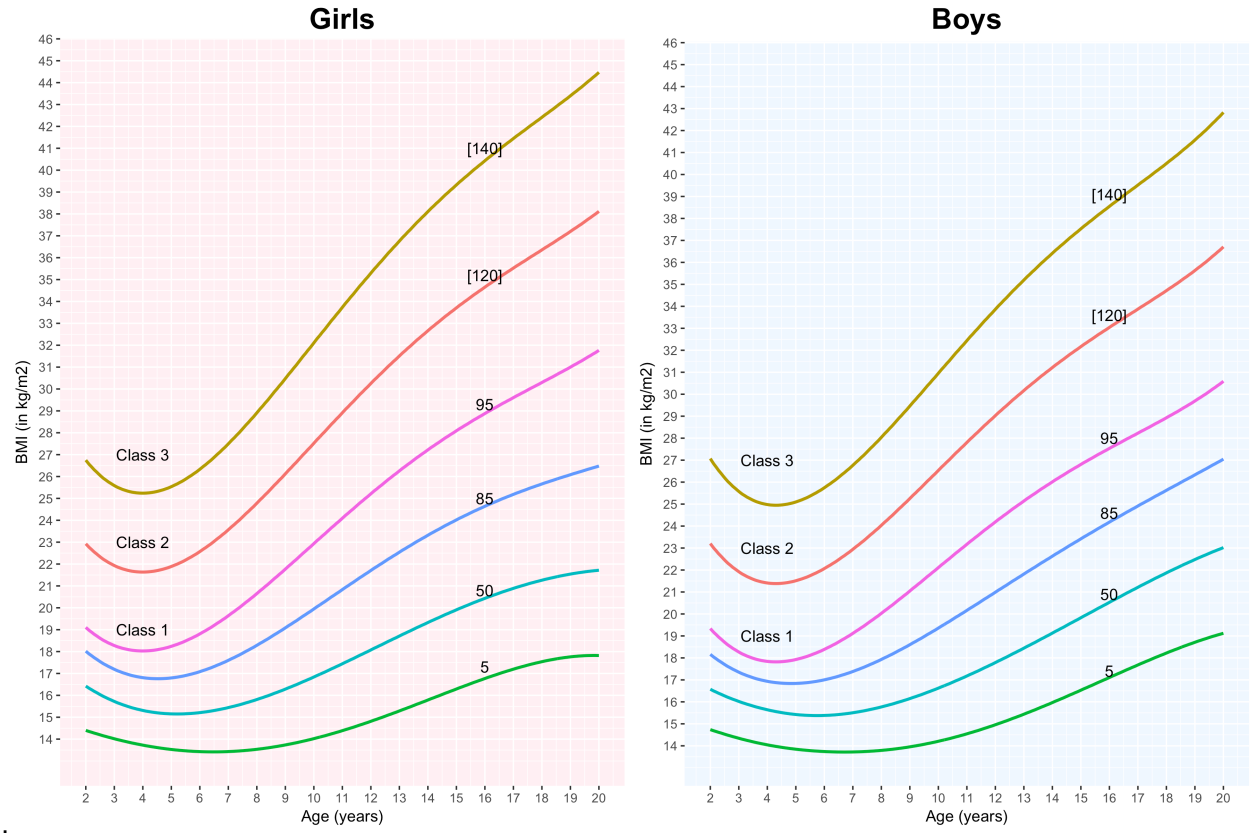
Pediatric obesity may be defined functionally as a maladaptive increase in the mass of somatic fat stores. The ideal diagnostic criteria of obesity would include some assessment of current adiposity-related co-morbidity, the risk of persistence of the obesity into adulthood, as well as the risk of future morbidities that would be worsened by excess weight. The degree or risk for such morbidities and the persistence of obesity into adulthood must be incorporated into decisions as to what therapeutic intervention is indicated.

A number of basic principles are pertinent to such an assessment:

- During the first year of life there is an increase in weight for height (or Body mass index [BMI, weight (kg)/ (height (m^2)]) followed by a decline in BMI and then a second increase at about 6 years of age (designated as "adiposity rebound"). Early adiposity rebound, one that occurs before 5 years of age, is independently associated with a higher risk of adult obesity (15, 16).
- The risk of persistence of pediatric obesity into adulthood increases with age, independent of the length of time that the child has been obese (2, 6).
- Growth patterns are familial and may be predictive of adult adiposity. A mildly overweight teenager with a family history of excessive weight gain in adulthood may be at greater risk for subsequent obesity than a more severely overweight teenager with a negative family history of obesity in adulthood (2, 6).
- The risk of adiposity-related morbidity is strongly influenced by family history of such morbidities, regardless of whether affected family members are obese, and is different between racial/ethnic groups (2, 6, 17).

Body mass index is often used as a "surrogate" for body fatness. Although it does not measure body fat, it does correlate with direct measures of body fatness within a population (18, 19). Adults are classified as <u>overweight</u> if their BMI is between 25 and 30 kg/m^2 and as <u>obese</u> if their BMI is ≥ 30 kg/m^2 (20). These adult definitions cannot be used in children because normative values for BMI are highly age-dependent (21). Instead, the 2007 Expert Committee (22) recommended that children with BMI > 95th percentile are thereby classified as "obese" (approximately 17-20% of US children) and those with a BMI between the 85th and 95th percentile are classified as "overweight" (approximately 16-17% of children) (4) to more accurately reflect the serious health risks associated with higher levels of adiposity in children. These recommendations were based on the CDC 2000 Growth Charts, which are constructed primarily from data collected between 1963-1980 (23). These charts only characterize children in 10 empirically selected percentiles between the 3rd and 97th percentiles. Extrapolation of these data to percentiles outside of this range using a least-mean-square (LMS) method cannot be used to accurately characterize severely obese children (24). Instead, it is recommended that clinicians utilize BMI curves specifically developed to reflect different degrees of obesity (**Figure 2**) because they are more sensitive and useful in terms of tracking progress during a weight loss intervention and for sharing these findings with children with obesity and their families (24). More recently the 2017 Endocrine Society guidelines for pediatric obesity assessment, treatment, and prevention suggested that obesity in children less than two years of age be defined as weight/recumbent length > 97.7th percentile based on World Health Organization (WHO) growth curves (17, 25). In the case of defining obesity in youths and older adolescents, the Expert Committee recommended using a BMI cutoff of greater than the 95th percentile or ≥ 30 kg/m^2, the same as used in adults, whichever is lower (22).

Figure 2. Normative growth curves for boys and girls. **A**. Expanded BMI curves for girls and boys reformatted based on data from Gulati et al (24) by Dr. Vidhu Thaker at Columbia University Medical Center. Extreme BMIs were calculated by multiplying the BMI at the 95th percentile (Class 1 obesity) by a factor of 1.2 through 1.4 to derive the 120th to 140th percentiles – definitions of the equivalent to Class 2 and Class 3 obesity in adults, respectively, for both genders aged 2 to 20 years.



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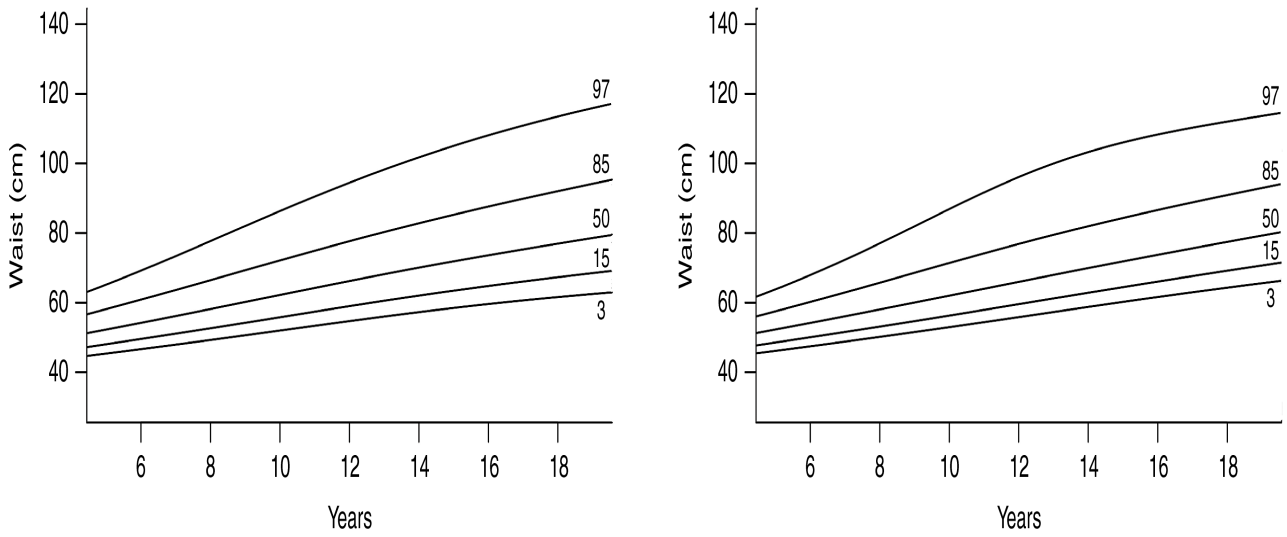
Of interest, normative data on wait circumferences during childhood have also been established (**Figure 3**). These data are most helpful in identifying children at risk for insulin resistance, type 2 diabetes, and dyslipidemia.

Figure 3. 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 (26) 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.

GIRLS BOYS

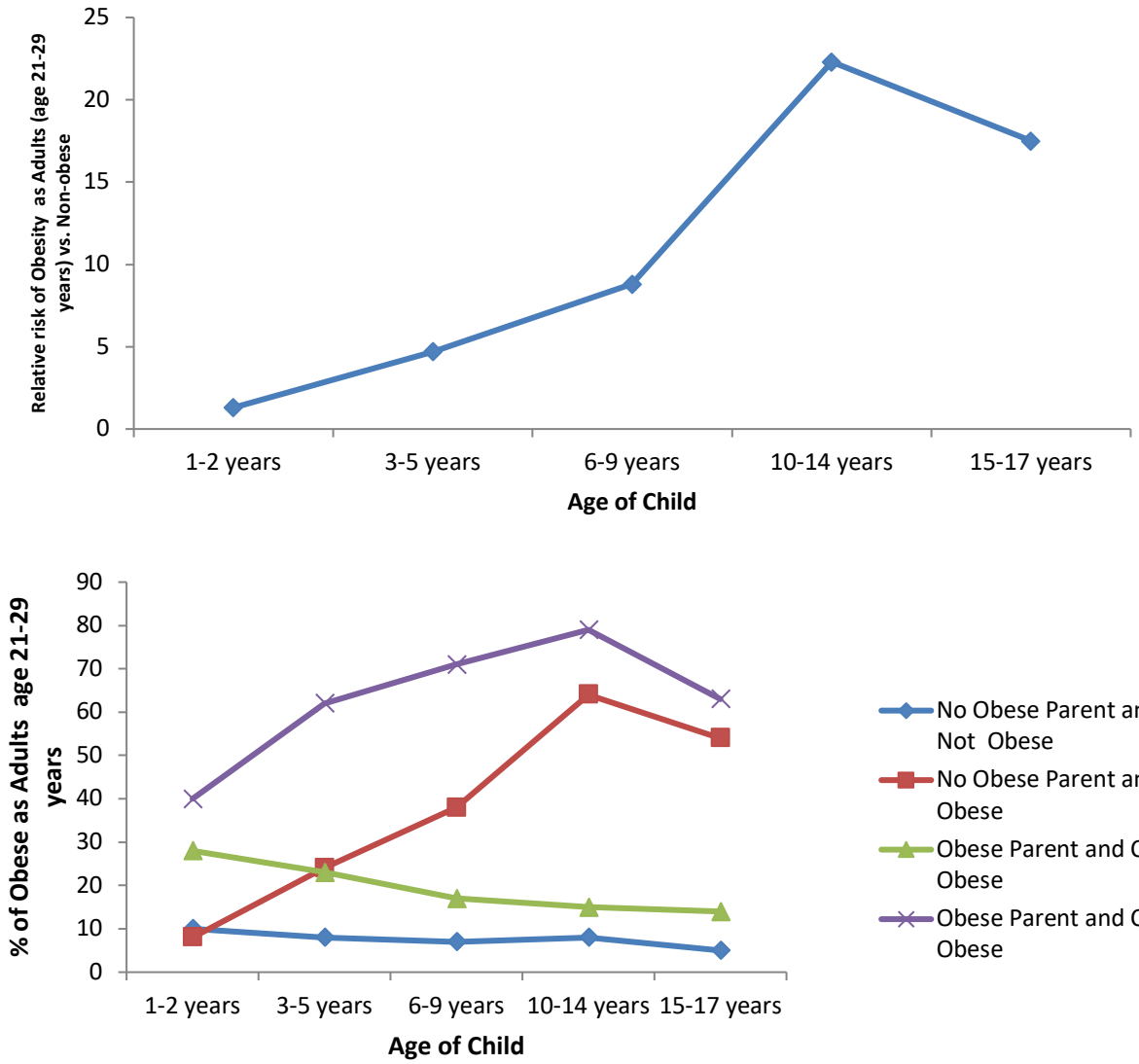


As noted above, BMI does not directly measure body fat. Individuals at either extreme (low or high) of percent body fat may be incorrectly labeled as non-overweight or overweight solely based on BMI. In such cases, if the clinician is uncertain whether a child has an elevated body weight predominantly due to an abnormally large adipose tissue or lean body mass, or suspects that a child with a normal or low BMI has an inordinately high percentage of body fat, then further evaluation may be indicated. This might include measurement of body fat using bioelectrical spectorscopy (BIS), air displacement plethysmography (BOD POD), dual-energy X-ray absorptiometry (DEXA) scanning, or Quantitative Magnetic Resonance (QMR) (27, 28).

Until recently, the prevalence's of overweight and obesity of the United States pediatric population were increasing. For example, a six-year-old female with a BMI of 16.1 kg/m^2 would have been at the 85th percentile for BMI in the National Household Education Surveys (NHES) Program I (1971-74), but would be the average BMI for a child of the same age and gender in National Health and Nutrition Examination Survey (NHANES) III (1988-94). This trend in the pediatric population is especially evident at the extremes. From NHES (1963-70) to NHANES (1988-91), the prevalence of overweight and obesity rose, respectively from approximately 15 to 22% and 5 to 11%, respectfully, in children (29-31). Thus, while the prevalence of overweight increased by an average of about 40% over this time period, the prevalence of obesity has more than doubled. Such skewing of weight increases is consistent with impact of relevant environmental changes on a genetically susceptible subgroup within the population. Of note, recent studies suggest that, while still at unhealthy and unacceptably high frequencies, the prevalence of overweight and obesity in children (defined by BMI) in the United States are stabilizing (32, 33).

As shown in **Figure 4**, genetic factors predominate in influencing the likelihood of early childhood obesity persisting into adulthood. Therefore, the pediatrician should be alert to establishing early preventative dietary and exercise habits in younger children who are overweight and have overweight parents. Regardless of parental adiposity, the likelihood of childhood obesity persisting into adulthood simply increases with age with a sharp increase in the peri-pubertal period (6). The sharp increase in the relative risk of a child older than age 10 years with obesity becoming an adult with obesity suggests that obesity treatment started prior to puberty is more likely to be effective **see Figure 1**), as has recently been demonstrated in a number of studies (13, 14).

Figure 4. Relative risk of being an adult with obesity aged 21-29 years based on whether one is obese as a child at different ages (upper graph) and having parent(s) who are obese (lower graph). (Based on Whitaker et al (6)).



ENERGY HOMEOSTASIS

The first law of thermodynamics dictates that the accumulation of stored energy (fat) must be due to caloric intake in excess of 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 FFM gain was reached to that results 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 (34, 35). 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 (36-41), and the tendency for individuals to maintain a relatively stable body weight over long periods of time despite variations in caloric intake (42), 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 (34, 43). 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 (34, 44-48). 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) (49-52), and appetite (increased hunger, reduced sense of fullness) (53) 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 (**figure 1**), albeit still with a relatively high rate of recidivism, suggests that these same systems appear to be more malleable in children prior to puberty (13, 14, 54)(35, 41-44).

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 by increasing the fertility of women and enhancing their ability to breastfeed. 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 would become manifest were both very 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 (55, 56). Conversely, there would be very 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 continuous 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%)) (57) depending somewhat on how adiposity is

measured (58). 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 (59-67). 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 (68).

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 (69), illustrating the complex interactions of many obesity-risk allelic variants with the environment.

Single Gene Mutations Producing Obesity

The pivotal role of genetics in the control of body weight is confirmed by the existence of relatively rare single gene mutations capable of producing profound increases in body fat content (e.g. Prader-Labhart Willi, Bardet-Biedl, Ahlstrom, and Cohen syndromes). Most of these monogenic forms of obesity occur in association with other distinctive dysmorphic phenotypes (59, 70) (**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. For example, recent studies of the Prader-Labhart Willi Syndrome (71, 72) have demonstrated that the endocrine phenotype of this genetic syndrome is due to a deficiency in prohormone convertase, an enzyme that has also been identified as a single gene mutation cause of obesity (**Table 1**).

Table 1. Human Single Gene Mutations Associated with Obesity (59)

Syndrome/Mutation	Chromosome	Phenotype
Alström	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	16q21 15q22-q23	Retinitis pigmentosa, mental retardation, polydactyly, hypothalamic hypogonadism, rarely glucose intolerance, deafness, or renal disease
Beckwith-Wiedemann	11p15.5 (Recessive)	Hyperinsulinemia, hypoglycemia, neonatal hemihypertrophy (Beckwith-Wiedemann Syndrome), intolerance of fasting
Börjeson-Forssmann-Lehman	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	Unknown (Recessive)	Mental retardation, acrocephaly, poly- or syndactyly, hypogonadism (males only)
Cohen	8q22-q23 (Recessive)	Mental retardation, microcephaly, short stature, dysmorphic facies
Leptin Protein	7q31.3 (Recessive)	Hypometabolic rate, hyperphagia, pubertal delay, infertility, impaired glucose tolerance due to leptin deficiency.
Leptin Receptor	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-Labhart-Willi	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 α-MSH in hair follicles and the hypothalamus, respectively; adrenal insufficiency due to impaired POMC production of ACTH.
Prohormone Convertase	5q15-q21 (Recessive)	Abnormal glucose homeostasis, hypogonadotropic hypogonadism, hypocortisolism, and elevated plasma proinsulin and POMC
Pseudohypo-parathyroidism (type IA, aka Albright's)	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 4** are almost invariably associated with distinct, easily identifiable phenotypes and a marked (if not extreme) obesity phenotype. On the other hand, while Genome-Wide Association Studies (GWAS) of large populations have identified over 100 genetic loci as unequivocally associated with obesity-related traits (73-75) and over 500 loci associated with obesity-susceptibility (76), these allelic variants generally have been shown to exert only a small, but cumulative, effect on BMI (77).

In 2007, Frayling et al (78) 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 (79, 80). 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 (81)) and the fact that the behavioral phenotype is evident in early childhood before obesity is manifest. Cecil et al. (3) 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. (81) 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 (78, 82). There appears to be no effect of the A allele on energy output (80, 83). 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 (84) including decreased dietary restraint following a caloric preload (85, 86), and ratings of hunger prior to or satiety after a meal (87) are not seen in already-overweight adults. These data emphasize the importance of studying eating behavior in subjects "at risk" for weight gain in order to understand the dynamics of food intake that favor the development of obesity.

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 (88, 89).

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 will decrease the transcription of relevant genes and has been shown to be 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 (90, 91)**.** 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 (92, 93). 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 (94), which 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, 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 (95). Weight gain during pregnancy has a strong positive correlation with the incidence of large for gestational age babies and subsequent childhood obesity (96) that is augmented 2-5 fold in mothers with pre-partum obesity compared to those who were neither overweight nor obese prior to pregnancy.

- *Pre-Natal undernutrition* 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”) (97) 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, and therefore demonstrating clinical evidence of prenatal undernutrition, have reported that, even when corrected for adult adiposity, birthweight is negatively correlated with the incidence of adiposity-related morbidities, including type 2 diabetes mellitus, hypertension, stroke, and cardiovascular disease, in adulthood (98-103). 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 (104-106), 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 (55).

- *Prenatal Overnutrition* 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 having GDM is still associated with an increased risk of obesity in the offspring, independent of the degree of maternal obesity (107-110).

- *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 (111, 112).

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 (113). A number of meta-analyses have found that breastfeeding was associated with a moderate, but consistent, protective effect against childhood obesity and suggested that predominantly breastfeeding for at least 3-6 months is associated with significant reductions in the prevalence of obesity of their offspring (defined as BMI > 95th percentile for age and sex) through young adulthood (114-116), even when controlled for other adiposity-risk variables.

In addition to any benefits of the relative 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 body composition (117). Numerous studies have found significant positive correlations between the number of sugar-sweetened soft drinks consumed, caloric density of snacks, fast food consumption, the portion size of meals, food labeling as from a popular fast food chain, and the hours of television watched (see below) with weight gain (117-123) in children, especially those with parents who are overweight or obese.

Physical Activity

Physical activity in adults and children is considered to be an essential part of any effective therapeutic intervention or prevention strategy for obesity (124). Regular exercise improves many risk factors for adiposity-related co-morbidities in both lean and overweight children (125) and has been reported to improve cognitive function and activity in frontal/prefrontal cortex brain areas involved in dietary restraint (126). In addition, behaviors related to physical activity established in childhood have been shown to track well into adulthood (127, 128). The American Academy of Pediatrics, American Heart Associated, Centers for Disease Controls, and National Institutes of Health have all made similar recommendations for the amount and type of exercise for children at different ages. It should be noted that children's exercises should involve the entire family and are not the same exercise regimens that would be utilized in adults (124). While these interventions have been shown to reduce visceral fat, improve insulin sensitivity, and reduce the risk for multiple co-morbidities related to obesity (129-132), adherence to these regimens remains poor (133), especially outside of a controlled environment such as schools (134) where some studies have reported longer term program efficacy.

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 (135) and pediatric obesity may be considered as an independent risk factor for adult adiposity-related morbidities, even if the obesity does not persist (136). 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 the relative centrality of 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 (137, 138). 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 (139).

Table 2. Pediatric Adiposity-Related Morbidities (135, 137-143)	
Cardiovascular	Most common identifiable cause of pediatric 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, sleep apnea, Pickwickian Syndrome , more frequent and severe upper respiratory infections
Orthopedic	Coxa vara, slipped capital femoral epiphyses, Blount's disease, Legg-Calve-Perthe's disease , degenerative arthritis. Vitamin D deficiency
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	Body dissatisfaction, anxiety, somatization, depression, eating disorders

Pediatric Obesity and Cardiovascular Risk Factors

Obesity, hyperlipidemia, hypertension, and other risk factors for cardiovascular disease in children track well into adulthood (6, 135, 140-143). In 40 to 50 year follow-up studies of adolescents who are lean and obese (defined on the basis of body weight-for-height indices), 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 (136, 142). It may be said, therefore, that the metabolic groundwork for the chronic diseases of adulthood is laid down in childhood. Even more so than in adults, the overweight pediatric patient must be assessed for both current adiposity-related morbidities and the risk that such morbidities will develop in the future. The clinician should seek to identify the child "at-risk" for adiposity-related morbidity (primarily identifying genetic risk), as well as the already-obese child, with the goal of encouraging a healthy lifestyle (one that primarily reduces environmental risk) and, in some cases, recommending more aggressive therapeutic intervention that will minimize obesity and its co-morbidities.

Pediatric Obesity and Type 2 Diabetes Mellitus

Like pediatric obesity, the prevalence of T2DM in childhood is increasing in epidemic proportions. Until recently, T2DM was considered an ‘adult’ disease and, as of 10 years ago, constituted less than 2% of the new cases of diabetes in children compared with 98% having type 1 diabetes mellitus. Currently, the burden of diabetes, the prevalence of which is increasing at a rate of 20-30% per decade, falls disproportionately on African- and Hispanic- Americans, in whom between 25% and 50% of children with new-onset diabetes have T2DM (144). Thus, T2DM has become a “pediatric” disease, producing the same renal, ophthalmological, neurological and cardiovascular morbidities in children with T2DM as in adults (145-147), with some indications that these diabetes-related co-morbidities accrue faster in children than in adults (144).

Obesity is the major risk factor for T2DM in adolescents (148, 149) and adiposity accounts for approximately 55% of the variance in insulin sensitivity in children (150). As in adults, 50-90% of children with T2DM, especially those of African-American or Latino descent, have a BMI > 85th percentile (21, 30, 147-149, 151-153). After controlling for adiposity and body fat distribution,

insulin sensitivity has been reported to be approximately 40% higher in African-American than Caucasian pre-pubertal children, but about 35% lower in adolescents (154-157), suggesting that the African-American teenager tends to become insulin resistant at a lower level of body fatness.

The pathophysiology of T2DM is discussed in the *Endotext* section, *Diabetes Mellitus and Carbohydrate Metabolism—DiabetesManager* (158). Like obesity, type 2 diabetes mellitus is a complex metabolic disorder reflecting, in most instances, interactions among genes that influence an individual's susceptibility to diabetes and an environment which favors the expression of that susceptibility, including promotion of processed, calorically-dense beverages and foods and opportunities for a sedentary lifestyle (159). 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 type 2 DM, while in other populations, insulin resistance is the first identifiable phenotype (160, 161). 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 (162, 163), 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 (30, 152), coincidentally with the known decline in insulin-sensitivity and increase in adiposity in the peripubertal period (149, 164, 165).

Central body fat distribution, usually defined on the basis of waist circumference (**Figure 2**) or the ratio of waist-to-hip circumference, is an independent predictor of adiposity-related insulin resistance in adolescents and adults (149, 166, 167) as well as other co-morbidity risk factors (26, 168, 169). 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 (149). 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 (155, 156, 170). 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 (171). Because of the increasing frequency of T2DM among adolescents who are obese, 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 (172).

ENDOCRINE CHANGES ASSOCIATED WITH OBESITY IN CHILDREN

While certain endocrinopathies, such as hypothyroidism, may precipitate weight gain, 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 (173-177)	
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
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, a number of 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-Labhart-Willi; Bardet-Biedl) (**Table 1**). Assessment of skeletal maturation by bone age, and physical examination for the presence or absence of 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 (59, 177)		
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
Growth Hormone Deficiency	Impaired production of GH (pituitary)or GHRH (hypothalamus)	Short stature, obesity, increased risk of elevated cholesterol.
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.

OVERWEIGHT AND OBESITY: CLINICAL APPROACH TO THE PEDIATRIC PATIENT

Initial Evaluation and Decision Whether or Not to Initiate Therapy

Not every child who is obese requires or will benefit from treatment. As discussed previously, the likelihood of persistence of pediatric obesity into adulthood increases with age and with the number of parents who are obese. In large epidemiological studies, if neither of a child's parents is obese, the likelihood of childhood obesity persisting into adulthood may actually be less than the risk for a non-obese child with one or two parents who are obese (6) (**Figure 4**).

The 2017 Endocrine Society guidelines for pediatric obesity assessment, treatment, and prevention provide an excellent algorithmic approach to pediatric obesity (17) (Figure 5). Basic screening should begin with a detailed physical examination focused on identifying both causes of unwanted weight gain (e.g., enlarged thyroid gland, cushingoid body habitus) and weight–related co-morbidities (acanthosis nigricans, hypertension, etc.). Laboratory studies should at least 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. Thyroid function tests (TSH, free T4) should also be obtained. Although hypothyroidism is an unusual cause of obesity in infants, the profound neurologic sequelae of untreated hypothyroidism in infancy justify heightened attention to this possibility in children who develop obesity in the first two years of life, are developmentally delayed, are taking medications that interfere with thyroid secretion (e.g., lithium), or have other clinical stigmata of hypothyroidism (e.g., constipation, bradycardia, thin hair, weakness). 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 (178).

Children less than 2 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-Labhart-Willi) discussed above (**Table 1**), should be referred to a physician who specializes in the treatment and genetic evaluation of pediatric obesity (179). Genetic testing is suggested in patients with extreme early-onset obesity (before 5 years of age) and who have clinical features of genetic obesity syndromes (in particular extreme hyperphagia) and/or a family history of extreme obesity, in particular for polymorphisms of the melanocortin 4 receptor (MC4R) with the caveat that knowledge of these polymorphisms will not currently dictate treatment (180).

The decision as to whether to initiate therapy in the toddler/prepubertal period (ages 2-9) should be strongly influenced by family history of obesity and adiposity-related morbidities. For the pre-adolescent or adolescent child with obesity-related morbidity (e.g., hypertension), the child with central obesity, and/or the child with a strong family history of adiposity-related morbidity (e.g., hyperlipidemia, hypertension, diabetes mellitus), family-based intervention is recommended.

Before beginning any type of therapy it is essential to have the cooperation of the child and his/her family (181, 182). Clinicians should not assume that the child who is obese is necessarily depressed or significantly motivated to lose weight. Beginning weight-loss therapy if the overweight child and his/her family are not motivated to do so is likely to be unsuccessful and may have negative influences on the child's self-esteem and likelihood of future successful weight loss (179). Therapy should not be initiated in such a family environment. Ideally, a significant amount of effort should be devoted to assessing the home environment to decide upon an optimal treatment modality. 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 (183). The logical extension of these findings is that optimal therapeutic interventions must include support for the child's family, including those who are lean as well as overweight or obese (184).

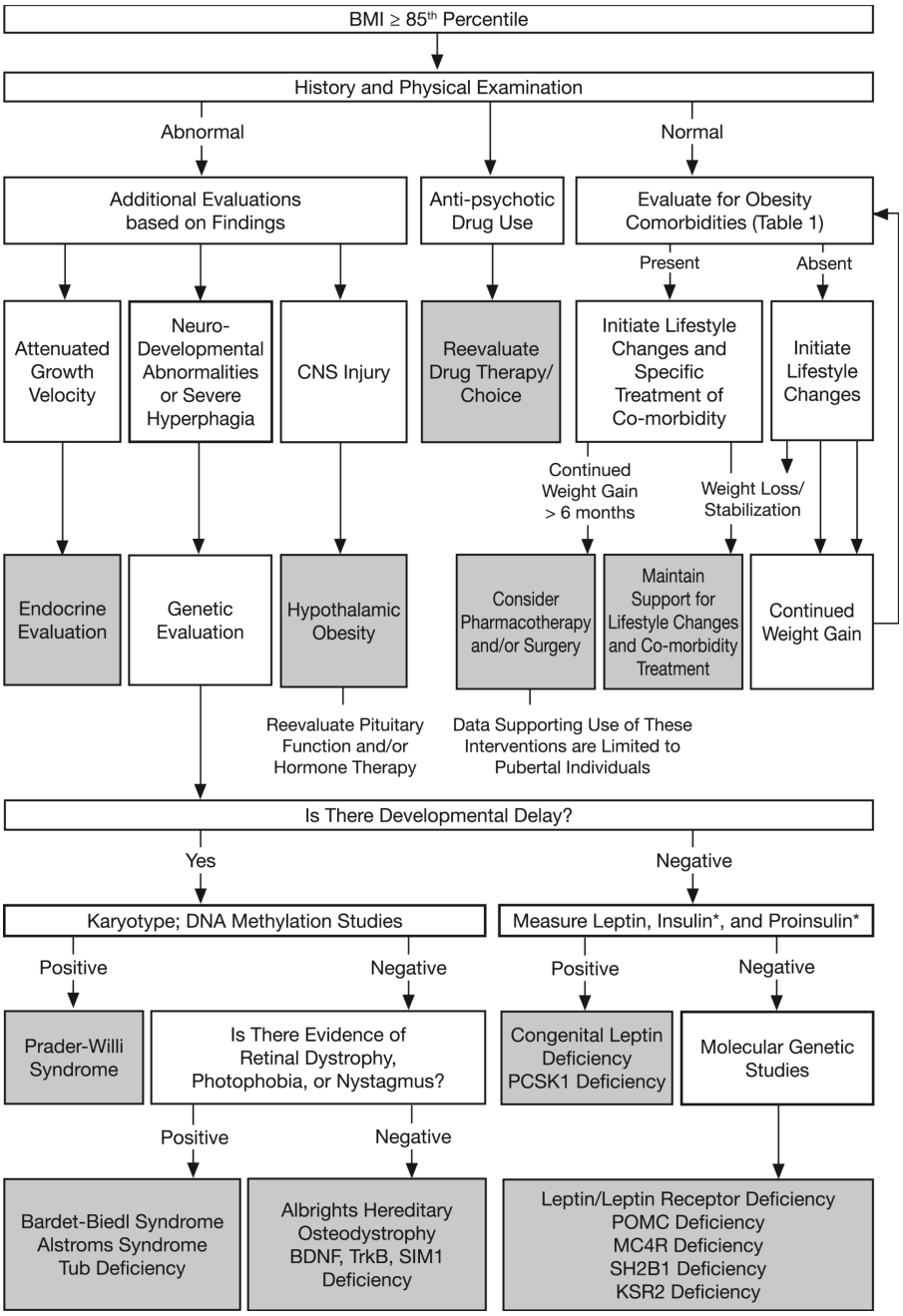


Figure 5. Algorithm for implementing the 2017 Endocrine Society recommendations regarding evaluation and treatment recommendations of the child who is overweight or obese (17).

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 if a more healthy lifestyle is adopted earlier, the fact that there are potential medical complications of obesity (some of which may already be evident in

other family members), and that the entire family will benefit from adopting a healthier lifestyle. It is also important to emphasize that whatever lifestyle changes are made to diminish body fatness will take time and must be continued in the long-term if body fatness reduction is to be maintained.

Initial evaluation before beginning therapy 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).

Treatment of the overweight child 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.

A complete physical examination should also be performed with special attention to the possibility of adiposity-related morbidities (hypertension, dyslipidemia, acanthosis nigricans (indicative of insulin resistance), etc., see **Tables 2-4**). As discussed below, the child who is morbidly obese requires more aggressive therapeutic intervention.

Therapeutic Intervention

The approach to therapy for a child who is overweight or obese is in many ways more complex than the same choice in an adult. Too severe a dietary restriction may result in impairment of statural growth. 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. Too much 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 (137). This is particularly true for children from the peri-pubertal period onward.

The major goal of obesity therapy should be to diminish morbidity and morbidity-risk rather than to achieve a "cosmetically endorsed" body weight. The "severity" of obesity should be assessed by degree of overweight (BMI > 95%ile for age and sex should be considered severely obese), presence of current morbidities (any overweight child (BMI > 85th percentile for age and sex) who has current adiposity-related morbidity such as T2DM should be considered severely obese), and risk of future adiposity-related morbidity (based on family history) (179).

In the otherwise healthy overweight child with no evidence of adiposity-related morbidity, clinicians and parents are generally concerned that the child will become an adult who is obese. Initial therapy in such instances should be directed towards decreasing or eliminating weight growth while allowing height growth to continue at age and sex appropriate velocity so that height eventually becomes appropriate for weight. Avoidance of calorically dense foods and substitution of fruit and vegetable snacks for sugar-added beverages such as sodas and juices, and cookies, without restricting access to such snacks, will, in most cases, result in significant slowing of weight velocity (185). The time required to significantly reduce adiposity can be estimated. One to two years of weight maintenance (one year during normally rapid weight gain periods such as adolescence and two years during periods of slower weight gain) compensates for 20% of excess weight-for-height.

If gradual statural growth into the child's weight is not possible because weight is already overweight or obese by adult standards (i.e., body mass is so great that BMI will still be > 85th percentile even if weight remains stable until adult stature is achieved), then a weight loss regimen, as outlined below, should be considered. Therapeutic weight reduction is usually indicated for the child with evidence of current adiposity-related morbidity. The child with hypertension or diabetes should endeavor to reduce weight or alter body composition within one year to the point that the morbidity is no longer evident. If the morbidity is more severe, e.g., Pickwickian Syndrome, then more rapid weight-reduction, even in an in-patient setting, may be necessary. The obese child with poor self-image, feelings of isolation from peers, and depression, should also attempt weight reduction, perhaps with adjunctive psychotherapy. The initial therapeutic approach for children with predominantly psychiatric obesity-related morbidities (186) should combine exercise and a closely supervised dietary plan, preferably with the involvement of a nutritionist. Studies of compliance with weight-reduction plans have emphasized the importance of a family-oriented approach. As emphasized above, any therapeutic regimen should involve the entire family, as well as the child's school. Frequent physical examination of the child and monitoring of school performance should be included. Patients and their families should be made aware that the treatment period does not end once the prescribed reduction in body fatness has been achieved, and that caloric restriction must continue beyond the period of weight reduction.

OVERVIEW OF THERAPEUTIC OPTIONS

Before prescribing any type of weight reduction treatment for obesity, health personnel should assess the risk/benefit ratio for any treatment in the patient. In the older and otherwise healthy overweight child without family history of adiposity-related morbidity, the fact that adolescent obesity may constitute an independent risk factor for adult mortality and morbidity must be weighed against the possible morbidities (poor statural growth, precipitation of eating disorders, etc.) associated with therapeutic weight reduction. Standardized assessments of eating disorder risk, which is also associated with higher scores on questionnaires evaluating depression, anxiety, and stress in adolescents, are available (187).

Children with obesity and their families must recognize that maintenance of a reduced degree of body fatness may require a lifetime of attention to energy intake and expenditure. The cautions emphasized above in deciding who should undergo a therapeutic weight reduction, and the relatively slow rate at which weight reduction or slowing down of weight gain should be prescribed, reflect the significant morbidities associated with these processes. Diets extremely low in caloric content or with unusual distribution of calories as fat, protein, and carbohydrate may precipitate cardiac arrhythmias, severe electrolyte disturbances, or other morbidities. As many as 80% of children using unsupervised diets obtained from popular magazines have been found to suffer from weakness, headaches, fatigue, nausea, constipation, nervousness, dizziness, poor concentration, dysmenorrhea, and/or fainting. Children on a supervised diet must also be closely monitored for treatment-associated psychological morbidities (stigmatization of the child, precipitation of anorexia nervosa or bulimia).

Therapeutic intervention should emphasize the need for participation of the entire family and lifelong attention to, and benefits of, a healthy lifestyle, as well as positive reinforcement for even small degrees of compliance. Preparation of the family and child for therapeutic intervention is as important as the intervention itself.

DIET

Dietary restriction should never be presented in a punitive manner and, if possible, the child who is obese and the entire family should adhere to a similar diet to minimize feelings of isolation by the affected child. Family members, clinicians, and patients (especially adolescents) will be frustrated by the need for prolonged attention to diet and exercise that is required to achieve and maintain a reduced level of body fatness. 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.

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 (188) should result in weight loss of approximately one pound per week. Self-reported caloric intake is generally very inaccurate. For direct assessment, the child's *ad libitum* diet should be directly observed and recorded by the parents for a minimum of five consecutive days. 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 (34, 43, 59) 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.

Increasing consumption of high fructose corn syrup in sugar-sweetened beverages (189-191), bread, ketchup, and sweet snacks, and of “super-sized” portions of calorically dense (high fat, high glycemic index) foods have all contributed to the increasing prevalence of obesity and its associated co-morbidities (192-194). 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” (195, 196) and other aspects of energy intake which have been found to be correlated with subsequent weight gain in children .

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 (17) 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 (197) 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 (198, 199). 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 (200) 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 (201) and a recent meta-analysis by Hall and Guo (202) found that low fat diets promoted greater fat loss than low carbohydrate diets in adults

Based on the lack of conclusive evidence that dietary macronutrient composition affects weight loss or gain independent of energy intake and expenditure, the primary goal of dietary therapy for obesity is to decrease caloric consumption. The secondary goal is to decrease consumption of macronutrients that have been associated with increased prevalence of co-morbidities made worse by adiposity and increase consumption of beneficial nutrients. Examples of these nutrients would be sugar-sweetened beverage (203, 204) and whole grain (205, 206) consumptions which have, respectively been associated with increased and decreased risk of dyslipidemia and insulin resistance.

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 (185), at least transiently (207). 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

Regular exercise will allow the patient to ingest more calories and hopefully encourage the long-term continuation of such a regimen. Exercise will promote what is usually 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 (208-210). 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. Obviously, "treats", such as ice cream, potato chips, etc., should not be used as incentives to exercise. 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 (17) with other recommendations for physical activity in children (124), 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 (211-213).
- Reduce sedentary behaviors involving screen time such as television viewing, video games, social media, and internet "surfing." Specifically, screen time, other than homework, should be limited to less than 2 hours/day for children older than two years and should be avoided altogether in younger children.

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 (214), 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 (122). 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 (215) 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.

PHARMACOLOGICAL AND SURGICAL INTERVENTIONS

There are limited data regarding pharmacotherapies for obesity in childhood (216). The only medication currently FDA approved for the treatment of obesity in children, and only in those greater than 12 years of age, is orlistat which is a lipase inhibitor that blocks the absorption of about 1/3 of dietary fat with only modest efficacy (approximately 1 kg/m^2 additional reduction in BMI over 12 months compared to placebo) (217). Off-label pharmacotherapies for weight loss have included metformin (218), topiramate, and GLP-1 analogs such as exenatide (216). Metformin has been reported to result in an approximately 1-1.5 kg/m^2 additional reduction in BMI

with high inter-individual variability. Other off-label pharmacotherapies have not been sufficiently studied in children but pilot studies also suggest moderate efficacy in combination with lifestyle intervention in children with severe obesity (219, 220).

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 (221). 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%) (222). 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.

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 (223-225). 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 (226).

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 (227). 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 (228, 229). Recent federal efforts to remove funding from the Healthy, Hunger-free, Kids Act (230) 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.

REFERENCES

1. Y. Wang, M. Beydoun, L. Liang, B. Caballero and S. Kumanyika. Will all Americans become overweight or obese? estimating the progression and cost of the US obesity epidemic. *Obesity* 2008; 16:2323-30

2. M. Rosenbaum. Epidemiology of pediatric obesity. *Ped Annals* 2007; 36:89-95

3. J. Cecil, R. Tavendale, P. Watt, M. Hetherington and C. Palmer. An obesity-associated FTO gene variant and increased energy intake in children. *N Eng J Med* 2008; 359:2558-66

4. C. D. Fryar, M. D. Carroll and C. L. Ogden. Prevalence of Overweight and Obesity Among Children and Adolescents Aged 2–19 Years: United States, 1963–1965 Through 2013–2014. National Center for Health Statistics.

5. C. M. Hales, M. D. Carroll, C. D. Fryar and C. L. Ogden. Prevalence of Obesity Among Adults and Youth: United States, 2015-2016. *NCHS Data Brief* 2017:1-8

6. R. Whitaker, J. Wright, M. Pepe, K. Seidel and W. Dietz. Predicting obesity in young adulthood from childhood and parental obesity. *N Eng J Med* 1997; 337:869-73

7. NHLBI. Obesity trends in the United States. *www.nhlbi.nih.gov/research/resources/obesity/* 2015;

8. S. Phelan and R. Wing. Prevalance of successful weight loss. *Arch Int Med* 2005; 165:2430

9. T. Wadden, R. Neiberg, R. Wing, et al. Four-year weight losses in the Look AHEAD study: factors associated with long-term success. *Obesity* 2011; 19:1987-98

10. G. Bray and P. Siri-Tarino. The role of macronutrient content in the diet for weight management. *Endocinol Metab Clin North Am* 2016; 45:581-604

11. J. Unick, D. Beavers, D. Bond, et al. The long-term effectiveness of a lifestyle intervention in severely obese individuals. *Am J Med* 2013; 126:236-42

12. F. Sacks, G. Bray, V. Carey, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Eng J Med* 2009; 360:859-73

13. A. Magarey, R. Perry, L. Baur, et al. A parent-led family-focused treatment program for overweight children aged 5 to 9 years: the PEACH RCT. *Pediatr* 2011; 127:214-22

14. T. Reinehr, M. Kleber, N. Lass and A. Toschke. Body mass index patterns over 5 y in obese children motivated to participate in a 1-y lifestyle intervention: age as a predictor of long-term success. *Amer J Clin Nutr* 2010; 91:1156-71

15. R. Whitaker, M. Pepe, J. Wright, K. Seidel and W. Dietz. Early adiposity rebound and the the risk of adult obesity. *Pediatr* 1998; 101:E5

16. D. Freedman, L. Kettel Kahn, M. Serdula, S. Srinivasan and G. Berenson. BMI rebound, childhood height and obesity among adults: the Bogalusa Heart Study. *Int J Obes* 2001; 25:543-49

17. D. Styne, S. Arslanian, E. Connor, I. Farooqi, M. Murad and J. Silverstein. Pediatric obesity-assessment, treatment, and prevention: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2017; 102:709-57

18. A. Pietrobelli, M. Faith, D. Allison, D. Gallagher, G. Chiumello and S. Heymsfield. Body mass index as a measure of adiposity among children and adolescents: a validation study. *J Pediatr* 1998; 132:204-10

19. J. Reilly, A. Dorosty, P. Emmet and T. A. Study. Identification of the obese child: adequacy of the body mass index for clinical practice and epidemiology. *Int J Obes* 2000; 24:1623-27

20. e. Expert panel on the identification, and treatment of overweight in adults. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: Executive Summary. *Am J Clin Nutr* 1998; 68:899-917
21. R. Troiano and K. Flegal. Overweight children and adolescents: description, epidemiology, and demographics. *Pediatr* 1998; 101(suppl):497-504
22. SE Barlow and the Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: Summary report. *Pediatr* 2007; 120 (Suppl. 4):S164-92
23. S. Barlow and Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatr* 2007; 120:S164-92
24. A. Gulati, D. Kaplan and S. Daniels. Clinical tracking of severely obese childre: A new growth chart. *Pediatrics* 2012; 130:1136-40
25. W. H. Organization. Growth Charts. *https://www.cdc.gov/growthcharts/data/who/GrChrt_Boys_24HdCirc-L4W_rev90910.pdf* 2006;
26. A. Sharma, D. Metzger, C. Daymont, S. Hadjiyannakis and C. Rodd. LMS tables for waist-circumference and waist-height ratio Z-scores in children aged 5–19 y in NHANES III: association with cardio-metabolic risks. *Pediatr Res* 2015; 78:723-29
27. L. Chen, M. Tint, M. Fortier, et al. Body composition measurement in young children using quantitative magnetic resonance: a comparison with air displacement plethysmography. *Pediatr Obes* 2017; Epub Ahead of Print
28. M. Rosenbaum, T. Agurs-Collins, M. Bray, et al. The Accumulating Data to Optimally Predict Obesity Treatment (ADOPT): Recommendations from the bological domain. *Obesity* 2018; 26
29. R. Kuczmarski. Trends in body composition for infants and children in the U.S. *Crit Rev Food Sci Nutr* 1993; 33:375-87
30. R. Troiano, K. Flegal, R. Kuczmarski, S. Campbell and C. Johnson. Overweight prevalence and trends for children and adolescents. *Arch Pediatr Adol Med* 1995; 149:1085-91
31. K. Flegal, C. Ogden, R. Wei, R. Kuczmarski and C. Johnson. Prevalence of overweight in US children: comparison of US growth charts from the Centers for Disease Control and Prevention with other reference values for body mass index. *Am J Clin Nutr* 2001; 73:1086=93
32. C. Ogden, M. Carroll, B. Kit and K. Flegal. Prevalence of obesity and trends in body mass index among US children and adolescents 1999-2010. *JAMA* 2012; 307:483-90
33. S. Cunningham, M. Kramer and K. Narayan. Incidence of childhood obesity in the United States. *N Eng J Med* 2014; 370:403-11
34. M. Rosenbaum, R. Leibel and J. Hirsch. Medical Progress: Obesity. *N Engl J Med* 1997; 337:396-407
35. J. Dhurandhar, K. Kaiser, J. Dawson, A. Alcorn, K. Keating and D. Allison. Predicting adult weight change in the real world: a systematic review and meta-analysis accounting for compensatory changes in energy intake or expenditure. *Int J Obes* 2015; 39:1181-87
36. T. Wadden. Treatment of obesity by moderate and severe caloric restriction. *Ann Intern Med* 1993; 119:688-93
37. M. Knip and O. Nuutinen. Long-term weight control in obese children: persistence of treatment outcome and metabolic changes. *Int J Obes* 1992; 16:279-87
38. W. McGuire, R. Wing and J. Hill. The prevalence of weight loss maintenance among American adults. *Int J Obes* 1999; 23:1314-19
39. M. Klem, R. Wing, W. Lang, M. McGuire and J. Hill. Does weight loss maintenance become easier over time. *Obes Res* 2000; 8:438-44
40. M. Klem, R. Wing, M. McGuire, H. Seagle and J. Hill. A descriptive study of individuals successful at long term maintenance of substantial weight loss. *Am J Clin Nutr* 1998; 66:239-46
41. R. Wing and J. Hill. Successful weight loss maintenance. *Annu Rev Nutr* 2001; 21:323-41
42. B. Belanger, L. Cupples and R. D'Agostino. The Framingham study: An epidemiologic study investigation of cardiovascular disease. Section 36: Measures at each examination and interexamination consistency of specified characteristics. Framingham publication No. 88-2970. 1988;
43. M. Rosenbaum and R. Leibel. The physiology of body weight regulation: relevance to the etiology of obesity in children. *Pediatr* 1998; 101:525-38
44. M. Rosenbaum, J. Hirsch, E. Murphy and R. Leibel. The effects of changes in body weight on carbohydrate metabolism, catecholamine excretion, and thyroid function. *Amer J Clin Nutr* 2000; 71:1421-32
45. S. Wardlaw. Clinical review 127: Obesity as a neuroendocrine disease: lessons to be learned from proopiomelanocortin and melanocortin receptor mutations in mice and men. *J Clin Endocrinol Metab* 2001; 86:1442-6

46. M. Rosenbaum and R. Leibel. Leptin: a molecule integrating somatic energy stores, energy expenditure, and fertility. *Trends Endorcinol Metab* 1998; 9:117-23
47. R. Ahima, D. Prabakaran, C. Mantzoros, et al. Role of leptin in the neuroendocrine response to fasting. *Nature* 1996; 382:250-52
48. R. Ahima, J. Kelly, J. Elmquist and J. Flier. Distinct physiologic and neuronal responses to decreased leptin and mild hyperleptinemia. *Endocrinol* 1999; 140:4923-31
49. M. Rosenbaum and R. Leibel. 20 years of leptin: role of leptin in energy homeostasis in humans. *J Endocrinol* 2014; 223:T83-96
50. M. Rosenbaum and R. Leibel. Chapter 7: Adaptive response to weight loss. In: R. Kushner and D. Bessesen, eds. Treatment of the obese patient. Second ed. New York, NY: Springer-Verlag; 2014.
51. N. Knuth, D. Johannsen, R. Tamboli, et al. Metabolic adaptation following massive weight loss is related to the degree of energy imbalance and changes in circulating leptin. *Obesity* 2014; 22:2563-69
52. P. Sumithran, L. Prendergast, E. Delbridge, et al. Long-term persistance of hormonal adaptations to weight loss. *N Eng J Med* 2011; 365:1597-604
53. P. Maclean, J. Blundell, J. Mennella and R. Batterham. Biological control of appetite: A daunting complexity. *Obesity* 2017; 25, Suppl 1:S8-16
54. D. Kiortsis, I. Duraced and G. Turpin. Effects of a low-calorie diet on resting metabolic rate and serum tri-iodothyronine levels in obese children. *Eur J Pediatr* 1999; 158:446-50
55. M. Stern, M. Bartley, R. Duggirala and B. Bradshaw. Birth weight and the metabolic syndrome: thrifty phenotype or thrifty genotype? *Diab Met Res Rev* 2000; 16:88-93
56. J. S. Garrow and J. Webster. Are pre-obese people energy thrifty? Paper presented at: Lancet1985
57. A. Stunkard, T. Foch and Z. Hrubec. A twin study of human obesity. *JAMA* 1986; 256:51-54
58. S. Elder, S. Roberts, M. McCrory, et al. Effect of body composition methodology on heritability estimation of body fatness. *Open Nutr J* 2012; 5:48-58
59. R. Leibel, S. Chua and M. Rosenbaum. Chapter 157. Obesity. In: C. Scriver, A. Beaudet, W. Sly and D. Valle, eds. The metabolic and molecular bases of inherited disease. Vol III. eigth ed. New York: McGraw-Hill; 2001:3965-4028.
60. J.-M. Oppert, J. H. Dussault, A. Tremblay and J.-P. Despres. Thyriod hormones and thyrotropin variations during long term overfeeding in identical twins. *J Clin Endocrinol Metab* 1994; 79:547-553
61. E. Poehlman, A. Tremblay and E. fontaine. Genotype dependency of the thermic effect of a meal and associated hormonal changes following short-term overfeeding. *Metabolism* 1986; 35:30-36
62. E. Poehlman, J. Despres, M. Marcotte, A. Tremblay, G. Theriault and C. Bouchard. Genotype dependency of adaptation in adipose tissue metabolism after short-term overfeeding. *Am J Physiol* 1986; 250:E480-E485
63. E. T. Poehlman, A. Tremblay and J. P. Despres. Genotype controlled changes in body composition and fat morphology following overfeeding in twins. *Am J Clin Nutr* 1986; 43:723-731
64. A. Tremblay, E. T. Poehlman, A. Nadeau, J. Dessault and C. Bouchard. Heredity and overfeeding-induced changes in submaximal exercise VO2. *J Appl Physiol* 1987; 62:539-544
65. C. Bouchard, A. Tremblay, J. P. Despres, et al. The response to long-term overfeeding in identical twins. *N Engl J Med* 1990; 322:1477-1482
66. M. Rosenbaum and R. Leibel. Pathophysiology of childhood obesity. *Advances in Pediatrics* 1988; 35:73-137
67. M. Lehtovirta, J. Kaprio, C. Forsblom, J. Eriksson, J. Tuomilehto and L. Groop. Insulin sensitivity and insulin secretion in monozygotic and dizygotic twins. *Diabetologia* 2000; 43:285-93
68. M. Sun, B. Gower, A. Bartolucci, G. Hunter, R. Figueroa-Colon and M. Goran. A longitudinal study of resting energy expenditure relative to body composition during puberty in african american and white children. *Am J Clin Nutr* 2001; 73:308-15
69. C. Llewellyn, M. Trzaskowski, R. Plomin and J. Wardle. From modeling to measurement: developmental trends in genetic influence on adiposity in childhood. *Obes* 2014; 22:1756-61
70. R. Leibel, N. Bahary and J. Friedman. Genetic variation and nutrition in obesity. In: A. Simopoulos and B. Childs, eds. Genetic variation and nutrition. Basel: Karger; 1990:90-101.
71. L. Burnett, G. Hubner, C. LeDuc, M. Morabito, J. Carli and R. Leibel. Loss of the imprinted, non-coding Snord116 gene cluster in the interval deleted in the Prader Willi syndrome results in murine neuronal and endocrine pancreatic developmental phenotypes. *Hum Mol Genet* 2017; 26:4606-16
72. L. Burnett, C. LeDuc, C. Sulsona, et al. Deficiency in prohormone convertase PC1 impairs prohormone processing in Prader-Willi syndrome. *J Clin Invest* 2017; 127:293-305
73. M. Manco and B. Callapiccola. Genetics of pediatric obesity. *Pediatr* 2012; 130:123-33

74. R. Loos. Genetic determinants of common obesity and their value in prediction. *Best Pract Res Clin Endocrinol Metab* 2012; 26:211-26
75. S. Ghosh and C. Bouchard. Convergence between biological, behavioural and genetic determinants of obesity. *Nat Rev Genet* 2017; 18:731-748
76. K. Vimaleswaran, J. Tachmazidou, J. Zhao, J. Hirschhorm, F. Dudbridge and R. Loos. Candidate genes for obesity-susceptibility show enriched association within a large genome-wide association study for BMI. *Hum Mol Gen* 2012; 21:4537-42
77. W. C. Speliotes EK, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, Lango Allen H, Lindgren CM, Luan J, Mägi R, Randall JC, Vedantam S, Winkler TW, Qi L, Workalemahu T, Heid IM, Steinthorsdottir V, Stringham HM, Weedon MN, Wheeler E, Wood AR, Ferreira T, Weyant RJ, Segrè AV, Estrada K, Liang L, Nemesh J, Park JH, Gustafsson S, Kilpeläinen TO, Yang J, Bouatia-Naji N, Esko T, Feitosa MF, Kutalik Z, Mangino M, Raychaudhuri S, Scherag A, Smith AV, Welch R, Zhao JH, Aben KK, Absher DM, Amin N, Dixon AL, Fisher E, Glazer NL, Goddard ME, Heard-Costa NL, Hoesel V, Hottenga JJ, Johansson A, Johnson T, Ketkar S, Lamina C, Li S, Moffatt MF, Myers RH, Narisu N, Perry JR, Peters MJ, Preuss M, Ripatti S, Rivadeneira F, Sandholt C, Scott LJ, Timpson NJ, Tyrer JP, van Wingerden S, Watanabe RM, White CC, Wiklund F, Barlassina C, Chasman DI, Cooper MN, Jansson JO, Lawrence RW, Pellikka N, Prokopenko I, Shi J, Thiering E, Alavere H, Alibrandi MT, Almgren P, Arnold AM, Aspelund T, Atwood LD, Balkau B, Balmforth AJ, Bennett AJ, Ben-Shlomo Y, Bergman RN, Bergmann S, Biebermann H, Blakemore AI, Boes T, Bonnycastle LL, Bornstein SR, Brown MJ, Buchanan TA, Busonero F, Campbell H, Cappuccio FP, Cavalcanti-Proença C, Chen YD, Chen CM, Chines PS, Clarke R, Coin L, Connell J, Day IN, den Heijer M, Duan J, Ebrahim S, Elliott P, Elosua R, Eiriksdottir G, Erdos MR, Eriksson JG, Facheris MF, Felix SB, Fischer-Posovszky P, Folsom AR, Friedrich N, Freimer NB, Fu M, Gaget S, Gejman PV, Geus EJ, Gieger C, Gjesing AP, Goel A, Goyette P, Grallert H, Grässler J, Greenawalt DM, Groves CJ, Gudnason V, Guiducci C, Hartikainen AL, Hassanali N, Hall AS, Havulinna AS, Hayward C, Heath AC, Hengstenberg C, Hicks AA, Hinney A, Hofman A, Homuth G, Hui J, Igl W, Iribarren C, Isomaa B, Jacobs KB, Jarick I, Jewell E, John U, Jørgensen T, Jousilahti P, Jula A, Kaakinen M, Kajantie E, Kaplan LM, Kathiresan S, Kettunen J, Kinnunen L, Knowles JW, Kolcic I, König IR, Koskinen S, Kovacs P, Kuusisto J, Kraft P, Kvaløy K, Laitinen J, Lantieri O, Lanzani C, Launer LJ, Lecoeur C, Lehtimäki T, Lettre G, Liu J, Lokki ML, Lorentzon M, Luben RN, Ludwig B; MAGIC, Manunta P, Marek D, Marre M, Martin NG, McArdle WL, McCarthy A, McKnight B, Meitinger T, Melander O, Meyre D, Midthjell K, Montgomery GW, Morken MA, Morris AP, Mulic R, Ngwa JS, Nelis M, Neville MJ, Nyholt DR, O'Donnell CJ, O'Rahilly S, Ong KK, Oostra B, Paré G, Parker AN, Perola M, Pichler I, Pietiläinen KH, Platou CG, Polasek O, Pouta A, Rafelt S, Raitakari O, Rayner NW, Ridderstråle M, Rief W, Ruokonen A, Robertson NR, Rzehak P, Salomaa V, Sanders AR, Sandhu MS, Sanna S, Saramies J, Savolainen MJ, Scherag S, Schipf S, Schreiber S, Schunkert H, Silander K, Sinisalo J, Siscovick DS, Smit JH, Soranzo N, Sovio U, Stephens J, Surakka I, Swift AJ, Tammesoo ML, Tardif JC, Teder-Laving M, Teslovich TM, Thompson JR, Thomson B, Tönjes A, Tuomi T, van Meurs JB, van Ommen GJ, Vatin V, Viikari J, Visvikis-Siest S, Vitart V, Vogel CI, Voight BF, Waite LL, Wallaschofski H, Walters GB, Widen E, Wiegand S, Wild SH, Willemsen G, Witte DR, Witteman JC, Xu J, Zhang Q, Zgaga L, Ziegler A, Zitting P, Beilby JP, Farooqi IS, Hebebrand J, Huikuri HV, James AL, Kähönen M, Levinson DF, Macciardi F, Nieminen MS, Ohlsson C, Palmer LJ, Ridker PM, Stumvoll M, Beckmann JS, Boeing H, Boerwinkle E, Boomsma DI, Caulfield MJ, Chanock SJ, Collins FS, Cupples LA, Smith GD, Erdmann J, Froguel P, Grönberg H, Gyllensten U, Hall P, Hansen T, Harris TB, Hattersley AT, Hayes RB, Heinrich J, Hu FB, Hveem K, Illig T, Jarvelin MR, Kaprio J, Karpe F, Khaw KT, Kiemeney LA, Krude H, Laakso M, Lawlor DA, Metspalu A, Munroe PB, Ouwehand WH, Pedersen O, Penninx BW, Peters A, Pramstaller PP, Quertermous T, Reinehr T, Rissanen A, Rudan I, Samani NJ, Schwarz PE, Shuldiner AR, Spector TD, Tuomilehto J, Uda M, Uitterlinden A, Valle TT, Wabitsch M, Waeber G, Wareham NJ, Watkins H; Procardis Consortium, Wilson JF, Wright AF, Zillikens MC, Chatterjee N, McCarroll SA, Purcell S, Schadt EE, Visscher PM, Assimes TL, Borecki IB, Deloukas P, Fox CS, Groop LC, Haritunians T, Hunter DJ, Kaplan RC, Mohlke KL, O'Connell JR, Peltonen L, Schlessinger D, Strachan DP, van Duijn CM, Wichmann HE, Frayling TM, Thorsteinsdottir U, Abecasis GR, Barroso I, Boehnke M, Stefansson K, North KE, McCarthy MI, Hirschhorn JN, Ingelsson E, Loos RJ. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* 2010; 42:937-48
78. T. Frayling, N. Timpson, M. Weedon, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 2007; 316:888-94
79. G. Liu, H. Zhu, Y. Dong, R. Pdoolsky, F. Treiber and H. Snieder. Inluence of common variants in FTO and near INSIG2 and MC4R on growth curves for adiposity in African- and European-American youth. *Eur J Epidemiol* 2011; 26:463-73
80. A. Haupt, C. Thamer, H. Staiger, et al. Variation in the FTO gene influences food intake but not energy expenditure. *Exp Clin Endocrinol Diabetes* 2009; 117:194-97

81. J. Wardle, C. Llewellyn, S. Sanderson and R. Plomin. The FTO gene and measured food intake in children. *Int J Obes* 2008; 33:42-45
82. M. Hakanen, O. Raitakari, T. Lehtmake, et al. FTO genotype Is associated with Body Mass Index after the age of 7 years but not with energy intake or leisure-time physical activity
J Clin Endocrinol Metab 2009; Epub ahead of print
83. J. Speakman, K. Rance and A. Johnstone. Polymorphisms of the FTO gene are associated with variation in energy intake, but not energy expenditure. *Obesity* 2008; 16:1961-65
84. B. Barkeling, S. Rossner and A. Sjoberg. Methodological studies on single meal food intake characteristics in normal weight and obese men and women. *Int J Obes* 1995; 19:284-90
85. A. Himaya and J. Louis-Sylvestre. The effect of soup on satiation. *Appetite* 1998; 30:199-210
86. J. Bowen, M. Noakes and P. Clifton. Appetite regulatory hormone responses to various dietary proteins differ by body mass index status despite similar reductions in ad libitum energy intake. *J Clin Endocrinol Metab* 2006; 91:2913-19
87. H. Kissileff, M. Thornton, M. Torres, K. Pavlovich, R. Leibel and M. Rosenbaum. Maintenance of reduced body weight in humans is associated with leptin-reversible declines in satiation. *Amer J Clin Nutr* 2012; 95:309-17
88. R. Holliday. DNA methylation and epigenetic inheritance. *Phils Trans R Soc Lond B Biol Sci* 1990; 326:329-38
89. R. Holliday. Epigenetics: a historical overview. *Epigenetics* 2006; 1:76-80
90. R. Reynolds, G. Jacobsen and A. Drake. What is the evidence in humans that DNA methylation changes link events in utero and later life disease? *Clin Endocrinol* 2013; 78:814-22
91. H. Inadera. Developmental origins of obesity and type 2 diabetes: molecular aspects and role of chemicals. *Environ Health Prev Med* 2013; 18:185-97
92. H. Kirchner, M. Osler, A. Krook and J. Zierath. Epigenetic flexibility in metabolic regulation: disease cause and prevention? *Trends Cell Biol* 2013; 23:203-09
93. K. Menzies, H. Zhang, E. Katsyuba and J. Auwerx. Protein acetylation in metabolism - metabolites and cofactors. *Nat Rev Endocrinol* 2016; 12:43-60
94. M. Zaiou, H. El Amri and A. Bakillah. The clinical potential of adipogenesis and obesity-related microRNAs. *Nutr Metab Cardiovasc Dis* 2017; Epub ahead of print
95. F. Guenard, Y. Deshaies, K. Cianflone, J. Kral, P. Marceau and M. Vohl. Differential methylation in glucoregulatory genes of offspring born before vs. after maternal gastrointestinal bypass surgery. *Proc Nat Acad Sci USA* 2013; 110:11439-44
96. E. Oken, K. Kleinman, M. Belfort, J. Hammitt and M. GIllman. Associations of gestational weight gain with short- and longer-term maternal and child health outcomes. *Am J Epidemiol* 2009; 170:123-80
97. G. Ravelli, Z. Stein and M. Susser. Obesity in young men after famine exposure in utero and early infancy. *N Engl J Med* 1976; 295:349-353
98. A. Ravelli, J. v. d. Meulen, R. Michels, et al. Glucose tolerance in adults after prenatal exposure to famine. *Lancet* 1998; 351:173-77
99. V. Moore, R. Cockington, P. Ryan and J. Robinson. The relationship between birthweight and blood pressure amplifies from childhood to adulthood. *J Hypertens* 1999; 17:883-88
100. A. Hattersley and J. Tooke. The fetal insulin hypothesis: an alternative explanation of the association of low birthweight with diabetes and vascular disease. *Lancet* 1999; 353:1789-92
101. D. Yarborough, E. Barrett-Connor, D. Kritz-Silverstein and D. Wingard. Birth weight, adult weight, and girth as predictors of the metabolic syndrome in postmenopausal women: the Rancho Bernardo Study. *Diab Care* 1998; 21:1652-58
102. D. Barker. Maternal nutrition, fetal nutrition, and diseases later in life. *Nutr* 1997; 13:807-13
103. K. Godfrey and D. Barker. Fetal nutrition and adult disease. *Am J Clin Nutr* 2000; 71:1344S-52s
104. D. Barker and P. Clark. Fetal undernutrition and disease in later life. *Rev Reprod* 1997; 2:105-12
105. D. Barker. Maternal nutrtion, fetal nutrtion, and disease in later life. *Nutr* 1997; 13:807-13
106. D. Barker. Fetal origins of cardiovascular disease. *Ann Med* 1999; 31(Suppl):3-6
107. D. Pettit, H. Baird, K. Allech and W. Knowler. Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. *N Engl J Med* 1983; 308:242-45
108. D. J. Pettitt, R. Baird, K. A. Aleck, P. H. Bennett and W. C. Knowler. Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. *N Engl J Med* 1983; 308:242-245
109. D. J. Pettitt, W. C. Knowler, P. H. Bennett, K. A. Aleck and H. R. Baird. Obesity in offspring of diabetic Pima Indian women. Despite normal birth weight. *Diabetes Care* 1987; 10:76-80

110. D. J. Pettitt, K. A. Aleck, H. R. Baird, M. J. Carraher, P. H. Bennett and W. C. Knowler. Congential susceptibility to NIDDM: Role of interauterine environment. *Diabetes* 1988; 37:622-628
111. S. Entringer, C. Buss, J. Swanson, et al. Fetal programming of body composition, obesity, and metabolic function: the role of intrauterine stress and stress biology. *J Nutr Metab* 2012; 2012:http://dx.doi.org/10.1155/2012/632548
112. S. Entringer and P. Wadhwa. Developmental programming of obesity and metabolic dysfunction: role of prenatal stress and stress biology. *Nestle Nutr Inst Workshop Ser* 2013; 74:107-20
113. M. Hediger, M. Overpeck, R. Kuczmarski and W. Ruan. Association between infant breastfeeding and overweight in young children. *JAMA* 2001; 285:2506-07
114. B. Horta, C. de Mola and C. Victoria. Long term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure, and type 2 diabetes: A systematic review and meta-analysis. *Acta Pediatric* 2015; 105:30-37
115. J. Yan, L. Liu, Y. Zhu, G. Huaming and P. Wang. The association between breastfeeding and childhood obesity: A meta-analysis. *BMC Public Health* 2014; 14:1267
116. P. Rzehak, W. Oddy, M. Mearin, et al. Infant feeding and growth trajectory patterns in childhood and body composition in young adulthoo. *Amer J Clin Nutr* 2017; 106:568-80
117. G. Osei-Assibey, S. Dick, J. Macdiarmid, et al. The influence of the food environment on overweight and obesity in young children: a systematic review. BMJ Open 2012;2.
118. W. Dietz and S. Gortmaker. Do we fatten our children at the television set ? Obesity and television viewing in children and adolescents. *Pediatrics* 1985; 75:807-12
119. A. Salbe, M. Nicolson and E. Ravussin. Total energy expenditure and physical activity correlate with plasma leptin concentrations in five-year-old children. *J Clin Invest* 1997; 99:592-95
120. L. Ku, L. Shapiro, P. Crayford and R. Huenemann. Body composition and physical activity in 8 year old children. *Am J Clin Nutr* 1981; 34:2770-2775
121. P. Davies, J. Gregory and A. White. Physical activity and body fatness in pre-school children. *Int J Obes* 1995; 19:6-10
122. D. Borzekowski and T. Robinson. The 30-second effect: an experiment revealing the impact of television commercials on food preferences of preschoolers. *J Am Diet Assoc* 2001; 101:42-46
123. C. Krespo, E. Smit, R. Troiano, S. Bartlett, C. Macera and R. Andersen. Television watching, energy intake, and obesity in US children: results from the third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med* 2001; 155:360-65
124. C. Foster, J. Moore, C. Singletary and J. Skelton. Physical activity and family-based obesity treatment: a review of expert recommendations on physical activity in youth. *Clinical Obesity* 2018; 8:68-79
125. M. Rosenbaum, C. Nonas, R. Weil, et al. School-based intervention acutely improves insulin sensitivity and decreases inflammatory markers in early adolescence. *J Clin Endocrinol Metab* 2007; 92:504-08
126. A. Bruce, L. Martin and C. Savage. Neural correlates of pediatric obesity. *Prev Med* 2011; 52:S29-35
127. R. Telama, X. Yang, J. Vikari, I. Valimaki, O. Wanne and O. Raitakari. Physical activity from childhood to adulthood: a 21-year tracking study. *Am J Prev Med* 2005; 28:267-73
128. A. Craigie, A. Lake, S. Kelly, A. Adamson and J. Mathers. Tracking of obesity-related behaviours from childhood to adulthood: a systematic review. *Maturitas* 2011; 70:266-84
129. E. Marson, R. Delevatti, A. Pardo, N. Netto and L. Kruel. Effects of aerobic, resistance, and combined exercise training on insulin resistance markers in overweight or obese children and adolescents: A systemic review and meta-analysis. *Prev Med* 2016; 93:211-18
130. M. Estaki, J. Pither, P. Baumeister, et al. Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions. *Microbiome* 2016; 4:42-55
131. K. Dias, D. Green, C. Ingul, T. Pavey and J. Coombes. Exercise and vascular function in child obesity: A meta-analysis. *Pediatr* 2015; 136:e648-59
132. K. Gonzalez-Ruiz, R. Ramirez-Velez, J. Correra-Bautista, M. Peterson and A. Garcia-Hermoso. The effects of exercise on abdominal fat and liver enzymes in pediatric obesity: A systematic review and meta-analysis. *Child Obes* 2017; 13:272-82
133. C. Nooijen, M. Galanti, K. Engstrom, J. Moller and Y. Forsell. Effectiveness of interventions on physical activity in overweight or obese children: a systematic review and meta-analysis including studies with objectively measured outcomes. *Obes Rev* 2017; 18:1950213
134. H. Mei, Y. Xiong, S. Xie, et al. The impact of long-term school-based physical activity interventions on body mass index of primary school children - a meta-analysis of randomized controlled trials. *BMC Public Health* 2016; 16:205

135. L. Webber, S. Srinivasan, W. Wattigneyy and G. Berenson. Tracking of serum lipids and lipoproteins from childhood to adulthood: the Bogalusa Heart Study. *Am J Epidemiol* 1991; 133:884-99
136. A. Must, P. Jacques, G. Dallai, D. Bajema and W. Dietz. Long-term morbidity and mortality of overweight adolescents. *N Eng J Med* 1992; 327:1350-55
137. S. Pont, R. Puhl, S. Cook, W. Slusser and t. O. S. Section on Pediatric Obesity. Stigma experienced by children and adolescents with obesity. *Pediatr* 2017; 140:e20173034.
138. J. Juvonen, L. Lessard, H. Shater and L. Suchlit. Emotional implicaiton of weight stigma across middle school: The role of weight-based peer discrimiatnion. *J Clin Child Adolesc Psychol* 2017; 46:150-58
139. M. Pugliese, F. Lifshitz, G. Grad, P. Fort and M. Marks-Katz. Fear of obesity. *N Engl J Med* 1983; 309:513-18
140. C. Magnussen, A. Venn, R. Thomson, et al. The association of pediatric low- and high-density lipoprotein cholesterol dyslipidemia classifications and change in dyslipidemia status with carotid intima-media thickness in adulthood evidence from the cardiovascular risk in Young Finns study, the Bogalusa Heart study, and the CDAH (Childhood Determinants of Adult *J Am Coll Cardiol* 2009; 53:860-69
141. J. Juhola, C. Magnussen, J. Viikari, et al. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: the Cardiovascular Risk in Young Finns Study. *J Pediatr* 2011; 159:584-90
142. D. Freedman, D. Patel, S. Srinivasan, et al. The contribution of childhood obesity to adult carotid intima-media thickness: the Bogalusa Heart Study. *Int J Obes* 2008; 32:749-56
143. W. Clarke, H. Schrott, P. Leaverton, W. Connor and R. Lauer. Tracking of blood lipids and blood pressure in school age children. The Muscatine study. *Circulation* 1978; 58:626-34
144. R. Viner, B. White and D. Christie. Type 2 diabetes in adolescents: a severe phenotype posing major clinical challenges and public health burden. *Lancet* 2017; 389:3-9
145. A. Rosenbloom, J. Joe, R. Young and W. Winter. Emerging epidemic of type 2 diabetes in youth. *Diab Care* 1999; 22:345-54
146. M. Rosenbaum, S. Accacha, L. Altshuler, et al. The Reduce Obesity and Diabetes (ROAD) project: design and methodological considerations. *Childhood Obesity* 2011; 7:223-34
147. M. Rosenbaum, I. Fennoy, S. Accacha, et al. Racial/ethnic differences in clinical and biochemical type 2 diabetes mellitus risk factors in children. *Obesity* 2013 21:2081-90
148. T. Young, H. Dean, B. Flett and P. Wood-Steinman. Childhood obesity in a population at high risk for type 2 diabetes. *J Pediatr* 2000; 136:365-69
149. S. Caprio and W. Tamborlane. The metabolic impact of obesity in childhood. *Endocrinol Metab Clin N Amer* 1999; 28:731-47
150. S. Arslanian and C. Suprasongsin. Insulin sensitivity, lipids, and body composition in children: Is "syndrome X" present? *J Clin Endocrinol Metab* 1996; 81:1058-62
151. M. Harris, K. Flegal, C. Cowie, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994. *Diab Care* 1998; 21:518-24
152. D. Dablea, D. Pettitt, K. Jones and S. Arslanian. Type 2 diabetes mellitus in minority children and adolescents. *Endocrinol Metab Clin N Amer* 1999; 28
153. K. Flegal and P. Troiano. Changes in the distribution of body mass index of adults and children in the US population. *Int J Obes* 2000; 24:807-18
154. S. Arslanian and C. Suprasongsin`. Differences in the in vivo insulin sensitivity in healthy black vs white adolescents. *J Pediatr* 1996; 129:440-44
155. B. Gower, T. Nagy, C. Trowbridge, C. Dezenberg and M. Goran. Fat distribution and insulin response in prepubertal African American and white children. *Am J Clin Nutr* 1998; 67:821-27
156. B. Gower, T. Nagy and M. Goran. Visceral fat, insulin sensitivity, and lipids in prepubertal children. *Diabetes* 1999; 48:1515-21
157. F. Svec, K. Nastasi, C. Hilton, W. Bao, S. Srinivasan and G. Berenson. Black-white contrasts in insulin levels during pubertal development. The Bogalusa Heart Study. *Diabes* 1992; 41:313-17
158. E. Cersosimo, C. Triplitt, L. J. Mandarino and R. A. DeFronzo. Pathogenesis of Type 2 Diabetes Mellitus. In: L. J. De Groot, G. Chrousos, K. Dungan, K. R. Feingold, A. Grossman, J. M. Hershman, C. Koch, M. Korbonits, R. McLachlan, M. New, J. Purnell, R. Rebar, F. Singer and A. Vinik, eds. Endotext. South Dartmouth (MA)2000.
159. C. Kahn, D. Vincent and A. Doria. Genetics of non-insulin-dependent (type II) diabetes mellitus. *Annu Rev Med* 1996; 47:509-31
160. A. Natali, E. Muscelli, A. Mari, et al. Insulin sensitivity and beta-cell function in the offspring of type 2 diabetes patients: impact of line of inheritance. *J Clin Endocrinol Metab* 2010; 95:4703-11

161. S. Chernausek, S. Arslanian, S. Caprio, et al. Relationship between parental diabetes and presentation of metabolic and glycemic function in youth with type 2 diabetes: baseline findings from the TODAY Trial. *Diab Care* 2016; 39:110-17
162. C. Johnston, W. Ward, J. Beard, B. McKnight and D. Porte. Islet function and insulin sensitivity in the non-diabetic offspring of conjugal type 2 diabetic patients. *Diab Med* 1990; 7:119-25
163. K. S. Polonsky, J. Sturis and G. I. Bell. Non-insulin dependent diabetes mellitus - A genetically programmed failure of the beta cell to compensate for insulin resistance. *N Engl J Med* 1996; 334:777-783
164. S. Caprio, L. Hyman, S. McCarthy, R. Lange, M. Bronson and W. Tamborlane. Fat distribution and cardiovascular risk factors in obese adolescent girls: importance of the intraabdominal fat depot. *Am J Clin Nutr* 1996; 64:12-17
165. L. Caprio. Central adiposity and its metabolic correlates in obese adolescent girls. *N Engl J Med* 1995;
166. R. Frerichs, L. Webber, A. Voors, S. Srinivasan and G. Berenson. Cardiovascular disease risk factor variables in children at two successive years - the Bogalusa heart study. *J Chron Dis* 1979; 32:251-62
167. D. Freedman, S. Srinivasan, G. Burke, et al. Relationship of body fat distribution to hyperinsulinemia in children and adolescents: The Bogalusa heart study. *Am J Clin Nutr* 1987; 46:403-10
168. R. Kelishadi, P. Mirmoghtadaee, H. Majafi and M. Keikha. Systematic review on the association of abdominal obesity in children and adolescents with cardio-metabolic risk factors. *J Res Med Sci* 2015; 20:294-307
169. P. Katzmarzyk, W. Shen, A. Baxter-Jones, et al. Adiposity in children and adolescents: correlates and clinical consequences of fat stored in specific body depots. *Pediatr Obes* 2012; 7:e42-61
170. K. Osei and D. Schuster. Effects of race and ethnicity on insulin sensitivity, blood pressure, and heart rate in three ethnic populations: comparative studies in African-Americans, African immigrants (Ghanaians), and white Americans using ambulatory blood pressure monitoring. *Am J Hypertens* 1996; 9:1157-64
171. J. Yanovski, S. Yanovski, K. Filmer, et al. Differences in body composition of black and white girls. *Am J Clin Nutr* 1996; 64:833-39
172. B. Mitchell, C. Kammerer, L. Reinhart and M. Stern. NIDDM in Mexican-American families. Heterogeneity by age of onset. *Diab Care* 1994; 17:567-73
173. S. Daniels. Obesity in the pediatric patient: cardiovascular complications. *Prog Pediatr Cardiol* 2001; 12:161-67
174. M. Sothern, M. Loftin, U. Blecker and J. Udall. Impact of significant weight loss on maximal oxygen uptake in obese children and adolescents. *J Investig Med* 2000; 48:411-16
175. P. S. C Boucher-Berry, DE Carey, SP Shelov and I. F. S Accacha, R Rapaport, Y Espinal, M Rosenbaum. Vitamin D, osteocalcin, and risk for adiposity as comorbidities in middle school children. *J Bone Miner Res* 2012; 27:283-93
176. M. Smotkin-Tangorra, R. Purushothaman, A. Gupta, G. Nejati, H. Anhalt and S. Ten. Prevalence of vitamin D insufficient in obese children and adolescents. *J Pediatr Endocrinol Metab* 2007; 20:817-23
177. S. Kumar and A. Kelly. Review of childhood obesity: from epidemiology, etiology, and comorbidities to clinical assessment and treatment. *Mayo Clin Proc* 2017; 92:251-65
178. R. Legro, S. Arslanian, D. Ehrmann, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2013; 98:4565-92
179. S. Barlow and W. Dietz. Obesity evaluation and treatment: Expert Committee recommendations. The Maternal and Child Health Bureau, Health Resources and Services Administration and the Department of Health and Human Services. *Pediatr* 1998; 102:E29
180. G. August, S. Caprio, I. Fennoy, et al. Prevention and treatment of pediatric obesity: an endocrine society clinical practice guideline based on expert opinion. *J Clin Endocrinol Metab* 2008; 93:4576-99
181. L. Epstein. Family-based behavioural intervention for obese children. *Int J Obes* 1996; 20:S14-S21
182. L. Epstein, A. Valoski, R. Wing and J. McCurley. Ten-year follow-up of behavioral, family-based treatment of obese children. *JAMA* 1990; 264:2519-23
183. G. Frohlich, W. Pott, O. Albavrak, H. Hedebrand and U. Pauli-Pott. Conditions of long-term success in a lifestyle intervention for overweight and obese youths. *Pediatr* 2011; 12:8e779-85
184. W. Pott, O. Albvarak, J. Hedebrand and U. Pauli-Pott. Treating childhood obesity: family background variables and the child's success in a weight-control intervention. *Int J Eat Disord* 2009; 42:284-89
185. L. Epstein, C. Gordy, H. Raynor, M. Beddome, C. Kilanowski and R. Paluch. Increasing fruit and vegetable intake and decreasing fat and sugar intake in families at risk for childhood obesity. *Obes Res* 2001; 9:171-78
186. J. Vander Wal and E. Mitchell. Psychological complications of pediatric obesity. *Pediatr Clin N Amer* 2011; 58:1393-401

187. A. Doyle, D. le Grange, A. Goldschmidt and D. Wilfley. Psychosocial and physical impairments in overwegiht adolescents at high risk for eating disorders. *Obes* 2007; 15:145-54
188. A. M. Roza, H. M. Shizgal, FRCS(C) and FACS. The Harris Benedict equation reevaluated: resting energy requirements and the body cell mass. *Am J Clin Nutr* 1984; 40:168-182
189. V. Malik and F. Hu. Fructose and cardiometabolic health: What the evidence form sugar sweetened beverages tells us. *J Am Coll Cardiol* 2015; 66:1615-24
190. N. Raissouni, A. Kolesnikov, R. Purushothaman, et al. Altered glucose disposition and insulin sensitivity in peri-pubertal first-degree relatives of women with polycystic ovary syndrome. . *Int J Pedaitr Endocrinol* 2012 doi: 10.1186/1687-9856-2012-14
191. V. Malik, M. Schulze and G. Hu. Intake of sugar-sweetened beverages and weight gain: a systematic review. *Am J Clin Nutr* 2006; 84:274-88
192. Y. Wang, S. Bleich and S. Gortmaker. Increasing caloric contribution from sugar-sweetened beverages and 100% fruit juices among US children and adolescents, 1988-2004. *Pediatr* 2008; 121:e:1604-14
193. C. Ford, M. Slining and B. Popkin. Trends in dietary intake among US 2- to 6- year old children, 1989-2008. *J Acad Nutr Diet* 2013; 113:35-42
194. E. Banfield, Y. Liu, J. Davis, S. Chang and A. Frazier-Wood. Poor adherence to US Dietary Guidelines for children and adolescents in the National Health and Nutrition Examination Survey population. *J Acad Nutr Diet* 2016; 115:21-27
195. K. Asta, A. Miller, L. Retzloff, K. Rosenblum, N. Kaciroti and J. Lumeng. Eating in the absence of hunger and weight gain in low-income toddlers. *Pediatr* 2016; 137:e20153786
196. R. Lansigan, J. Edmond and D. Gilbert-Diamond. Understanding eating in the absence of hunger among young children: a systematic review of existing studies. *Appetite* 2015; 85:36-47
197. M. Gow, M. Ho, T. BUrrows, et al. Impact of dietary macronutrient distribution on BMI and cardiometabolic outcomes in overweight and obese children and adolescents: a systematic review. *Nutr Rev* 2014; 72:453-70
198. G. Foster, H. Wyatt, J. Hill, et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. *Ann Int Med* 2010; 153:147-57
199. N. Mirza, M. Palmer, K. Sinclair, et al. Effects of a low glycemic load or a low-fat dietary intervention on body weight in obese Hispanic American children and adolescents: a randomized controlled trial. *Amer J Clin Nutr* 2013; 97:276-85
200. J. Davis, S. Whaley and M. Goran. Effects of breastfeeding and low sugar-sweetened beverage intake on obesity prevalence in Hispanic toddlers. *Amer J Clin Nutr* 2012; 95:3-8
201. N. Mirza, M. Palmer, K. Sinclair, et al. Effects of a low glycermic load or low fat-dietary intervention on body weight in obese Hispanic American children and adolescents: a randomized controlled trial. *Am J Clin Nutr* 2013; 97:276-85
202. K. Hall and J. Guo. Obesity energetics: Body weight regualtion and effects of diet composition. *Gastroenterol* 2017; 152:1718-27
203. E. Kosova, P. Auinger and A. Bremer. The relationships between sugar-sweetened beverage intake and cardiometabolic markers in young children. *J Acad Nutr Diet* 2013; 113:219-27
204. A. Bremer, P. Auinger and R. Byrd. Relationship between insulin resistance-associated metabolic parameters and anthropometric measurements with sugar-sweetened beverage intake and physical activity levels in US adolescents: findings from the 1999-2004 National Health and Nutrition Examination Survey. *Arch Pediatr Adolesc Med* 2009; 163:328-35
205. C. Damsgaard, A. Biltoft-Jensen, I. Tetens, et al. Whole-grain intake, reflected by dietary records and biomarkers, is inversely associated with circulating insulin and other cardiometabolic markers in 8- to 11-year-old children. *J Nutr* 2017; 147:816-24
206. I. Hur and M. Reicks. Relationship between whole-grain intake, chronic disease risk indicators, and weight status among adolescents in the National Health and Nutrition Examination Survey, 1999-2004. *J Acad Nutr Diet* 2012; 112:46-55
207. C. Ebbeling, H. Feldman, V. CHomitz, et al. A randomized trial of sugar-sweetened beverages and adolescent body weight. *N Eng J Med* 2012; 367:1407-16
208. A. Albright, M. Franz, G. Hornsby, et al. American College of Sports Medicine position stand. Exercise and type 2 diabetes. *Med Sci Sports* 2000; 32:1345-60
209. L. Epstein, R. Wing, B. Penner, M. Kress and R. Koeske. The effect of controlled exercise on weight loss in obese children. *J Pediatr* 1985; 107:358-61
210. D. Kelley and B. Goodpaster. Effects of exercise on glucose homeostasis in type 2 diabetes mellitus. *Med Sci Sports Exerc* 2001; 33:S495-501

211. M. Sekine, T. Yamagami, K. Handa, et al. A dose-response relationship between short sleeping hours and childhood obesity: results of the Toyama Birth Cohort Study. *Child Care Health Dev* 2002; 28:163-170
212. S. Anderson and R. Whitaker. Household routines and obesity in US pre-school-aged children. *Pediatr* 2010; 125:420-28
213. R. Felso, S. Lohner, K. Hollody, E. Erhardy and D. Molnar. Relationship between sleep duration and childhood obesity: Systematic review including the potential underlying mechanisms. *Nutr Metab Cardiovasc Dis* 2017; 27:751-61
214. B. Hernandez, S. Gortmaker, G. Colditz, K. Peterson, N. Laird and S. Parra-Cabrera. Association of obesity with physical activity, television programs and other forms of video viewing among children in Mexico city. *Int J Obes* 1999; 23:845-54
215. P. Schweizer, M. Lenz and H. Kirschner. Pathogenesis and symptomatology of cholelithiasis in childhood. A prospective study. *Dig Surg* 2000; 17:459-67
216. A. Kelly, C. Fox, K. Rudser, A. Gross and J. Ryder. Pediatric obesity pharmacotherapy:current status of the field, review of the literature and clinical trial considerations. *Int J Obes* 2016; 40:1043-50
217. J. Chanoine, S. Hampl, C. Jensen, M. Boldrin and J. Hauptman. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *JAMA* 2005; 293:2873-2883
218. M. McDonagh, S. Selph, A. Ozpinar and C. Foley. Systematic review of the benefits and risks of metformin in treating obesity in children aged 18 years and younger. *JAMA Pediatr* 2014; 168:178-84
219. C. Fox, K. Marlatt, K. Rudser and A. Kelly. Topiramate for weight reduction in adolescents with severe obesity. *Clin Pediatr* 2015; 54:19-24
220. A. Kelly, K. Rudser, B. Nathan, et al. The effect of Glucagon-like peptide-1 receptor agonist therapy on body mass index in adolescents with severe obesity. *JAMA Pediatr* 2013; 167:355-60
221. N. Zwintscher, K. Azarow, J. Horton, C. Newton and M. Martin. The increasing incidence of adolescent bariatric surgery. *J Pediatr Surg* 2013; 48:2401-07
222. T. Inge, A. Courcoulas, T. Jenkins, et al. Weight loss and health status 3 years after bariatric surgery in adolescents. *N Eng J Med* 2016; 374:113-23
223. M. Sanchez, S. Panahi and A. Tremblay. Childhood obesity: a role for gut microbiota? *Int J Environ Res Public Health* 2014; 23:162-75
224. M. Hume, A. Nicolucci and R. Reimer. Prebiotic supplementation improves appetite control in children with overweight and obesity: a randomized controlled trial. *Am J Clin Nutr* 2017; 105:790-99
225. A. Nicolucci, M. Hume, I. Martinez, S. Mayengbam, J. Walter and R. Reimer. Prebiotics reduce body and alter intestinal microbiota in children who are overweight or with obesity. *Gastroenterol* 2017; 153:711-22
226. M. Oosterhoff, M. Joore and I. Ferreira. The effects of school-based lifestyle interventions on body mass index and blood pressure: a multivariate multilevel meta-analysis of randomized controlled trials. *Obes Rev* 2016; 17:1131-53
227. S. Gortmaker, Y. Wang, M. Long, et al. Three interventions that reduced chilhood obesity are projected to save more than they cost to implement. *Health Aff* 2015; 34:1932039
228. J. Mansfield and D. Saviano. Effect of school wellness policies and the Healthy, Hunger-Free Kids Act on food-consumption behaviors of students, 2006-2016: a systematic review. *Nutr Rev* 2017; 75:533-32
229. N. Vaudrin, K. Lloyd, M. Yedidia, M. Todd and P. Ohri-Vacjaspati. Impact of the 2010 US Healthy, Hunger-Free Kids Act on school breakfast and lunch participation rates between 2008 and 2015. *Am J Pub Heal* 2018; 108:84-86
230. United States Department of Agriculture. Ag Secretary Perdue moves to make school meals great again. *USDA Press Release* 2017:https://www.usda.gov/media/press-releases/2017/05/01/ag-secretary-perdue-moves-make-school-meals-great-again