Published in final edited form as:

Pediatr Clin North Am. 2006 August ; 53(4): 777–794. doi:10.1016/j.pcl.2006.05.011.

Obesity and Its Therapy: From Genes to Community Action

Joseph A. Skelton, MD^{a,b,*}, Laure DeMattia, DO^{b,c}, Lawrence Miller, PsyD^b, and Michael Olivier, PhD^d

^aDivision of Pediatric Gastroenterology and Nutrition, Medical College of Wisconsin, 8701 Watertown Plank Road, PO Box 26509, Milwaukee, WI 53226, USA

^bThe NEW (Nutrition, Exercise, and Weight-management) Kids™ Program, Children's Hospital of Wisconsin, 9000 West Wisconsin Avenue, Milwaukee, WI 53226, USA

^cFamily and Community Medicine, Medical College of Wisconsin, 8701 Watertown Plank Road, PO Box 26509, Milwaukee, WI 53226, USA

^dDepartment of Physiology, Human and Molecular Genetics Center, Medical College of Wisconsin, 8701 Watertown Plank Road, PO Box 26509, Milwaukee, WI 53226, USA

The increase in the number of overweight children over the last several decades is obvious to anyone who cares for or works with children. To the general practitioner, this is an especially frustrating problem. Few treatment modalities exist, and despite great knowledge of contributing factors, little can be accomplished in a brief office visit. Additionally, exciting advances in basic science research, beginning with the discovery of leptin in 1994 [1], have not led to novel tools for use in everyday clinical practice. Leptin turned out to be the tip of the iceberg in the scientific investigation of obesity and its comorbidities. To date, more than 600 genes, markers, and regions of chromosomes have been linked to obesity [2]. Does this mean we are closer or further away from finding better ways to treat and prevent obesity?

Traditionally, the biopsychosocial model of obesity as a disease has been considered appropriate, as all elements of the model are relevant (Fig. 1). This model shows disease arising from the overlap of components. In applying this model to obesity research, biologic systems are viewed in isolation, not taking into account their interaction with the environment and behaviors until there is “disease” present. Although strides have been made exploring the pathophysiology of obesity, treatment and prevention have focused on the other two components: psychological and social. The best interventions have been in the fields of dietary management and behavioral change [3–5]. Drug therapy has been limited, especially in children [6–8]. Genetic testing is applicable to only a small number of those affected by obesity. Exploring the cellular and molecular mechanisms behind obesity while clinically treating from the other end of the spectrum can result in slow progress. By integrating basic science with clinical research, treatments and interventions will be better focused and more quickly translated into care plans. To facilitate this, a paradigm shift has taken place.

A more comprehensive model of childhood overweight is the Ecological Systems Theory [9], which helps conceptualize the contributors to obesity (Fig. 2). Physiologic, behavioral, and environmental components are intertwined, and none can be fully considered without understanding the systems in which they are embedded. Instead of dissecting out the

contributors to weight status, they are viewed holistically. This “clinical” approach can also be applied to research.

Using an ecological model, known therapies such as cognitive behavioral modification and modified nutrition can be translated into genetic research. Investigating the genomics of behavior can allow for targeted interventions in those predisposed to dysfunctional eating or parenting behaviors. Nutritional genomics could one day identify particular individuals that may require supplementation of essential fatty acids to maintain a healthy weight. The complex nature of the obesity epidemic is no longer a hindrance to effective research, but complements the translational medicine approach. This chapter summarizes research efforts aimed at elucidating the complex genetic, behavioral, and social relationships causing overweight and obesity, and highlights targeted efforts to advance treatment and prevention using an integrated approach.

Complex diseases require complex approaches

The completion of the sequence of the human genome has been heralded as the advent of a new era in biomedical research [10]. However, despite all efforts, the impact on clinical medicine and disease management, not only in the area of obesity, has been relatively small. The primary reason for this slow progress is the fact that the genetic factors influencing obesity are complex and multifaceted. The early success stories in medical genetics have shown that mutated genes can be identified in disorders such as cystic fibrosis [11] and sickle cell anemia [12]. However, in all of these cases, a single gene in the human genome is mutated so that it no longer produces a functional protein. In almost all cases, these so-called “monogenic disorders” are recessive—that is, the child needs to inherit one mutated copy of the gene from each parent. Although the clinical consequences of these disorders are usually severe, only a relatively small number of individuals are affected, and the diseases are relatively rare in the general population.

Unfortunately, most common diseases that affect a much larger percentage of children, such as obesity, have a more complicated genetic basis. For these disorders, not just one but several genes are believed to be mutated [13]. However, in contrast to diseases like cystic fibrosis, each of these mutations by itself does not cause the disease, and only the accumulation of a relatively large number of mutations in different genes across the entire genome will ultimately lead to the clinical manifestations of these polygenic disorders. The identification of all these genetic changes is further complicated by the fact that the clinical manifestations of the disorder are also influenced by environmental factors such as nutrition and behavior in the case of obesity. Only the complex interplay of a significant number of genetic mutations and the “wrong” environmental conditions will result in obesity.

This complexity is the primary reason for the slow progress in the identification of genetic causes of obesity. However, despite the adversity of this complex research challenge, significant progress has been made in the last few years, albeit with as-of-yet little impact on clinical disease management in children or adults. The development of high-throughput technologies to examine large numbers of single nucleotide polymorphisms (SNPs) across the human genome has permitted the systematic analysis of the role of these sequence differences in the development of obesity [14]. SNPs are single base pair changes in the DNA sequence. Humans are genetically 99.9% identical on the sequence level [15], which in turn means that an individual's genome sequence differs (on average) from another individual's sequence in three million positions. The majority of these differences consists of single base pair differences in the DNA sequence (“spelling errors”), and includes known mutations responsible for disorders such as cystic fibrosis. However, nothing is known about the effect of the majority of these sequence changes, and it is possible that some of these in combination are responsible

for the development of common polygenic disorders such as obesity. In addition to our improved ability to interrogate and examine these SNPs across the entire human genome [16], the clinical ascertainment of large patient cohorts and the accurate diagnosis of obesity-related abnormalities in these individuals allow researchers for the first time to identify sequence changes shared among large numbers of obese individuals [17].

Although it has become easier to identify potential sequence changes that are associated with obesity, the actual verification of the genetic effect and the analysis of its physiologic consequences have been even more challenging. Historically, researchers have examined the effect of mutations on gene function by expressing the mutated gene in cells in vitro and examining the effect of the resulting mutated protein on physiologic responses to external stimuli such as hormones (eg, leptin or insulin). The approach is labor intensive but has yielded significant insights into gene function of individual genes and its mutations. However, such an analysis is no longer feasible when numerous sequence changes in a significant number of different genes have to be examined in parallel. Not only is the sheer number of genes that need to be examined beyond our current capabilities, it is also unclear what kind of effect the different sequence changes will have on the physiology of target organs. The numerous mutations will not have as dramatic an effect as the mutations reported for monogenic disorders. If they did, it is likely that only one or a few mutations would suffice to cause disease, and the onset and severity of the disorder would be much more dramatic than the gradual onset commonly seen in polygenic disorders such as obesity. Thus, research needs to advance from its current state of functional analysis to integrate genomic approaches with extensive clinical analyses to fully understand the complex interplay of genes, nutrition, and behavior that leads to the development and progression of obesity. Genetics can only provide a small yet crucial portion of the answer to this medical challenge, and it cannot do this in the isolation of a basic science research laboratory.

Genetics of feeding behavior

Treatment of obesity has been best conceptualized as an interdisciplinary (ie, physicians, dietitians, psychologists, physical therapists) approach to a chronic disease [18], but there is not a single, effective, standardized treatment approach. Behavioral treatment programs typically result in some short-term weight loss; however, long-term weight maintenance is extremely difficult and successful in a marginal number of patients [19]. In the field of pediatrics, the most successful interventions have been in controlled studies involving behavioral modification [20–23]. In keeping with the ecological model of obesity, translational medicine and research should include investigation of behaviors.

It is challenging to identify which behaviors are genetically related to obesity owing to a variety of research methodologic issues [24]. In their review of the obesity genetic literature, Faith and coauthors [24] recognized that food intake, parenting behavior, physical activity, and eating disorders have genetic influences, whereas personality styles do not. Behavioral genetics studies have identified the genetic preference for specific food types, but the majority of the variance in eating behavior is owing to shared environmental and genetic factors. These can be difficult to clearly separate from genetics [25,26]. Twin studies have found that children with parents who are obese preferred vegetables less, responded greater to cues for food, had a higher desire for drinks, but did not have greater food intake compared with children with parents of normal weight [26]. Animal studies have found links between chromosomes 1 and 4 on weight gain at 8 and 10 weeks, and for 2-week weight gain (ie, difference between weeks 10 and 8), chromosome 6 (which coincides with human 7q) was found to play a role [27]. In review of human studies, the β -2 adrenergic receptor Gln27Gln genotype, and mutations in the *MC4R* gene have been linked with changes in body composition and for the latter in binge eating [25,28]. In addition, dietary restraint has been coupled with chromosomes 3 and 6, and

taste sensitivity to 6-*n*-propylthiouracil (PROP) (ie, ability to perceive fat) has been linked to chromosome 7q and relates to food preferences [25].

Children are born with the inherent preference for sweet and salty tastes and reject sour and bitter tastes, and they have the capacity to regulate their amount of food consumption in 24-hour periods. However, parents that do not allow self-control over foods can dominate the child's inborn system that results not only in the disruption of the internal hunger and satiety cues but also in child food preferences [29]. Well-intending parents that seek to control their child's eating practices, especially if the child is at greater risk for obesity [30], set the stage for negativity around food by limiting food choices, a cascade that ultimately leads to weight gain. These findings could influence anticipatory guidance and feeding recommendations in the near future.

Little work has been done to account for the genetic role in physical activity as it relates to obesity. Reviews of animal studies find that “diet, hypothalamic lesions, genetics, age, and sex all affect activity as well as weight gain [31].” One study of adult monozygotic twins found that vigorous exercise can lower the genetic influences on body mass index (BMI), but that it has little influence on blood chemistry results illustrating the strength of genetic vulnerability with regard to medical comorbidities from overweight [32]. A study of adult women found that the β -2 adrenergic receptor Glu27Glu genotype corresponded to lower endurance performance when compared with women with the Gln27Gln and Gln27Glu genotypes [33]. Clearly, more research is needed in this area to ascertain the relationship between diet, physical activity, genetics, and environmental factors and obesity development and weight reduction.

There has been ongoing debate as to whether obesity and psychopathology are connected. Does psychopathology cause obesity, or does obesity cause psychopathology? Although there are no answers to the questions above, studies have found individuals with greater overweight have greater psychosocial problems [34]. Is there a genetic link? Comings and coauthors [35] pioneered one of, if not the most instrumental study that correlated chromosome 7 with obesity and depression. However, not all obese persons are depressed, especially men; yet, evidence has indicated that the BMI–depression relationship is consistent across ethnicities [36]. It appears that researchers are getting closer to uncovering the genetic associations of obesity and its related comorbidities, but sex and socioeconomic status and associated factors may mediate the differences [34,37]. Considering that exercise reduces levels of depression, what might the gene–environment/behavioral interaction be that also helps lessen body weight? Both obesity and psychopathology are linked with other health problems that make untangling this complex web of interaction extremely difficult.

One of the most exciting areas of research is the use of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) to pinpoint areas of the brain underlying lifestyle experiences commonly associated with obese individuals. Review of the existing literature identified several studies that examined dopaminergic areas tied to the anticipation, not necessarily the consumption, of food [38]. Differences in the functional architecture between the brains of lean and obese individuals have been identified. However, these investigators note poignantly that in the attempt to uncover the cause of obesity, we are often left with more questions, reaffirming that there is no simple test to recognize those at greatest risk.

Nutrition meets genetics

The underpinnings of nutrition's role in obesity become much more complicated with the tools of genetics and genomics. In particular, the fields of proteomics and metabolomics provide key insight into how the body uses nutrients. For every turn of the Krebs cycle, there are vast arrays of proteins, metabolites, enzymes, and transporters that are controlled by genes. For

every one of these genes, there is variation between individuals, all adding up to slight differences in how we use calories. And for every gene, there may be a key vitamin or mineral that influences expression of the gene, which, if not ingested in proper quantities, can lead to abnormal function. This study of food–gene interaction is called *nutritional genomics*, or *nutrigenomics*.

The goal of this research is to elucidate how diet can regulate gene function, why components of a person's diet can increase risk of one disease and lower the risk of another, and how dietary intervention can be tailored to genotype to improve health. Still in its infancy, nutritional genomics has already found applications in cancer, diabetes, and heart disease [39]. In terms of obesity treatment and prevention, this field could unlock the differences in human response to exercise, caloric deprivation, and basal metabolic rate.

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that regulate genes involved in the storage and metabolism of fats. A polymorphism in one subtype, PPAR- γ , has been linked to dietary-induced obesity. PPAR- γ affects insulin resistance and blood pressure. Individuals with the Pro12Ala polymorphism appear to be prone to obesity and hyperinsulinism depending on dietary intake of fats. A low polyunsaturated-to-saturated (P/S) fat ratio is associated with an increase in body mass index and fasting insulin levels in individuals who carry the Ala allele, with the reverse occurring with high P/S fat ratios (Ala carriers have lower BMIs and insulin levels) [40]. This relationship is further modified by physical activity [41].

In a mouse model, adiposity has been shown to be altered by maternal diet. When the agouti gene is overexpressed in mice, they develop a yellow coat and early-onset obesity, as well as increased mortality levels [42]. Investigators were able to modify the phenotypes of genetically identical mice by manipulating maternal dietary methyl supplementation, with mice having different color coats depending on the amount of supplementation [43]. Subsequent genomic studies have revealed 28 genes regulated by diet, genotype, or diet–genotype interaction that map to diabetes/obesity quantitative trait loci [44].

Nutrigenomic research is making its way quickly into clinical medicine and could yield relevant findings in the near future. Researchers studying a gene involved in adipocyte fatty acid release (perilipin) found that carriers of the minor allele on a low-calorie diet were resistant to weight loss yet had a lower body weight at baseline (before dietary intervention) [45]. The framework for studies such as this were in animal models, but more such research could soon lead to “personalized” dietary interventions based on genotype.

The neuroendocrine pathway

The discovery of leptin in 1994 was important in many ways. It showed that hunger was more than a craving centered in the brain or a signal from an empty stomach. In a story that continues to evolve, leptin and many other hormones, in conjunction with the nervous system and its signals, regulate short- and long-term control of hunger and weight. Additionally, the adipocyte, previously thought to be a passive reservoir of lipids, is a hormonal organ with multiple actions. The complex pathways delineated to date are all targets for therapy and intervention, both in treating comorbidities resulting from obesity as well as weight issues themselves. Fig. 3 represents some of the major elements of hunger and weight control.

Leptin, produced primarily by adipocytes, acts as the main signal to the brain from fat stores. Therefore, when a person becomes obese, leptin levels should increase, signaling the brain to decrease intake and increase energy expenditure. The gene for leptin was discovered in the *ob/ob* mouse, which was homozygous for a mutation in the gene, resulting in a deficiency in leptin production. As a consequence, mice gained weight at an increased rate [1]. Despite the promise of leptin as a treatment target for obesity, it has found limited clinical use. There have

only been a few cases of either leptin deficiency or leptin receptor mutations, with the former being amenable to leptin replacement therapy [46,47]. In obese patients with normal (ie, functional) leptin and leptin receptor genes, treatment with leptin has not resulted in dramatic effects [48], and it appears that obese patients have a form of “leptin resistance.” Regardless, leptin is still under investigation as a treatment modality [49].

Ghrelin is one of the many enteric hormones discovered in the wake of leptin. It was originally discovered in the rat, with the human homolog identified shortly thereafter [50]. It is expressed mainly in the fundus of the stomach and acts as an appetite stimulant, primarily in short-term appetite control. Further studies in humans have found that levels are lower in obese patients [51], who also appear to have increased sensitivity to the appetite-stimulating effects of the hormone [52]. The role of ghrelin in appetite and obesity make the development of antagonists likely as potential therapeutic agents.

Alpha-melanocyte-stimulating hormone, found in mice to increase energy expenditure and decrease energy intake, has been studied extensively as an anorexigenic agent in animals [53]. Studies in mice and humans have identified defects in the melanocortin 4 receptor (MC4R, the target of α -melanocyte-stimulating hormone), with null mutations increasing food intake and insulin levels [54]. Nearly 6% of people with long-term, severe obesity were found to have a mutation in the *MC4R* gene [55], making *MC4R* deficiency the most common monogenic form of obesity. Therapies are under development for those with this form of severe obesity [56]. In addition, neuropeptide Y, an orexigenic (appetite stimulating) peptide released from the arcuate nucleus, is another potential target for an intervention. Antagonists of neuropeptide Y could lead to sustained decreases in appetite [53].

Peptide YY (PYY) is an enteric-derived hormone that was identified in studies of rodents [57,58]. Released by enteroendocrine cells of the ileum and colon, PYY acts as an “ileal brake” and delays gastric emptying, thereby decreasing energy intake. It acts centrally as well on the arcuate nucleus to inhibit appetite. Animal studies were translated quickly to human studies, and results on feeding inhibition were promising. Much like leptin, the initial promise of therapies using PYY analogs have not materialized, but interest remains high [59].

Another peptide hormone, glucagon-like peptide-1 (GLP-1), is produced in the central nervous system and the small intestine and acts on satiety by multiple mechanisms. It slows gastric emptying, decreases gastric acid secretion, and stimulates insulin release [60,61]. Much like other appetite-suppressing peptides, it is a rational target for drug investigation. GLP-1 may have positive effects on diabetes and cardiovascular function and may have potential in the treatment of heart disease and diabetes [61].

Finally, amylin is a peptide cosecreted with insulin that has been shown to slow gastric emptying and lower food intake in animals [62,63]. The amylin analog pramlintide has been studied primarily as adjunctive therapy in diabetes, but has resulted in sustained weight loss [64].

A promising therapy using newly discovered mechanisms of appetite control is rimonabant. Whereas currently available appetite suppressants rely on stimulant properties to reduce appetite, rimonabant selectively blocks the cannabinoid-1 receptor, a G protein-coupled receptor found in the central nervous system and in various peripheral tissues. Blocking the action of this receptor prevents overactivation of the endocannabinoid system, centrally and peripherally [65]. In the first large-scale trial in North America, rimonabant produced sustained weight loss above dietary intervention alone [66]. More exciting is the independent effect the drug appeared to have on the amelioration of cardiovascular risk factors (diabetic risk, high-density lipoprotein, triglycerides, waist circumference). Given its lack of stimulant properties, rimonabant may offer the promise of long-term weight control.

Is obesity an infection?

There is mounting evidence of possible infectious contributions to the etiology of obesity. An adenovirus inoculation (and later other viruses) has been identified as a cause of increased adiposity in animals [67,68]. Mice and chickens were then inoculated with human adenovirus, which resulted in increased adipose tissue and lower cholesterol and triglycerides [69]. This was later found to be a transmissible effect in other animal studies [70]. Human studies found that a higher percentage of obese subjects had adenovirus-36 antibodies when compared with nonobese controls [71]. Paradoxically, the patients with adenovirus antibodies had lower serum cholesterol and triglycerides, as was found in human virus inoculation of chickens and mice. These relatively new findings imply that treating infections (using antivirals) at an early age could potentially prevent later onset of obesity.

Adipocytes as an endocrine organ

The further investigation of the role of adenovirus infection may not lead to a focused antiviral treatment for obesity but may find new pathways and mechanisms, similar to the discovery of leptin and subsequent research into weight control that has found the adipocyte to be an active endocrine organ. Increasing adiposity leads to increasing levels of “adipokines,” adipocyte-derived inflammatory markers that act in pro- and antiinflammatory pathways [72,73]. Additionally, macrophages found in adipose tissue likely have a role in the obese-inflammatory state and its related disease [74]. Laboratory and animal research has led to the understanding that obesity is a state of chronic inflammation. Infection may be the link among adipocytes, macrophages, and inflammation, or at least a contributor.

Translating clinical knowledge into community action

In 1998, health care providers, public health officials, schools, and communities were asked to start working together to bring attention to the epidemic of childhood obesity. This condition, not defined as a disease, was prioritized with diseases such as diabetes, asthma, and cancer [75]. Rapid increases in obesity rates [76–78], rising health care costs (estimates of \$14 billion per year is spent caring for overweight children and their comorbid conditions), [79] and media attention have accelerated interest in this epidemic.

In 2003 the National Institute of Health Obesity Research Task Force was formed and began to develop a strategic focus of research agenda. National collaborative programs such as Action for Kids, VERB, 5 a day, Ways to Enhance Children's Nutrition and Physical Activity (WE CAN), Active Living by Design, and Steps to a Healthier US were launched to help the prevention of overweight and obesity in both children and adults through community action, strategic partnership, and national outreach. These initiatives could be enhanced further by using techniques that were successful in other public health campaigns such as smoking cessation [80]. Clinical intervention, educational programs, regulatory policies, economic approaches, and comprehensive programs that incorporate these facets have synergistically influenced the reduction of smoking [81,82]. Applying the above characteristics within the context of the Ecological Model of Childhood Overweight [9] framework has the potential to reduce modifiable risk factors in genetically susceptible individuals and reverse the obesity epidemic (Table 1).

Clinical interventions

Health care providers of children have been advised by the American Academy of Pediatrics policy statement to monitor high risk patients, calculate and plot BMI yearly, encourage breastfeeding, and discuss physical activity and snacks as part of each anticipatory guidance opportunity [83]. Many health care providers report decreased self-efficacy when attempting

to counsel patients on nutrition and physical activity. Physicians are more likely to counsel regarding exercise if they are currently active themselves [84]. With education, health care providers can become more confident. As Crawford and coworkers [85] report, staff wellness training improved the perceptions of their own health beliefs and counseling self-efficacy.

One of the most modifiable risk factors for childhood obesity is reducing the amount of television screen time [86]. Proposed mechanisms for pediatric weight gain owing to television consumption include displacement of physical activity, lowering of metabolic rate during viewing, and negative effects on nutritional intake [87]. Consistent evidence supports the direct correlation between television exposure time and increased weight [88,89]. Although associated with obesity and poor school performance [90], 30% of children younger than 3 years, 43% of children aged 4 to 6 years, and 68% of those aged 8 to 18 years have televisions in their bedrooms [91,92]. Helping families understand that excessive television viewing can have a negative impact on their child's long-term health is a necessary part of every well child visit.

Family environment risk factors

Whereas the effect of guidance from health care providers can be influential on health behaviors [93], family environment is paramount. Children are exposed to both the genes and the environment of their parents. Davison and Birch [94] report that overweight parents tend to exercise less, derive less enjoyment from physical activity, and consume an increased percentage of calories from fat. Although modeling poor dietary and physical activity habits increases the risk of pediatric overweight, parental support and modeling physical activity have been shown to increase girls' physical activity [95]. Parental health behavior change predicts the initial and the maintained decrease in a child's BMI in family-based weight management programs [96]. Discussions with families regarding the weight status of their children should therefore include an assessment of the parental health practices to facilitate long-lasting healthy habits.

Community-based change

Children are currently exposed to an "obeseogenic" environment in the larger community. Children spend the majority of their time away from home at school. Changes to their environment at school can be successful, acceptable, and efficacious to decrease screen time, increase fruit and vegetable intake, and increase moderate to vigorous activity in middle school children [97,98]. Children also spend on average 2 to 5 hours per day in the media environment [99] in which they will see between 12 and 30 food commercials. Ludwig and Gortmaker [87] describe children viewing food advertisements as increasing their energy intake significantly, increasing consumption of fast food and sweetened beverages, and decreasing consumption of fruits and vegetables. Health care providers must advocate for regulatory efforts to decrease such advertising policies. Sweden and the Netherlands have passed legislation that prevents direct food advertising toward children.

Summary

Obesity is becoming a major health problem in children. The number of overweight individuals is rapidly increasing, and the impact of basic research into the genetic and physiologic basis of obesity has not been successfully translated into clinical management and prevention of this new epidemic. The factors influencing the development and progression of obesity are complex, and comprehensive, integrated efforts are required to unravel the causes of the disorder and develop novel options for prevention and treatment. Using the Ecological Systems Theory as a model, a thorough understanding of the physiologic, behavioral, and environmental components and the systems in which they are embedded and interact will lead to a holistic

approach, maximizing the impact of translational medicine in the approach to childhood obesity.

Acknowledgments

The authors would like to thank Nancy Pejisa for her assistance in preparing the figures.

References

1. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994;372(6505):425–32. [PubMed: 7984236]
2. Perusse L, Rankinen T, Zuberi A, et al. The human obesity gene map: The 2004 update. *Obes Res* 2005;13(3):381–481. [PubMed: 15833932]
3. Kirk S, Scott BJ, Daniels SR. Pediatric obesity epidemic: treatment options. *J Am Diet Assoc* 2005;105(5 Suppl 1):S44–51. [PubMed: 15867895]
4. Stewart L, Houghton J, Hughes AR, et al. Dietetic management of pediatric overweight: development and description of a practical and evidence-based behavioral approach. *J Am Diet Assoc* 2005;105(11):1810–5. [PubMed: 16256768]
5. Bautista-Castano I, Doreste J, Serra-Majem L. Effectiveness of interventions in the prevention of childhood obesity. *Eur J Epidemiol* 2004;19(7):617–22. [PubMed: 15461192]
6. Kiess W, Reich A, Muller G, et al. Obesity in childhood and adolescence: clinical diagnosis and management. *J Pediatr Endocrinol* 2001;14(Suppl 6):1431–40.
7. Yanovski JA. Intensive therapies for pediatric obesity. *Pediatr Clin North Am* 2001;48(4):1041–53. [PubMed: 11494637]
8. Yanovski SZ, Yanovski JA. Obesity. *N Engl J Med* 2002;346(8):591–602. [PubMed: 11856799]
9. Davison KK, Birch LL. Childhood overweight: a contextual model and recommendations for future research. *Obes Rev* 2001;2(3):159–71. [PubMed: 12120101]
10. Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. *Nature* 2001;409(6822):860–921. [PubMed: 11237011]
11. Riordan JR, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 1989;245(4922):1066–73. [PubMed: 2475911]
12. Cao A, Galanello R, Rosatelli MC. Prenatal diagnosis and screening of the haemoglobinopathies. *Baillieres Clin Haematol* 1998;11(1):215–38. [PubMed: 10872479]
13. Clement K. Genetics of human obesity. *Proc Nutr Soc* 2005;64(2):133–42. [PubMed: 15960858]
14. Zak NB, Shifman S, Shalom A, et al. Genetic dissection of common diseases. *Isr Med Assoc J* 2002;4(6):438–43. [PubMed: 12073418]
15. Sachidanandam R, Weissman D, Schmidt SC, et al. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature* 2001;409(6822):928–33. [PubMed: 11237013]
16. Kwok PY. Methods for genotyping single nucleotide polymorphisms. *Annu Rev Genomics Hum Genet* 2001;2:235–58. [PubMed: 11701650]
17. Hirschhorn JN. Genetic approaches to studying common diseases and complex traits. *Pediatr Res* 2005;57(5 Pt 2):74R–7R.
18. Rippe JM, Crossley S, Ringer R. Obesity as a chronic disease: modern medical and lifestyle management. *J Am Diet Assoc* 1998;98(10 Suppl 2):S9–15. [PubMed: 9787730]
19. Wilson, GT.; Brownell, KD. Behavioral Treatment for Obesity. Vol. 2nd edition. The Guilford Press; New York: 2002.
20. Epstein LH. Family-based behavioural intervention for obese children. *Int J Obes Relat Metab Disord* 1996;20(Suppl 1):S14–21. [PubMed: 8646260]
21. Epstein LH, McCurley J, Wing RR, et al. Five-year follow-up of family-based behavioral treatments for childhood obesity. *J Consult Clin Psychol* 1990;58(5):661–4. [PubMed: 2254515]
22. Epstein LH, Roemmich JN, Raynor HA. Behavioral therapy in the treatment of pediatric obesity. *Pediatr Clin North Am* 2001;48(4):981–93. [PubMed: 11494647]

23. Epstein LH, Valoski A, Wing RR, et al. Ten-year outcomes of behavioral family-based treatment for childhood obesity. *Health Psychol* 1994;13(5):373–83. [PubMed: 7805631]
24. Faith MS, Johnson SL, Allison DB. Putting the behavior into the behavior genetics of obesity. *Behav Genet* 1997;27(4):423–39. [PubMed: 9519566]
25. Faith MS, Keller KL, Johnson SL, et al. Familial aggregation of energy intake in children. *Am J Clin Nutr* 2004;79(5):844–50. [PubMed: 15113724]
26. Faith MS. Development and modification of child food preferences and eating patterns: behavior genetics strategies. *Int J Obes* 2005;29(6):549–56.
27. Zhang S, Gershenfeld HK. Genetic contributions to body weight in mice: relationship of exploratory behavior to weight. *Obes Res* 2003;11(7):828–38. [PubMed: 12855751]
28. Potoczna N, Branson R, Kral JG, et al. Gene variants and binge eating as predictors of comorbidity and outcome of treatment in severe obesity. *J Gastrointest Surg* 2004;8(8):971–81. [PubMed: 15585384]
29. Birch LL, Fisher JO. Development of eating behaviors among children and adolescents. *Pediatrics* 1998;101(3 Pt 2):539–49. [PubMed: 12224660]
30. Faith MS, Berkowitz RI, Stallings VA, et al. Parental feeding attitudes and styles and child body mass index: prospective analysis of a gene-environment interaction. *Pediatrics* 2004;114(4):e429–36. [PubMed: 15466068]
31. Tou JC, Wade CE. Determinants affecting physical activity levels in animal models. *Exp Biol Med* 2002;227(8):587–600.
32. Williams PT, Blanche PJ, Krauss RM. Behavioral versus genetic correlates of lipoproteins and adiposity in identical twins discordant for exercise. *Circulation* 2005;112(3):350–6. [PubMed: 16009789]
33. Moore GE, Shuldiner AR, Zmuda JM, et al. Obesity gene variant and elite endurance performance. *Metabolism* 2001;50(12):1391–2. [PubMed: 11735081]
34. Stunkard AJ, Faith MS, Allison KC. Depression and obesity. *Biol Psychiatry* 2003;54(3):330–7. [PubMed: 12893108]
35. Comings DE, Gade R, MacMurray JP, et al. Genetic variants of the human obesity (OB) gene: association with body mass index in young women, psychiatric symptoms, and interaction with the dopamine D2 receptor (DRD2) gene. *Mol Psychiatry* 1996;1(4):325–35. [PubMed: 9118359]
36. Faith MS, Matz PE, Jorge MA. Obesity-depression associations in the population. *J Psychosom Res* 2002;53(4):935–42. [PubMed: 12377306]
37. Butler MG, Hedges L, Hovis CL, et al. Genetic variants of the human obesity (OB) gene in subjects with and without Prader-Willi syndrome: comparison with body mass index and weight. *Clin Genet* 1998;54(5):385–93. [PubMed: 9842990]
38. Tataranni PA, DelParigi A. Functional neuroimaging: a new generation of human brain studies in obesity research. *Obes Rev* 2003;4(4):229–38. [PubMed: 14649373]
39. Kaput J, Rodriguez RL. Nutritional genomics: the next frontier in the postgenomic era. *Physiol Genomics* 2004;16(2):166–77. [PubMed: 14726599]
40. Luan J, Browne PO, Harding AH, et al. Evidence for gene-nutrient interaction at the PPARgamma locus. *Diabetes* 2001;50(3):686–9. [PubMed: 11246892]
41. Franks PW, Luan J, Browne PO, et al. Does peroxisome proliferator-activated receptor gamma genotype (Pro12ala) modify the association of physical activity and dietary fat with fasting insulin level? *Metabolism* 2004;53(1):11–6. [PubMed: 14681835]
42. Wolff GL, Roberts DW, Mountjoy KG. Physiological consequences of ectopic agouti gene expression: the yellow obese mouse syndrome. *Physiol Genomics* 1999;1(3):151–63. [PubMed: 11015573]
43. Cooney CA, Dave AA, Wolff GL. Maternal methyl supplements in mice affect epigenetic variation and DNA methylation of offspring. *J Nutr* 2002;132(8 Suppl):2393S–400S. [PubMed: 12163699]
44. Kaput J, Klein KG, Reyes EJ, et al. Identification of genes contributing to the obese yellow Avy phenotype: caloric restriction, genotype, diet × genotype interactions. *Physiol Genomics* 2004;18(3):316–24. [PubMed: 15306695]

45. Corella D, Qi L, Sorli JV, et al. Obese subjects carrying the 11482G > A polymorphism at the perilipin locus are resistant to weight loss after dietary energy restriction. *J Clin Endocrinol Metab* 2005;90(9):5121–6. [PubMed: 15985482]
46. Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* 1997;387(6636):903–8. [PubMed: 9202122]
47. Farooqi IS, Matarese G, Lord GM, et al. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest* 2002;110(8):1093–103. [PubMed: 12393845]
48. Bell-Anderson KS, Bryson JM. Leptin as a potential treatment for obesity: progress to date. *Treat Endocrinol* 2004;3(1):11–8. [PubMed: 15743109]
49. Lo KM, Zhang J, Sun Y, et al. Engineering a pharmacologically superior form of leptin for the treatment of obesity. *Protein Eng Des Sel* 2005;18(1):1–10. [PubMed: 15790575]
50. Kojima M, Hosoda H, Date Y, et al. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* 1999;402(6762):656–60. [PubMed: 10604470]
51. Tschöp M, Weyer C, Tataranni PA, et al. Circulating ghrelin levels are decreased in human obesity. *Diabetes* 2001;50(4):707–9. [PubMed: 11289032]
52. Druce MR, Wren AM, Park AJ, et al. Ghrelin increases food intake in obese as well as lean subjects. *Int J Obes* 2005;29(9):1130–6.
53. Ramos EJ, Meguid MM, Campos AC, et al. Neuropeptide Y, alpha-melanocyte-stimulating hormone, and monoamines in food intake regulation. *Nutrition* 2005;21(2):269–79. [PubMed: 15723758]
54. Vaisse C, Clement K, Guy-Grand B, et al. A frameshift mutation in human MC4R is associated with a dominant form of obesity. *Nat Genet* 1998;20(2):113–4. [PubMed: 9771699]
55. Farooqi IS, Keogh JM, Yeo GS, et al. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *N Engl J Med* 2003;348(12):1085–95. [PubMed: 12646665]
56. Boyce RS, Duhl DM. Melanocortin-4 receptor agonists for the treatment of obesity. *Curr Opin Investig Drugs* 2004;5(10):1063–71.
57. Batterham RL, Cohen MA, Ellis SM, et al. Inhibition of food intake in obese subjects by peptide YY3–36. *N Engl J Med* 2003;349(10):941–8. [PubMed: 12954742]
58. Batterham RL, Cowley MA, Small CJ, et al. Gut hormone PYY(3–36) physiologically inhibits food intake. *Nature* 2002;418(6898):650–4. [PubMed: 12167864]
59. Boggiano MM, Chandler PC, Oswald KD, et al. PYY3–36 as an anti-obesity drug target. *Obes Rev* 2005;6(4):307–22. [PubMed: 16246216]
60. Dhillon WS, Bloom SR. Gastrointestinal hormones and regulation of food intake. *Horm Metab Res* 2004;36(11–12):846–51. [PubMed: 15655718]
61. Edwards CM. The GLP-1 system as a therapeutic target. *Ann Med* 2005;37(5):314–22. [PubMed: 16179267]
62. Reidelberger RD, Kelsey L, Heimann D. Effects of amylin-related peptides on food intake, meal patterns, and gastric emptying in rats. *Am J Physiol Regul Integr Comp Physiol* 2002;282(5):R1395–404. [PubMed: 11959682]
63. Reidelberger RD, Haver AC, Arnelo U, et al. Amylin receptor blockade stimulates food intake in rats. *Am J Physiol Regul Integr Comp Physiol* 2004;287(3):R568–74. [PubMed: 15130879]
64. Schmitz O, Brock B, Rungby J. Amylin agonists: a novel approach in the treatment of diabetes. *Diabetes* 2004;53(Suppl 3):S233–8. [PubMed: 15561917]
65. Cota D, Marsicano G, Tschöp M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest* 2003;112(3):423–31. [PubMed: 12897210]
66. Pi-Sunyer FX, Aronne LJ, Heshmati HM, et al. Group RI-NAS. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 2006;295(7):761–75. [PubMed: 16478899]
67. Dhurandhar NV, Kulkarni P, Ajinkya SM, et al. Effect of adenovirus infection on adiposity in chicken. *Vet Microbiol* 1992;31(2–3):101–7. [PubMed: 1320784]
68. Dhurandhar NV, Whigham LD, Abbott DH, et al. Human adenovirus Ad-36 promotes weight gain in male rhesus and marmoset monkeys. *J Nutr* 2002;132(10):3155–60. [PubMed: 12368411]

69. Dhurandhar NV, Israel BA, Kolesar JM, et al. Increased adiposity in animals due to a human virus [see comment]. *Internat J Obes Relat Metab Disord* 2000;24(8):989–96.
70. Dhurandhar NV, Israel BA, Kolesar JM, et al. Transmissibility of adenovirus-induced adiposity in a chicken model. *Int J Obes Relat Metab Disord* 2001;25(7):990–6. [PubMed: 11443497]
71. Atkinson RL, Dhurandhar NV, Allison DB, et al. Human adenovirus-36 is associated with increased body weight and paradoxical reduction of serum lipids. *Int J Obes* 2005;29(3):281–6.
72. Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 2005;115(5):911–9. [PubMed: 15867843]quiz 920
73. Hutley L, Prins JB. Fat as an endocrine organ: relationship to the metabolic syndrome. *Am J Med Sci* 2005;330(6):280–9. [PubMed: 16355012]
74. Bouloumie A, Curat CA, Sengenès C, et al. Role of macrophage tissue infiltration in metabolic diseases. *Curr Opin Clin Nutr Metab Care* 2005;8(4):347–54. [PubMed: 15930956]
75. Hill JO, Trowbridge FL. Childhood obesity: future directions and research priorities. *Pediatrics* 1998;101(3 Pt 2):570–4. [PubMed: 12224663]
76. Hedley AA, Ogden CL, Johnson CL, et al. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA* 2004;291(23):2847–50. [PubMed: 15199035]
77. Popkin BM, Udry JR. Adolescent obesity increases significantly in second and third generation US immigrants: the National Longitudinal Study of Adolescent Health. *J Nutr* 1998;128(4):701–6. [PubMed: 9521631]
78. Freedman DS, Srinivasan SR, Valdez RA, et al. Secular increases in relative weight and adiposity among children over two decades: the Bogalusa Heart Study. *Pediatrics* 1997;99(3):420–6. [PubMed: 9041299]
79. Marder, W. Thomson Medstat Research Brief. Thompson Medstat; Ann Arbor (MI): 2006. Childhood Obesity: costs, treatment patterns, disparities in care, and prevalent medical conditions..
80. Mercer SL, Green LW, Rosenthal AC, et al. Possible lessons from the tobacco experience for obesity control. *Am J Clin Nutr* 2003;77(4 Suppl):1073S–82S. [PubMed: 12663321]
81. Reducing Tobacco use: a report of the Surgeon General. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease and Health Promotion, Office of Smoking and Health.; 2000. p. 2-16.
82. Population-based smoking cessation: proceedings of a conference on what works to influence cessation in the general population.; Department of Health and Human Services, National Institutes of Health, National Cancer Institute. 2000. Monograph Number 12
83. Krebs NF, Jacobson MS. American Academy of Pediatrics Committee on Nutrition. Prevention of pediatric overweight and obesity. *Pediatrics* 2003;112(2):424–30. [PubMed: 12897303]
84. Abramson S, Stein J, Schaefele M, et al. Personal exercise habits and counseling practices of primary care physicians: a national survey. *Clin J Sport Med* 2000;10(1):40–8. [PubMed: 10695849]
85. Crawford PB, Gosliner W, Strode P, et al. Walking the talk: Fit WIC wellness programs improve self-efficacy in pediatric obesity prevention counseling. *Am J Public Health* 2004;94(9):1480–5. [PubMed: 15333298]
86. Robinson TN. Reducing children's television viewing to prevent obesity: a randomized controlled trial. *JAMA* 1999;282(16):1561–7. [PubMed: 10546696]
87. Ludwig DS, Gortmaker SL. Programming obesity in childhood. *Lancet* 2004;364(9430):226–7. [PubMed: 15262082]
88. Berkey CS, Rockett HR, Field AE, et al. Activity, dietary intake, and weight changes in a longitudinal study of preadolescent and adolescent boys and girls. *Pediatrics* 2000;105(4):E56. [PubMed: 10742377]
89. Gordon-Larsen P, Adair LS, Popkin BM. Ethnic differences in physical activity and inactivity patterns and overweight status. *Obes Res* 2002;10(3):141–9. [PubMed: 11886936]
90. Borzekowski DL, Robinson TN. The remote, the mouse, and the no. 2 pencil: the household media environment and academic achievement among third grade students. *Arch Pediatr Adolesc Med* 2005;159(7):607–13. [PubMed: 15996991]
91. Center on Media and Child Health. Henry J. Kaiser Family Foundation. The effects of electronic media on children ages zero to six: a history of research. 2005. p. 1-16.Issue brief #7239

92. Roberts, DF.; Foehr, UG.; Rideout, V.; Henry J. Kaiser Family Foundation. Generation M: Media in the lives of 8–18 Year-olds. 2005. p. 1-145. Issue brief #7251
93. Galuska DA, Will JC, Serdula MK, et al. Are health care professionals advising obese patients to lose weight? JAMA 1999;282(16):1576–8. [PubMed: 10546698]
94. Davison KK, Birch LL. Child and parent characteristics as predictors of change in girls' body mass index. Int J Obesity Relat Metab Disord 2001;25(12):1834–42.
95. Davison KK, Cutting TM, Birch LL. Parents' activity-related parenting practices predict girls' physical activity. Med Sci Sports Exerc 2003;35(9):1589–95. [PubMed: 12972881]
96. Wrotniak BH, Epstein LH, Paluch RA, et al. Parent weight change as a predictor of child weight change in family-based behavioral obesity treatment. Arch Pediatr Adolesc Med 2004;158(4):342–7. [PubMed: 15066873]
97. Gortmaker SL, Peterson K, Wiecha J, et al. Reducing obesity via a school-based interdisciplinary intervention among youth: Planet Health. Arch Pediatr Adolesc Med 1999;153(4):409–18. [PubMed: 10201726]
98. Wiecha JL, El Ayadi AM, Fuemmeler BF, et al. Diffusion of an integrated health education program in an urban school system: planet health. J Pediatr Psychol 2004;29(6):467–74. [PubMed: 15277589]
99. Coon KA, Tucker KL. Television and children's consumption patterns. A review of the literature. Minerva Pediatr 2002;54(5):423–36. [PubMed: 12244280]
100. Brisbon N, Plumb J, Brawer R, et al. The asthma and obesity epidemics: the role played by the built environment—a public health perspective. J Allergy Clin Immunol 2005;115(5):1024–8. [PubMed: 15867861]
101. Sloane DC, Diamant AL, Lewis LB, et al. Improving the nutritional resource environment for healthy living through community-based participatory research. J Gen Intern Med 2003;18(7):568–75. [PubMed: 12848840]

Fig. 1.
Biopsychosocial model of obesity.

Fig. 2.
Ecological model of childhood overweight.

Fig. 3. Neuroendocrine control of appetite. Solid arrows represent stimulation, and dotted lines represent inhibition. AgRP, agouti-related peptide; CART, cocaine-amphetamine-regulated transcript; CCK, cholecystokinin; CRH, corticotrophin-releasing hormone; MCH, melanocortin hormone; α -MSH, alpha-melanocyte-stimulating hormone; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; TRH, thyrotropin-releasing hormone.

Table 1

Modifiable risk factors of the ecological model of childhood obesity

	Clinical interventions	Educational programs	Regulatory efforts	Economic factors
Child	Poor nutrition Sedentary activity Activity level	School curriculum Day care curriculum After school programs	School Wellness policy Limited physical education Competitive food Sales Vending machine Food as reward	Pricing of nutrient-poor foods
Family	Parent: • Style • Weight • Health • Media use • Nutrition knowledge Family: • Activity • Eating behaviors • Sedentary behavior Health care providers:	Worksite wellness programs	Work site policy: • Smoking cessation • Support • Breastfeeding • Food environment	Tax breaks for physical activity participation Working bonus for reducing excess weight
Community	Health care providers: • Relay consistent message • Improve self efficacy	Media campaign Health Fairs Public health messages	Built environment: • Urban sprawl • Walkability • Safety • Transportation • Recreational opportunities [100] Food environment • Access to nutrient-dense foods • Reduce marketing for unhealthful foods [101]	Tax on nutrient-poor foods Support for Farmers Markets