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Multi-etiological Perspective on Child Obesity Prevention

Tom Baranowski[1] · Kathleen J. Motil[1] · Jennette P. Moreno[1]

Abstract

Purpose of Review The simple energy balance model of obesity is inconsistent with the available findings on obesity etiology, prevention, and treatment. Yet, the most commonly stated causes of pediatric obesity are predicated on this model. A more comprehensive biological model is needed upon which to base behavioral interventions aimed at obesity prevention. In this light, alternative etiologies are little investigated and thereby poorly understood.

Recent Findings Three candidate alternate etiologies are briefly presented: infectobesity, the gut microbiome, and circadian rhythms.

Summary Behavioral child obesity preventive investigators need to collaborate with biological colleagues to more intensively analyze the behavioral aspects of these etiologies and to generate innovative procedures for preventing a multi-etiological problem, e.g., group risk analysis, triaging for likely causes of obesity.

Keywords Adenovirus-36 · Microbiome · Circadian rhythm · Children · Obesity · Prevention

Introduction

Obesity is currently the most common nutrition-related disease in the USA and a growing problem worldwide [1]. Given the high prevalence of obesity among adults (36%) [2], the general inability of obese individuals to achieve sustained weight loss [3], and the fact that obesity often starts in childhood [4], obesity prevention needs to target children. Overweight and obesity prevalence has steadily increased across childhood (2–19 years) in the USA [5], although recently the prevalence has been erratic among 2–5-year-olds and appears to have stabilized among 6–11-year-olds, while continuing to steadily increase among 12–19-year-olds [5]. Unfortunately, most of the existing child obesity prevention programs have had very small effects, with high heterogeneity; across studies, somewhat small effects have been observed among the 0–5-year-olds, but no effect among 13–18-year-olds [6]. Many of the shortcomings of the child obesity prevention trials have been delineated, including limits on our understanding of behavioral and environmental influences [7•]. Consistent with this, the dose of behavioral intervention was not related to outcome across the 133 studies included [8]. No or small effects have also been detected across multiple child obesity treatment trials [9]. Diet [10] and physical activity [11] behaviors, core behaviors which contribute to childhood weight status, have also proven remarkably intractable.

The resistance of populations to current obesity interventions has encouraged professionals to design ever more comprehensive and complex behavioral and environmental interventions, the latest employing systems modeling [12, 13]. While the jury remains to be convened on these latest efforts, the primary shortcoming may be understanding the underlying biological mechanism(s) causing obesity. Delineating the biological etiology of obesity should lead to more effective child obesity prevention. This paper admonishes those designing, implementing, evaluating, and/or otherwise researching behavioral and environmental-based child obesity prevention efforts to consider little studied etiologies, engage in research exploring those etiologies, and investigate the changes in practice they may imply.

Simple Energy Balance or Multi-etiological?

The biological model currently underpinning childhood obesity prevention interventions has been a simple energy balance

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✉ Tom Baranowski
tbaranow@bcm.edu

[1] USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, 1100 Bates Street, Houston, TX 77030, USA

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model. Ludwig and Ebbeling [14••] clearly specified this model indicating the difference in energy intake and expenditure influenced circulating fuels which led to fat storage (or fat depletion). Within this conceptualization, excessive caloric intake is a result of "ubiquitous tasty foods," overwhelming eating self-regulation, and the attractions of physical inactivity minimizing energy expenditure. Consistent with this model, virtually all childhood obesity prevention programs have attempted to influence children simply to consume fewer calories and increase activity to expend more calories, in the expectation that that difference will directly linearly affect adiposity. As indicated above, interventions based on this model have generally had little or no effect [6].

Ludwig and Ebbeling [14••] immediately dismissed their first model for reasons beyond just poor self-control. They recognized physiological adaptations, e.g., hormonal responses, in response to weight loss which work to return the body to a higher weight. In their second, preferred, model, the direction of influence reverses: dietary carbohydrates increase insulin secretion which directly leads to increased fat storage, which decreases circulating fuels, which leads to hunger and further increased energy intake and decreased energy expenditure [14••]. If this were the accepted model, child obesity prevention would focus on reducing carbohydrate intake and/or otherwise mitigating the influence of insulin.

In a companion article, however, Hall, Guyenet, and Leibel [15••] dismissed the insulin-based model as not being consistent with the literature on the biology of obesity. For example, the insulin model ignores both "neuroendocrine mechanisms that regulate energy homeostasis, genetic and epigenetic and other influences on obesity." They reported a lack of evidence that low-carbohydrate diets resulted in more weight loss than other diets [15••]. Hall and colleagues concluded "We believe that obesity is an etiologically more heterogeneous disorder that includes combinations of genetic, metabolic, hormonal, psychological, behavioral, environmental, economic, and societal factors" [15••]. From this perspective, there is not one, or even a primary, but many causes of obesity.

While individual or family-focused energy balance-related changes in diet and physical activity are the current tools of first choice for obesity treatment [16], obesity prevention requires identifying the major influencing factors and changing them. While some human adiposity may involve the simple difference between energy in and energy out, many factors (other than self-control or self-regulation) influence energy in and out and metabolic processes occurring within the individual. For example, multiple complex hormones (e.g., insulin, ghrelin, leptin) are generated by different organs in response to different aspects of food intake, and interact with other circulating hormones, which are interpreted in the brain, and in turn influence food intake [17]. Adipose tissue is one source of these circulating hormones, e.g., leptin, and some environmental pollutants disrupt energy balance which may minimize the ability to prevent obesity [18]. Inadequate self-control in the face of attractive environmental options may account for some, but not all, and perhaps not even most, cases of obesity. Many possible etiologic models of obesity have been identified [19, 20]. Others have identified a likely multi-etiological situation for obesity [21]. A few alternatives to the simple energy balance model are briefly considered.

Genes

The heritability of BMI in childhood varies, with heritability estimates ranging from a moderate ~ 42% (at 4 years of age in both genders) up to ~ 85% (at 10 years of age in boys and 16 years of age in girls) [22]. Genetic variants likely influence obesity risk by affecting both behavioral and metabolic processes, but identifying the specific genetic variants has proven challenging. Ninety-seven BMI-associated genetic variants from the largest meta-analysis of genome-wide association studies (GWAS) combined explained less than 3% of the variation in BMI [23]. Seventy-five percent of the newly identified BMI-raising alleles in this study were expressed in the brain, with expression enrichment in the hypothalamus and pituitary gland, sites of appetite control, further supporting that these help regulate eating or physical activity behaviors [24]. However, the influence of these 97 gene variants on BMI and waist circumference was only partially mediated by disinhibition and susceptibility to hunger [25]. Although expression enrichment was seen in centers related to appetite control, stronger enrichment was seen for genes expressed in the hippocampus and limbic system—tissues that play key roles in learning and memory. Several appetitive behaviors, e.g., eating in the absence of hunger and the reinforcing value of food (how hard one is willing to work for food), are heritable [26]. However, with the exception of rs9939609 in the Fat Mass and Associated (*FTO*) gene, which is consistently associated with child appetitive traits and has been associated with increased energy intake from fat [27–33], studies have yet to identify variants that robustly associate with appetitive behaviors [26, 34]. Since influences on obesity and the associated energy balance behaviors are genetically multifactorial [35], and our current understanding of genetic etiology is very complex [36, 37], genetics probably do not provide a clear foundation for obesity prevention in the near future.

Other biological models provide mechanisms which could lead to child obesity prevention interventions in the near term. While each may not have been definitively identified as a cause of some cases of obesity, each has shown extensive promising results and thereby provides a possible model deserving further research to clearly delineate the implications and test child obesity prevention procedures.

Infectobesity

One of the most unexpected likely causes of obesity is infection from select viruses, generally called infectobesity [38••]. While having obesity appears to make individuals more susceptible to infection [39], specific viruses have been identified that likely cause some cases of obesity [38••]. Meta-analysis of 16 studies revealed statistically significant odds ratio of 2.0 for obesity and a standardized mean difference of 0.28 for BMI when people with a demonstrated infection from adenovirus-36 were compared with those who did not [40]. Among several diverse effects, infection by the virus appears to increase obesity by signaling stem cells to become adipocytes, thereby increasing adipose cell number [38••]. In addition, adenovirus-36 alters fat and carbohydrate metabolism by decreasing fatty acid oxidation, increasing fat synthesis, and increasing cellular uptake of glucose and its conversion to fatty acids, the net result being increased adipose cell size [41, 42]. Finally, adenovirus-36 reduces leptin expression and secretion which may, in turn, have an obesogenic effect through increased food intake or decreased energy expenditure via altered fat metabolism [41]. Other viral infections have also been implicated in obesity [38••, 43], and the effects of viral agents may be stronger among children than adults [44]. If and when viral infections are demonstrated to cause sufficiently severe adiposity in substantially large numbers of people, obesity prevention programs would likely focus on enhancing avoidance (e.g., handwashing, sneezing into the back side of the elbow) [45] at times of outbreaks and promoting resistance to infection (e.g., moderate exercise [46]). When (or if) a vaccine appears, programs to encourage adenovirus vaccination would be important. Behavioral child obesity prevention experts could usefully collaborate with "infectobesity" experts, to better understand how exposure to the virus could be prevented, and whether this leads to lower incidence of child obesity.

Microbiome

The human body is host to a very large number and variety of microorganisms called the microbiome. Bacteria represent the major constituents of the microbiome with large numbers of organisms found in the colon and smaller numbers residing in the small intestine [47, 48]. Current research suggests that phylum-specific changes in the enteric microbiome might be significant indicators for childhood obesity.

In this regard, children with more Firmicutes, i.e., microorganisms that efficiently convert eaten polysaccharides (i.e., complex carbohydrates and dietary fiber) into digestible energy, were more likely to be obese, while those with more Bacteroidetes bacteria, which are less efficient at this conversion, were more likely to be lean [49]. Participants with more bacteria in their gut that efficiently converted carbohydrates to short-chain fatty acids lost less than 5% of their body weight in a weight loss trial [50]. Children receiving multiple antibiotics before age 24 months (which disrupts healthy microbial growth) were more likely to be obese later in life [51••]. Children receiving more types of antibiotics and acid suppression medications during the first 2 years of life were more likely to have increased obesity risk in childhood [52]. A strong case implicating the microbiome in the etiology of obesity has been made from rodent studies showing that permutations of transporting sections of the microbiome from obese animals to germ-free animals induced obesity, while transporting sections of the microbiome from lean animals did not [53••]. Within an ecological perspective, the use of household disinfectants early in life influenced BMI z-score at age 3, which was mediated by changes in the profile of gut microbiota [54]. The pattern of types of gut microbiota at 2 years of age explained over 50% of the variation in obesity at 12 years of age in Norway [55].

The biological pathways from the microbiome to obesity are not clearly known [56], but likely include increased energy harvesting from absorption of metabolites of the gut microbe action on food eaten, and numerous nervous and endocrine system mechanisms influencing appetite, food intake, and energy balance [56, 57]. Manipulations of gut microbiota influence emotional responses and lead to neurochemical brain changes, altered taste receptors, and hyperphagia in animal models [58]. All these and related influences (e.g., inflammation, gut permeability, genes, immune system, diet) are complexly interrelated, but the microbiome appears to play a central role [58]. A healthy microbiome would appear to include greater diversity in the component bacteria, greater abundance of *Bifidobacteri*a and *Lactobacillus*, and more short-chain fatty acid production [57]. Although microbiome research faces many threats to internal and external validity [59•], obesity prevention researchers will be expert in facing many of these challenges with human populations and thereby can assist biological colleagues in understanding and manipulating these obesity-influencing factors.

To definitively relate the microbiome to cases of obesity, behavioral obesity prevention investigators will likely encourage dietary changes related to a healthier microbiome. Extensive literature demonstrates many diverse and complex dietary influences (type, amount, and timing) on the microbiome and moderating microbiome effects on health outcomes [60]. At the beginning of life, breastfeeding appeared to be protective of being overweight by encouraging healthier microbiome bacteria; formula feeding was associated with increased risk of overweight and encouragement of less healthy bacteria; and the introduction of complementary foods without formula produced a pattern similar to those exclusively breastfed for 3 months [61]. Meta-analyses revealed that RCTs with higher (vs. lower) fiber diets had detectable desirable effects on the abundance of *Bifidobacteria*

and *Lactobacilli* [62]; and that supplementation with probiotics resulted in weighted mean differences of − 0.60 in body weight, − 0.27 in BMI, and − 0.60 in body fat percentage after only 3–12 weeks of exposure [63]. At least one fruit prevented weight gain by changing the proportions of microbiota in the guts of mice and increasing energy expenditure [64]. Some baseline types of microbiota impaired the effectiveness of a calorie-restricted (i.e., weight loss) diet in mice [65], and may do so among humans, but this requires more intensive investigation. Exercise has also been demonstrated to influence the microbiome [66], which also deserves more human research. An obvious behavioral dimension was disclosed when most parents minimized concern for an increased risk of obesity from taking an antibiotic when their child was faced with a symptomatic infectious illness [67].

Circadian Rhythms

In contrast to common belief, some elementary schoolchildren gained weight in the summer and others lost it during the school year, despite little evidence that diet or physical activity patterns seasonally vary in the same directions [68]. A subset of elementary schoolchildren started to gain weight in the summer after kindergarten, and went on to become obese, while another subset did so starting in the summer after second grade [69•]. Circadian rhythms [70••, 71, 72••, 73, 74], sleep duration, and quality [75–83] also vary by season.

Circadian rhythms have a cycle of about 24 h which are synchronized with environmental cues (e.g., light/dark) allowing humans to adapt to changes (e.g., travel between time zones and seasonal changes) [70••]. The suprachiasmatic nucleus (SCN) located in the brain is the primary synchronizer of the body's biological rhythms. The SCN receives light input via photoreceptors in the eyes that provide information about the time of day [84••]. The SCN sends signals to the clocks in other tissues throughout the brain and body (i.e., peripheral clocks), helping to synchronize the body's biological rhythms to ensure processes (e.g., metabolism (i.e., the chemical processes which maintain life), adipogenesis (i.e., the process of cell differentiation by which pre-fat cells become fat cells), and lipolysis (i.e., the breakdown of fats to release fatty acids)) and behaviors (e.g., sleeping, wake, and eating) occur at biologically advantageous times. While food-related circadian rhythms are controlled by the peripheral clocks and partially entrained (i.e., regulated) by food intake [85•, 86–89], the central body clock coordinates optimal timing of food intake with other bodily functions [90••].

Melatonin, released by the pineal gland, signals the sleep-related part of the daily cycle in humans and the wake phase in nocturnal mammals [90••]. The release of melatonin is signaled by the SCN in a circadian manner and is highly responsive to light exposure [91, 92]. Melatonin receptors, found in the central nervous and cardiovascular systems, liver, skin, pancreas, skeletal muscle, and adipocyte cells [90, 93], are one way the SCN synchronizes the body's rhythms.

In regard to seasonal weight gain, melatonin synchronizes metabolic function of the adipocytes (i.e., fat cells) for high lipogenesis (i.e., the formation of fat) during the melatonin phase and high lipolysis during the absence of melatonin [94]. This synchronization also occurs through sympathetic activation of white adipose tissue [95]. Among hamsters, short winter-like days led to longer nocturnal melatonin release, with greater stimulation of melatonin receptors in the forebrain, which is part of the sympathetic innervation of white adipose tissue. This increase in the sympathetic activation of white adipose tissue resulted in lipolysis and a decrease in seasonal adiposity [95]. Melatonin-induced browning of white adipose tissue in rodents [96] increased their thermogenic activity [97], which may explain seasonal weight changes in response to seasonal changes in day length [98••]. While high levels of leptin and low levels of adiponectin have been related to obesity, shortened release of melatonin, resulting from shortened sleep duration and exposure to artificial light at night, counteracts these obesogenic aspects of leptin and adiponectin, and influences body weight [90••]. Children's melatonin rhythms during summer may also be shortened due to the absence of school year demands, i.e., bedtimes are later [99, 100], and parents are likely to be more lenient on limits in screen media use, contributing to increased exposure to artificial light at night. In humans, melatonin supplementation moderated long-term weight gain and augmented weight loss for individuals on a low-calorie diet [101•].

Summer shifts in sleep, eating patterns, and screen media use may result in circadian misalignment which has been associated with increased adiposity, mediated by the mistiming of behavioral rhythms with endogenous rhythms [71, 84••, 102]. Misalignment of behavioral rhythms with endogenous rhythms has been associated with changes in metabolism and development of obesity [71, 72••, 73]. Proper timing within the adipocyte is important for adipogenesis and lipolysis [103]. Because food intake is the primary source of energy for adipose tissue, changes in the timing of food relative to adipose tissue phase may lead to changes in the extent of adipogenesis resulting from food intake, and so either weight gain or weight loss [72••]. Eating later in the day results in acute exposure to higher postprandial blood glucose levels, compared with eating earlier on, with higher blood glucose levels persisting through the following morning [104, 105]. Long-term dysregulation of glucose levels may lead to alterations in caloric intake and storage which have also been attributed to shortened sleep duration [106], suggesting that the mistiming of eating and sleep/wake patterns with endogenous rhythms may increase risk for obesity [107].

The gut microbiome also exhibits circadian rhythmicity controlled by food intake patterns [108•]. The microbiome shifts rapidly based on the typical feeding/fasting pattern, as

well as the type of food eaten [109–112]. Altered feeding patterns disrupt the rhythmicity of the gut microbiome [108•]. For example, mice transplanted with the gut microbiome of jetlagged humans did not increase their food intake, but demonstrated increased weight gain and lower glucose tolerance [108•]. Thus, changes in the timing of food intake may lead to weight gain through alterations in the circadian timing of the gut microbiome. However, disruption of the microbiome itself may alter host metabolic function by modulating circadian clock gene expression through variations in microbe-derived metabolites from dietary manipulation [110, 113]. Thus, perturbations in the gut microbiome may adversely affect circadian clock networks that lead to metabolic disturbances including diet-induced obesity. Future research should also examine how disturbed rhythmicity of the microbiome affects eating patterns.

Circadian misalignment through changes in the timing of light exposure and sleep/wake and feeding patterns is likely influential in unhealthy weight gain. Behavioral obesity prevention interventions may focus on promoting consistent sleep timing on both scheduled (e.g., school) and free days, optimal duration of sleep, limiting exposure to artificial light in the evenings [114], encouraging light exposure in the morning [115], encouraging physical activity (to enhance evening fatigue) [116–119], limiting caffeine intake in the afternoon and evening [120], promoting an overnight fast by limiting food intake in the evening [121], and maintaining consistent meal patterns even on non-school days [121].

Steps Forward

A multi-etiological approach to child obesity complicates prevention. No single biological model likely accounts for all cases, and thus, no single intervention appears likely to prevent all cases. Thus, obesity prevention interventions that manipulate energy balance as the single etiological pathway for all children appear misguided. Instead, the most common and/or the strongest influences on childhood obesity must be identified; next-generation interventions developed and tested that mitigate those influences; and triage mechanisms developed to attribute cases to likely causes, or to identify those at highest risk for the different causes, for which to provide the most likely to be effective preventive intervention. Large-data statisticians may analyze large clinical care data sets of children to identify subsets of children who transition from lean to the obese status to identify patterns and correlates of patterns for more intensive analysis.

While some interventions (e.g., moderate physical activity) may be preventive across a number of etiologies, most next-generation interventions will likely be cause specific. This shifts the efforts of prevention and behavioral scientists from delineating the causal behavioral and environmental energy balance pathways, including excessive dietary intake and inadequate energy expenditure, to working with biological colleagues to better understand which are the most common or strongest influences and help design and test next-generation interventions appropriate to these influences. For example, microbiome-related obesity prevention research could test the effects of different types of diet (e.g., probiotics) and physical activity on the development of obesity mediated by their influence on the microbiome, while identifying child characteristics that appear to predispose to or mitigate effectiveness [122•]. While linking etiological sources and obesity treatments would appear to be reasonably straightforward, child obesity prevention will likely require generating risk profiles for groups (e.g., children in categories of day care centers) and applying multiple preventive procedures for the highest probability causes.

With all of these (and more) possible etiologies, it is likely that any one individual is subject to more than one at any time, i.e., etiologies working in parallel. It appears likely that some may work in combination, i.e., an interaction effect, wherein each etiology has an enhanced effect in the presence of select other etiologies. A hypothetical example would be infectobesity having the biggest impact in the presence of a high-fat diet. Significant interactions have been reported among influences on obesity, including the home food or physical activity environment moderating heritability of obesity among young children [123] and variations in geographic location in a province moderated the effect of the microbiome on indicators of metabolic disease [124].

Research has attempted to isolate the effect(s) of one etiology at a time. While this may be possible in controlled laboratory research with animals, among humans, multiple etiologies are likely operative. While biological systems modeling may be able to account for these combinations of influences in the future, we probably do not know enough to effectively model them now. As the etiologies become causally implicated in the onset of obesity, research on any one etiology will need to account for the other known causal etiologies. An implication for prevention would be that no single procedure designed to prevent obesity for a specific etiology will be sufficient. Instead, prevention efforts will likely need to implement procedures to mitigate the effects of more than one etiology for which a target group is estimated to be at high risk.

New biological models not involving lack of self-control should minimize the problems of fat shaming [125] and bullying [126] since obesity becomes a medical problem/chronic disease, and not due to one's inability to self-regulate behavior. To the extent that weight stigma leads to eating disorders [127], the shift to new biological models may have positive externalities in this area, as well.

Switching to new biological models will change the control behavioral scientists have exercised over child obesity prevention research. When the biological model was assumed to be simple, easily understood, and amenable to volitional control

(diet, physical activity, self-regulation), behavioral scientists controlled the research agenda to find ways to manipulate the targeted behaviors and thereby influence adiposity/obesity. With the biology becoming more complex and perhaps minimally influenced by behaviors, behavioral prevention scientists must share control of the research agenda. At a minimum, behavioral scientists have to partner with biological scientists, who will be the lead scientists until the behaviors needing change are clearly delineated. Behavior scientists will likely resist losing control from accepting these new biological models upon which to predicate obesity prevention interventions. However, not getting involved in these new exciting lines of research could sideline behavioral scientists from future child obesity prevention.

As we can identify different obesity etiologies, and separate them from remaining cases, it should become easier to identify that subset of people for whom lack of dietary self-control and the attractions of inactivity do overwhelm our behavioral practices. At that time, we can retest our current forms of child obesity prevention interventions with an expectation of greater likelihood of success.

Conclusion

Child obesity prevention programs that utilize new biological insights to target and tailor behavior change procedures offer promise of more effective obesity prevention, thereby minimizing the toll of the currently escalating epidemic.

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Compliance with Ethical Standards

Conflict of Interest Tom Baranowski, Kathleen J. Motil, and Jennette P. Moreno declare they have no conflict of interest.

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