

Obesity: Nutrition and Genetics—A Short Narrative Review

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Abstract

Obesity has become a major global health challenge and it is a risk factor for the development of several comorbid conditions. Additionally, obesity has considerable economic consequences. Obesity is a multifactorial condition that arises from independent influences of genetic and social-environmental factors on food intake and physical activity. It has been difficult to establish clear associations between weight status and the intake of single foods or food groups. In most people, the predisposition to obesity has a polygenic basis, which means that obesity will develop if an individual has several polygenic variants that increase body weight. The FTO gene was the first GWAS-identified obesity-susceptibility gene and since then other polygenic variants that are associated with BMI and dietary intake have also been identified. However, this is still an active area of research as more polygenetic variants await discovery.

Keywords

Obesity, Nutrition, Genetics

1. Introduction

Obesity has become a major global health challenge [1]. A recent study, that estimated Body Mass Index (BMI) trends in 200 countries and territories in people 5 years and older, reported that the worldwide number of adult women with obesity increased from 69 million in 1975 to 390 million in 2016, while the number of men with obesity increased from 31 million to 281 million, over the same period. The study also shown that the rising trends in both, children's and adoles-

cent's BMI appear to be leveling off in many high-income countries, albeit at high levels [2].

Obesity is associated with higher mortality and it is a risk factor for the development of several comorbid conditions such as diabetes, hypertension and cardiovascular disease [3] [4] [5]. In addition, obesity also has considerable economic consequences. The direct healthcare costs of obesity are high and obese individuals have a 36% increase in annual health-care costs and a 77% increase in medication costs, in comparison with their average weight counterparts [4]. Moreover, obesity has several indirect costs caused by the reduction of productivity and absenteeism due to illness or disability and early premature mortality [6].

In this short review we will address the classification, etiology and role of genetics and nutrition in obesity.

2. Classification and Etiology

Obesity is defined as abnormal or excessive fat accumulation that may impair health [7]. It is defined in terms BMI, which constitutes a proxy of body fat. [8] For adults, a BMI between 25 kg/m² and 29.9 kg/m² and a BMI greater than or equal to 30 kg/m² define overweight and obesity, respectively [7]. For children, age and sex-specific BMI cut-off points are used to classify overweight and obesity [9]. According to the location of the adipose tissue deposition, two different types of obesity can be defined: android obesity—in which adipose tissue accumulation around the abdomen predominates; and gynoid obesity—in which adipose tissue accumulation occurs in the femoral region [10] [11]. Generally, an increase in both the number and the size of adipocytes is observed in obesity [10].

The excessive storage of fat that occurs in obesity, eventually leads to the release of excessive fatty acids that provoke lipotoxicity, since lipids and their metabolites create oxidant stress to the endoplasmic reticulum and mitochondria. This will affect both, the adipose and the non-adipose tissue, accounting for obesity's impact in several organs that drive a range of pathological outcomes including hypertension, type 2 diabetes and an increased risk of cardiovascular disease, that eventually translates in a reduced life expectancy [12] [13]. The multiple health consequences of obesity are shown in **Figure 1**.

Even though substantial advances have been made regarding the development and progression of obesity, our understanding of its etiology is still incomplete [12]. Ross *et al.* [15] conducted a review of reviews regarding the causes of obesity in children and adults and concluded that there is no consensus in the literature regarding the specific factors that contribute to obesity. Understanding the etiology of obesity presents a substantial challenge due its complexity and interactions between several factors. Therefore, social ecological models have been proposed for understanding the etiology of obesity, as they are useful in examining a wide range of factors that contribute to a complex health issue [16].

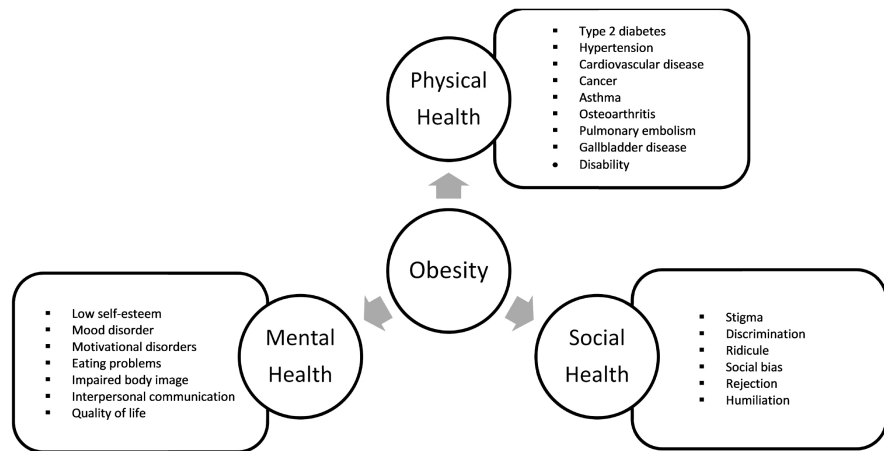


Figure 1. The multiple consequences of obesity on different dimensions of health [14].

The conceptual model proposed by Faith and Kral [17] hypothesizes that genetic and social-environmental factors lead to the development of obesity through their independent influences on food intake and physical activity. These intermediary behavioral variables may induce a positive energy balance that, if sustained over time, will promote obesity.

3. Nutrition and Obesity

At its most basic level, obesity results from a state of positive energy balance, where energy intake surpasses energy expenditure [18]. Human evolution has favored an accumulation of genes variants that result in an increased energy deposition as fat, in order to enhance survival to ancestral famine [19]. This leaves humans susceptible to an environment that facilitates overconsumption of energy—easy access to a wide variety of inexpensive energy dense foods and increased portion sizes; and promotes a reduction of energy expenditure by reducing physical activity—reduction in jobs requiring physical labor, reduced opportunities for physical activity and increased time spent in sedentary activities [20]. Thus, worldwide, a rise of almost 400 kcal per person per day has been reported between 1969/71 and 1999/2001 [21].

However, not all calories are equal [5] and there has been an ongoing debate about the optimal macronutrient content of the diet in relation to obesity. To date, multiple studies suggest that little difference exist in body weight and health outcomes between diets that differ markedly in macronutrients composition. However, diet macronutrient composition may affect long-term weight loss [22].

Regarding specific types of foods, fast food consumption, which is high in fat, energy density and has large portion sizes, has shown a positive association with increased BMI, although the findings are not entirely consistent [23]. The health effects of sugar-sweetened beverages (SSB) have also received substantial attention from the scientific and public communities [24]. A recent systematic review, that assessed the recent evidence (2013 to 2015) regarding the impact of SSB on obesity in both, children and adults concluded that SSB consumption is posi-

tively associated with or has an effect on obesity. The review included 26 prospective studies, of which 25 showed a positive association between SSB consumption and weight/BMI and 4 randomized controlled trials, of which 3 showed that SSB consumption had an effect on BMI/BMI z-score [25]. The association between dairy products intake and obesity remains controversial [26] [27] [28].

Overall, it has been difficult to establish clear associations between weight status and the intake of single foods or food groups [17]. Consequently, the association between several characteristics of dietary behavior and obesity have been studied, as they may reflect the joint effect of several foods and nutrients. It has been hypothesized that eating several small meals a day will improve fat loss and help achieve weight maintenance [29]. Data to support this hypothesis has been mainly provided by observational research [30]. However, in 2015 a meta-analysis that evaluated the experimental evidence on meal frequency with respect to changes in fat mass and lean mass in adults reported that eating frequency was positively associated with reductions in fat mass and body fat percentage. It is important to denote, however that after a sensitivity analysis of the data was done, the positive findings were the product of a single study [29]. Another eating behavior that is frequently advocated for controlling food intake and therefore body weight is eating rate. A recent meta-analysis found that eating fast is positively associated with excess body weight, with the mean difference in BMI between those individuals who ate faster and those who ate slowly being 1.78 kg/m² [31].

It also been suggested that deficiency levels of certain micronutrients may be associated with obesity, as micronutrients deficiencies have been observed in obese individuals worldwide [32] [33]. However, it is not well understood, whether a causal relationship exists, and if so, what is the direction of causality [32]. Results from a Chinese 26-week randomized, double-blinded, placebo-controlled intervention study have shown that in comparison with the placebo group, the group that received a 29-ingredient multivitamin and mineral supplementation had significant reductions in body weight, BMI and fat mass ($p < 0.01$). While the supplementation of calcium alone (162 mg/day) only improved lipid profiles, with the calcium group having a significantly higher HDL-C ($p < 0.01$) and a significantly lower LDL-C ($p < 0.05$) at 26 weeks when compared with the placebo group [34]. However, further well-designed experimental studies are needed to understand the role of micronutrients on obesity.

4. The Genetics of Obesity

For several decades it has been known that familial factors had an important role in the development of obesity and that the genetic basis was behind much of those factors [35]. However, the major piece in the puzzle of obesity genetics was published in December 1994, when the leptin (a cytokine-like polypeptide produced primarily in the white adipose tissue, that controls food intake through the activation of hypothalamic receptors [10] [36]) gene was cloned, triggering a

revolution in the understanding of the biology of obesity [37].

Prominence shifted from the question of whether genetics plays a role in human obesity to which specific genes are responsible [38]. In 2005, according to the 12th Update of Human Obesity Gene Map, 176 human obesity cases due to single-gene mutations in 11 different genes had been identified and 50 loci related to Mendelian syndromes relevant to obesity in humans had been mapped to a genomic region. Additionally, 426 studies reported positive associations between obesity and 127 candidate genes [39].

Twin studies, alongside family and adoption studies have provided evidence that a moderate to high heritability for BMI exists, however monogenic causes of obesity are rare [40]. In most people, the genetic mechanisms involved in the predisposition to obesity are polygenic and more than 100 “polygenes” harboring genetic variants associated with body weight regulation have been identified. This means that obesity will develop if an individual harbor several polygenic variants that increase body weight. However, the same variants, although at a lower frequency, can also be found in normal weight individuals [41]. A polygenic basis of obesity implies that a specific set of polygenic variants relevant for obesity in one individual will likely differ in another obese individual [19].

Recent progress in the clarification of polygenic predisposition to obesity points to an important role of the central nervous system in body weight regulation [42], as many of the genes located within or near the obesity-associated regions are highly expressed in the central nervous system and appear to be involved in appetite, satiety, energy expenditure and behavior [43]. The *FTO* gene—the first genome-wide association studies (GWAS)-identified obesity-susceptibility gene [44]—is highly expressed in the hypothalamus, pituitary and adrenal glands that are implicated in body weight and satiety regulation [45]. Several polymorphisms in the *FTO* gene have been associated with obesity in both, children and adults [46]. A common obesity-risk variant rs9939609 in the *FTO* gene has been associated with reduced satiety [47] and higher energy intake in adults [48]. Another strong obesity candidate gene is the *MC4R*, which is expressed in neurons in the hypothalamus and is essential for regulation of food intake and energy expenditure [45] [49]. The *MC4R* rs17782313 polymorphism has been widely studied and found to be significantly associated with obesity risk (OR = 1.18, 95% CI = 1.15 - 1.21, $p < 0.001$) in a systematic review and meta-analysis by Xi *et al.* [50]. The exact mechanism by which rs17782313 polymorphism may be associated with obesity is still unknown [51], however this variant has been associated with increased snacking and increased hunger in adults [52]. Contrarywise, a recent systematic review found limited significant evidence regarding the association between higher total energy intake and this polymorphism [53].

Other obesity genes identified by GWAS, such as, *KCTD15*, *MTCH2*, *NEGR1*, *BDNF*, have also been associated with dietary intake and BMI [54].

5. Final Considerations

Obesity is a complex polygenic disease that arises from an interaction between

multiple genetic, environmental and behavioral factors, making obesity research extremely challenging. A better understanding of the association between dietary habits/behaviors and the risk of developing obesity is necessary as it will help tailor new strategies to prevent and treat obesity. The GWAS revolutionized the field of genetics allowing the detection of variants with small effect sizes [19], and therefore leading to the discovery of obesity polygenetic basis. This is still an active area of research as more polygenetic variants await discovery, allowing new etiological pathways to be discovered that in turn, will provide the development of novel therapies for the treatment of obesity. A future promising research direction is the management of obesity using genotypic information in “personalized nutrition”.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

BMI: body mass index; SSB: sugar-sweetened beverages; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; FTO: fat mass and obesity associated; GWAS: genome-wide association studies; *MCR4*: melanocortin 4 receptor; *KCTD15*: potassium channel tetramerization domain-containing 15; *MTCH2*: mitochondrial carrier homolog 2; *NEGR1*: neuronal growth regulator 1; *BDNF*: brain-derived neurotrophic factor.