Current paradigms in the etiology of obesity

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A B S T R A C T

The global prevalence of obesity continues to rise at an alarming rate and 37.7% of US adults are obese. Understanding the causes of excessive weight gain is extremely important, as it paves the way for the development of new therapies to control this epidemic. Obesity is a heterogeneous chronic disease where multiple factors interact to produce a state of positive energy balance leading to an increase in body weight. This review focuses on the major biological, environmental, and behavioral determinants of obesity. The key biological factors include genetics, brain-gut axis, prenatal determinants, pregnancy, menopause, neuroendocrine conditions, medications, physical disability, gut microbiome, and viruses. Propensity to develop obesity owing to one or more of these elements is exacerbated by environmental and behavioral influences. Environmental factors include food abundance, built environments, socio-economic status, culture, social bias, and environmental chemicals. Behavioral factors comprise excessive calorie intake, eating patterns, sedentary lifestyles, insufficient sleep, and smoking cessation. It is essential to identify the determinants of adiposity in individuals with obesity to tailor prevention and treatment techniques effectively.

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1. Introduction

Obesity is a major public health problem that spans the world. The worldwide prevalence of obesity continues to increase at an alarming rate [1,2] and in the United States, 37.7% of adults are obese [3]. The effect of this pandemic on health-related quality of life of affected individuals has been detrimental. There is over-whelming epidemiologic evidence of serious obesity-related comorbidity, specifically cardiovascular disease, type 2 diabetes, cancer, osteoarthritis, and psychological disturbance [4]. The resulting economic burden has expanded dramatically [5,6]. Thus, obesity is regarded as a public health crisis with an urgent need for action to reverse the observed trends [7]. The complexity of this disease lies not only in its breadth of complications but also in its multifaceted etiology [8]. Understanding the causes of excessive weight gain is extremely important, as it paves the way for the development of new therapies to control this global epidemic.

There has been an increased interest in understanding the role of genetics in obesity [9]. Nevertheless, the overwhelming upsurge in obesity prevalence in the past 2 decades cannot possibly be explained by genetic changes that could conceivably have occurred in this short duration [10,11]. Therefore, variations in obesity prevalence are influenced predominantly by environmental and behavioral factors, particularly increased calorie intake and reduced physical activity [12-14]. This work reviews the major biological, environmental, and behavioral determinants of obesity.

2. Etiology of obesity, a multifactorial disease

Although consumption of calories in excess of the body's ability to expend energy is key to storage of excess calories in adipose tissue [15], obesity is a heterogeneous disease where multiple biological, environmental, and behavioral obesogenic factors inter-act to bring about a state of positive energy balance [16-18]. Energy balance comprises energy intake, energy expenditure, and energy storage [19]. Energy is acquired through the intake of calorie-containing nutrients namely protein, carbohydrate, and fat, as well as alcohol. Energy is expended through 3 metabolic processes: resting metabolic rate, thermic effect of food (TEF), and physical activity-induced energy expenditure. Resting meta-bolic rate determines the amount of energy the body uses for metabolic activities at rest, and is relative to body weight, mainly fat-free mass. TEF (8%-10% of total caloric intake) represents the energy used for digesting and metabolizing ingested food. The energy spent through physical activity is the most variable con-stituent of energy expenditure, as it is proportional to the duration

Weight Maintenance

Weight Gain   **Weight Loss**

Energy In   **Energy Out**
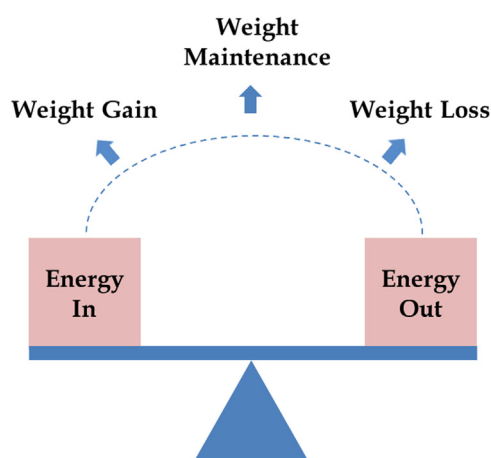
Fig. 1. Energy balance. In the human body, energy balance is the relationship between the intake of food and beverages (Energy In) and the expenditure of energy through the body's basal metabolism and physical activity (Energy Out). When Energy In = Energy Out for a prolonged period, body weight is maintained. However, when calorie intake exceeds the body's total energy expenditure (Energy In > Energy Out) for a prolonged period, a state of positive energy balance ensues, demonstrated by weight gain. Similarly, weight loss occurs owing to negative energy balance when energy expenditure exceeds energy intake (Energy Out > Energy In) persistently.(Color version of figure is available online.)

of physical activity in addition to the energy cost of that particular activity [20]. Stable energy homeostasis (Figure 1) is achieved when energy intake equals energy expenditure, thus representing a stable body weight. Changes in body weight occur when energy intake and energy expenditure are unequal, over a given time period [20]. Thus, energy intake in excess of energy expenditure creates a state of positive energy balance leading to an increase in body weight, predominantly as fat mass [21]. Hence, biological, environmental, or behavioral factors that influence body weight do so by altering energy intake or expenditure [20].

3. Biological factors

This section covers biological factors with an evidence-based association with obesity: genetics, brain-gut axis, prenatal determinants, pregnancy, menopause, neuroendocrine conditions, medications, physical disability, gut microbiome, and viruses. When one or more of these determinants is present, interaction with environmental and behavioral factors contributes to the expression of obesity.

3.1. Genetics of obesity

Despite the predominant effect of the environment and behavior on the propensity to develop obesity, there is an evidence of a genetic component to obesity [22]. In fact, studies of twins and adoptees suggest that up to 70% of the interindividual variation in fat mass has a genetic etiology [23]. Heritability of obesity has

been implicated in all the aspects of energy homeostasis, such as food intake, TEF, spontaneous physical activity, and basal metabolic rate, [24]. For instance, data from the Quebec Family Study cohort was recently used to examine the influence of genetic heritability on body fat distribution and behaviors that affect energy balance. The authors detected significant genetic heritability for total body fat, fat-free mass, body fat distribution, basal metabolic rate, physical activity, macronutrient intake, and eating behavior. They also reported evidence of influence of gene-behavior interplay on these observations. These findings represent a polygenic basis for common obesity [25].

The discovery of the *ob* (Lep) gene that encodes the peptide leptin and learning that an alteration in this gene causes obesity elevated the interest of scientists in the genetics of obesity [26]. Thus, candidate gene and genome-wide association studies have led to the identification of more than 300 different genes and gene markers that are linked to obesity and appear to interact with the environment for obesity to be expressed [27,28]. This suggests the classification of obesity into 3 subgroups, from a genetics standpoint: monogenic obesity (single candidate gene defect, eg, leptin), syndromic obesity (chromosomal abnormalities, eg, Prader-Willi syndrome), and polygenic obesity (common obesity; multiple gene variants) [18].

3.1.1. Candidate genes and monogenic obesity

To date, several rare forms of severe early-onset human obesity have been identified, mostly stemming from mutations in genes controlling the leptin-melanocortin pathway that regulates food intake. These candidate genes [18,29,30] are listed in Table 1. The identification of these genes and continued research efforts toward the discovery of other potential candidate genes for obesity permit the diagnosis of affected individuals and the possibility of introducing effective treatment options.

3.1.2. Syndromic obesity

At least 25 forms of syndromic obesity are known. The following are some of the most common types for which the genetic basis is partly or fully understood: Prader-Willi syndrome; Bardet-Biedl syndrome; Alstrom syndrome; and Wilms tumor, aniridia, genitourinary anomalies, and mental retardation [31]. The most common form of syndromic obesity, Prader-Willi syndrome, is a complex genetic disease caused by alterations in gene expression on the paternally inherited chromosome 15q11.2-q13 region. The phenotype is characterized by short stature, overeating, excessive weight gain, cognitive disability, and behavioral problems. Obesity is the chief cause of morbidity and mortality among affected individuals [32,33].

3.1.3. Polygenic obesity

Of major clinical importance is the detection of genetic modifications with polygenic effects on body weight, as this represents most human cases of obesity, as opposed to the very rare monogenic forms of the disease [34]. Some obesogenic traits arise from

Table 1
Candidate genes associated with severe early-onset obesity. (Adapted with permission from Huvenne et al [30]).

Gene	Encoded protein	Obesity onset	Diagnosed cases
LEP	Leptin	First few days of life	Fewer than 100 patients worldwide
LEPR	Leptin receptor	First few days of life	Overall 2%-3% of severe early-onset obesity
POMC	Proopiomelanocortin	First few months of life	Fewer than 10 patients worldwide
MC4R	Melanocortin-4 receptor	Childhood	Overall 2%-3% of obesity in adults and children
PCSK1	Proprotein convertase subtilisin/kexin type 1	Childhood	Fewer than 20 patients worldwide
SIM1	Single-minded 1	Childhood	Fewer than 50 patients worldwide
NTRK2	Neurotrophic tyrosine receptor kinase 2	First few months of life	Fewer than 10 patients worldwide
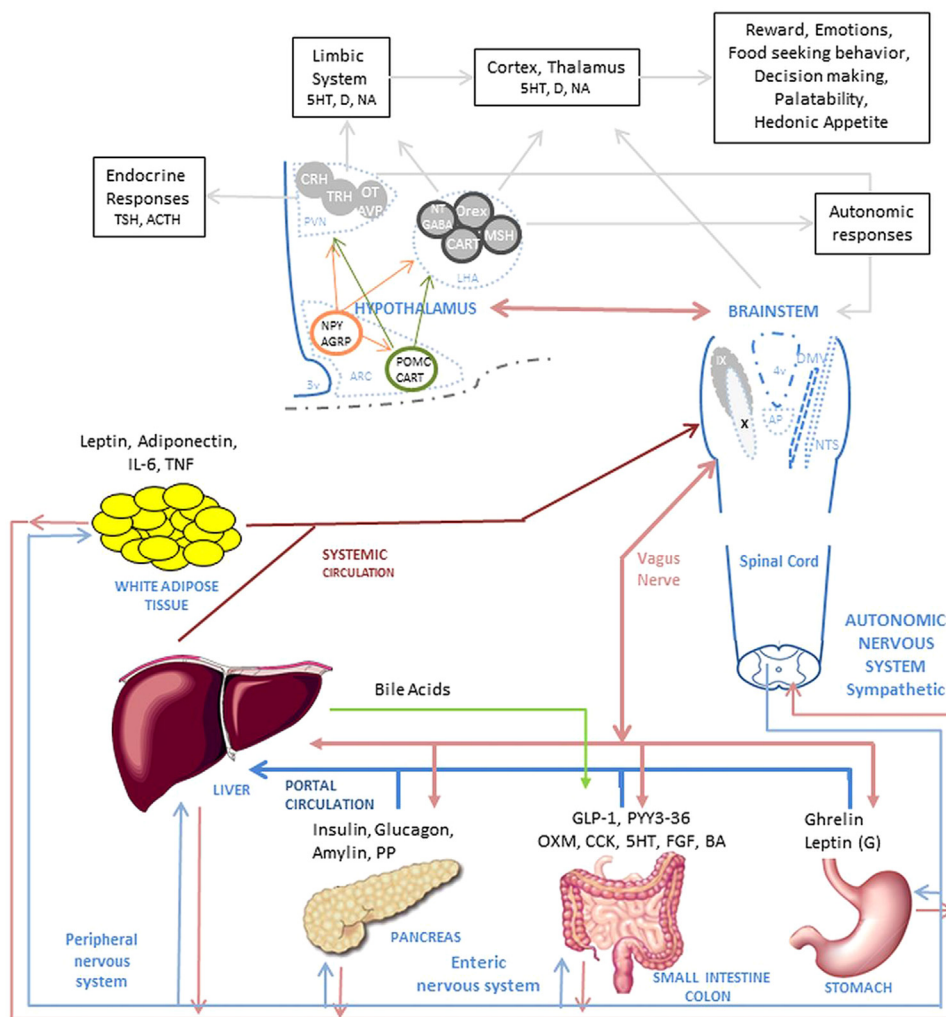
Fig. 2. The brain-gut axis and regulation of food intake. The food intake process initiates when nutrients enter the gastrointestinal tract. Digestion starts when the nutrients enter the stomach and produce mechanic dilation decreasing acyl-ghrelin and increasing desacyl-ghrelin and gastric leptin. Stomach dilation sends signals through the vagus nerve and peripheral nervous system to the brainstem and hypothalamus. The digested nutrient passes to the small intestine and colon producing further mechanic-dilation, GI hormones release, bile acid, and pancreatic juices secretion. These GI hormones have a local effect (paracrine) and peripheral effect, when secreted into circulation, passed through the liver and affect the muscle, adipose tissue, gastrointestinal motility and function, and nucleus of the hypothalamus and brainstem. The paracrine and endocrine effect induces satiation and satiety. The muscle and adipose tissue release hormones, which affect similar nuclei in the brain. The effect on the hypothalamus and brainstem trigger higher brain area responses, modulating behavior, and enhancing nutrient-related reward. In the hypothalamus, first-order neurons in the arcuate nucleus (ARC) modulate appetite by NPY/AGRP pathway and satiation by the POMC/CART pathway. The neurons interact with second-order neurons in the paraventricular nucleus (PVN) and lateral hypothalamic (LHA) area to send signals to higher brain areas and to the brainstem. In the brainstem, the nucleus of the tractus solitarius (NST) and dorsal vagal complex (DMNV) interact with the periphery and gastrointestinal system and brings signals to the higher brain areas and the hypothalamus. 5-HT, serotonin; ACTH, adrenocorticotropic hormone; AGRP, agouti-related peptide; ARC, arcuate nucleus; AVP, arginine vasopressin; BA, bile acids; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; CRH, corticotropin-releasing hormone; D, dopamine; DMNV, dorsal vagal complex; FGF, fibroblast growth factor-19; GABA, gamma-aminobutyric acid; GLP-1, glucagon-like peptide-1; IL-6, interleukin-6; LHA, lateral hypothalamic; MSH, melanocortin stimulating hormone; NA, noradrenaline; NPY, neuropeptide Y; NST, nucleus of the tractus solitaries; NT, neurotensin; OT, oxytocin; Orex, orexin; OXM, oxyntomodulin; PP, pancreatic polypeptide; PVN, paraventricular nucleus; PYY3-36, peptide tyrosine-tyrosine 3-36; POMC, proopiomelanocortin; TNF, tumor necrosis factor; TRH, thyroid-releasing hormone; and TSH, thyroid stimulating hormone. (Used with permission from Acosta et al [38].)

the concomitant occurrence of nucleotide variation in multiple genes. Polygenic variants are alleles at different gene loci that jointly influence the inheritance and expression of quantitative and qualitative phenotypes. The complexity of the polygenic basis of obesity lies in the fact that each individual with obesity likely possesses a unique set of polygenic variants in association with the disease [35]. Genome-wide association and Metabochip studies have been successful in the detection of single-nucleotide polymorphisms with polygenic effects on body mass index (BMI). So far, numerous such variants have been detected. In the most recent meta-analysis of genome-wide association studies and Metabochip studies involving a total of 339,224 individuals, 97 loci (novel and previously known) were found to be associated with BMI. The study also indicated that the identified loci account for 2.7% of

variation in BMI [36]. However, extensive research has yet to be performed to discover a wider range of susceptible loci that potentially exist, and understand how they interact with the environment to express obesity [18].

3.2. Brain-gut axis

The brain-gut axis (Figure 2) controls food consumption in response to homeostatic and nonhomeostatic signals [37,38]. In the homeostatic (energy balance) system, the arcuate nucleus of the hypothalamus integrates neural, nutrient, and hormonal signals to regulate hunger, satiation, and satiety via higher cortical centers that in turn relay these signals to stimulate the sympathetic and parasympathetic nervous system, gastric function, and

hormone secretion [37]. These signals are merely a means of communication among the gastrointestinal system, adipose tissue, and the brain [37]. Individual characteristics pertaining to these systems lead to variations in energy consumption and storage among individuals [39,40]. For instance, gastric function affects appetite, satiation, and satiety. Hence, caloric overconsumption may result from alterations in gastric function [41].

Interestingly, in common obesity, there are alterations in the brain-gut axis in comparison with healthy lean controls. Obesity is associated with decreased satiation (with a difference of 50 calories per 5 kg/m^2 of BMI), higher fasting gastric volume, accelerated gastric emptying of solids and liquids, lower levels of the satiation-associated hormone peptide YY (PYY) [42], lower levels of glucagon-like peptide-1 and cholecystokinin [38], higher levels of acyl-ghrelin [43], and increased levels of leptin with leptin resistance (receptor downregulation) [44]. Furthermore, most of the biological etiologies of obesity disturb the brain-gut axis homeostasis.

The phenotypic study of the brain-gut axis in common obesity has led to a novel working hypothesis which subclassifies obesity based on the main abnormality to brain-gut axis. The subclassification is based on a principal component analysis of traits from 232 patients with obesity that accounted for approximately 81% of the variation in obesity. The latent dimensions identified included satiety—satiation (21%), gastric capacity—volume (14%), behavioral factors (13%), and gastric emptying (11%), suggesting that these traits can distinguish obesity subphenotypes based on: abnormal satiety, abnormal gastric motor function, or affect [42]. It is conceivable that future weight loss therapy may be customized based on these traits [45]. However, it remains unclear whether brain-gut axis alterations associated with excessive food intake are a cause or an effect of obesity [41], implying a need to conduct further research aimed at understanding these characteristics.

3.3. Prenatal determinants

A vast body of evidence suggests that environmental and nutritional exposures during fetal and neonatal life can permanently influence the structure and function of key organs, thus dictating the predisposition to chronic metabolic diseases such as obesity [46]. For instance, high prepregnancy BMI and excessive gestational weight gain can influence future body composition of the child and are in fact predictors of future childhood obesity [47,48]. Moreover, gestational diabetes is associated with childhood overweight in offspring [48]. Similarly, smoking during pregnancy appears to predispose the infant to future excessive weight gain [49]. The method of childbirth has also been implicated in the risk of obesity in offspring. In fact, epidemiologic data suggest a positive relationship between cesarean delivery and child adiposity [50], and a systematic review and meta-analysis of 15 studies (163,796 participants) reported a strong connection between cesarean delivery and increased offspring BMI in adulthood [51].

3.4. Pregnancy

Weight gain during pregnancy is a subject of concern to women of childbearing age, as it is paralleled with fears of postpartum retention of excess weight [52]. Indeed, epidemiologic evidence suggests that gestational weight gain is associated with weight retention after pregnancy, though not necessarily to a large extent [53]. In a large cohort study with 5 years of follow-up, women experienced 2-3 kg weight gain and greater increases in waist-to-hip ratio after a first pregnancy during the 5-year period, when compared with women who had never been pregnant [54]. Weight retained shortly after pregnancy may be a predictor of long-term

obesity. A study examined this relationship by observing 540 women during pregnancy and at 6 months postpartum and recording their weight 10 years later. The authors reported an average weight gain of 6.3 kg from prepregnancy to follow-up, with weight gain at 10 years being proportional to both weight gain during pregnancy and weight retention by 6 months postpartum [55]. Thus, these findings suggest a positive relationship between pregnancy-induced weight changes and future risks of weight gain.

3.5. Menopause

Another life event that exacerbates weight gain in a woman's body is menopause. A higher prevalence of obesity is reported among postmenopausal American women more than 50 years old in comparison with premenopausal women, as an estimated 48% of postmenopausal women are overweight, of which more than 25% have obesity [56,57]. Menopause is known to be associated with alterations in body composition, such as a decline in fat-free mass and an increase in fat mass. The loss of lean body weight is thought to induce weight gain by reducing energy expenditure [58]. Perimenopausal hormonal changes are associated with significantly increased abdominal adiposity, and estrogen therapy may assist in preventing these body composition changes and their metabolic repercussions [59].

3.6. Neuroendocrine conditions contributing to weight gain

A number of acquired neuroendocrine conditions are known to cause excessive weight gain through differing mechanisms [60]. The relationships of hypothalamic obesity, Cushing syndrome, hypothyroidism, and polycystic ovary syndrome (PCOS) with obesity are reviewed here.

3.6.1. Hypothalamic obesity
Hypothalamic obesity is a rare subtype of obesity in humans, resulting from injury to the hypothalamic centers that regulate body weight and energy expenditure (Brain-gut axis section) [61,62]. In this disorder, patients with hypothalamic dysfunction resulting from a variety of mechanisms (tumors, surgery, trauma, etc) develop an imbalance of anorexigenic and orexigenic pathways [63]. Hence, severe hyperphagia and reduced energy expenditure ensue, resulting in excessive, chronic weight gain [64-66]. In fact, rodent models of hypothalamic obesity have been available for decades and have long shown that lesions to the ventromedial hypothalamus and paraventricular nucleus result in remarkable overeating and weight gain [67,68]. Despite continued progress in studying hypothalamic obesity, it remains challenging to prevent and treat [69].

3.6.2. Cushing syndrome
Cushing syndrome, sometimes referred to as hypercortisolism, arises from prolonged overexposure to glucocorticoids originating endogenously (eg, pituitary adenoma) or exogenously (eg, corticosteroid therapy) [70]. Excess glucocorticoids likely induce 11-betahydroxysteroid dehydrogenase type 1 activity in visceral adipose tissue, thus increasing the lipogenic capacity of these cells [71]. Increased lipogenesis in addition to enhanced adipocyte differentiation and adipogenesis contributes to one of the clinical manifestations of this disease, excessive adiposity [60,72]. In fact, sudden weight gain is the most common symptom of the disease [73]. Patients usually experience progressive centripetal obesity spanning the face, neck, trunk, and abdomen, in addition to internal vicinities such as the mediastinum and the spinal canal

[74]. Some clinicians have observed generalized obesity among patients with Cushing syndrome [75].

3.6.3. Hypothyroidism

Hypothyroidism is a common endocrine disorder where the thyroid gland does not produce sufficient amounts of thyroid hormone [76]. It is estimated that this deficiency afflicts approximately 4.6% of the US population aged 12 years and older [77]. Individuals with overt hypothyroidism experience low energy expenditure [60,78] independent of physical activity [79], and patients often complain of irreversible weight gain [80]. Indeed, studies have shown an inverse relationship between thyroid function and body weight. In the Danish DanThyr 1997-1998 population cohort, small differences in thyroid function appeared to be associated with differences in BMI. Precisely, a positive association was observed between serum thyroid stimulating hormone and BMI with a difference of 1.9 kg/m^2 in BMI among the groups with the highest and lowest thyroid stimulating hormone levels, whereas a negative association was observed between serum-free T4 and BMI [81].

3.6.4. Polycystic ovary syndrome

PCOS is a disorder that is characterized by hyperandrogenism, oligoanovulation and polycystic ovaries [82]. It is one of the most common endocrinopathies among women of reproductive age, with an estimated 5%-10% of women suffering from the disease [83]. This polygenic, yet environmentally influenced disorder poses metabolic and reproductive challenges on afflicted women [82,84]. Common manifestations comprise menstrual irregularity, hirsutism, acne, and frequently obesity [85,86]. Other metabolic abnormalities that accompany PCOS include insulin resistance, dyslipidemia, and arterial hypertension, all of which are precipitated by obesity [82,87]. The pathophysiology of obesity in connection with PCOS is complex, as it is possible that obesity could concurrently be the cause and the effect of the syndrome [82]. However, excess androgen is currently a plausible cause of the development of central obesity in the context of PCOS [60], knowing that androgens play an important role in manipulating fat distribution and body composition [88].

3.7. Medications contributing to weight gain

Weight gain as a result of the use of prescription drugs is not uncommon. In fact, a wide range of commonly used medications are known to have an obesogenic effect or—in other words—induce weight gain [89,90]. Table 2 provides a summary of known medications with a positive association with body weight [91]. Weight gain propensities are commonly seen with psychoactive drug therapy. A systematic review of weight gain tendencies associated with drugs labeled as "obesogenic" revealed that mean weight gain after 10 weeks of therapy was highest with thioridazine (3.2 kg) among the first generation antipsychotics, and olanzapine and clozapine (4.2 and 4.4 kg) among the second generation antipsychotics [89]. Similarly, diabetic patients suffer from weight gain in relation to glucose-lowering treatments. Intensive insulin therapy was associated with 5.1 kg average weight gain, whereas the mean increase in weight gain was 2.4 kg in patients receiving conventional insulin treatment, in the Diabetes Control and Complications Trial [92]. Similar trends have been observed among patients with epilepsy. For instance, Biton et al [93] demonstrated in a randomized, double-blind study that valproate (antiepileptic) therapy was associated with steady weight gain up to a mean gain of 12.8 kg at 32 weeks, as when compared with 1.3 kg with lamotrigine therapy.

Table 2
List of medications associated with weight gain. (Adapted with permission from Apovian et al [91]).

Class	Medication
Antidepressants	Amitriptyline, imipramine Citalopram Doxepin Fluoxetine (> 1 y) Mirtazapine Nortriptyline Paroxetine Phenelzine Sertraline (> 1 y)
Antidiabetics	Insulin Sulfonylureas (eg, glyburide) Thiazolidinediones (eg, rosiglitazone and pioglitazone)
Antiepileptics	Carbamazepine Gabapentin and pregabalin Valproic acid Vigabatrin
Antihistamines	Cyproheptadine and diphenhydramine Meclizine
Antihypertensives	Doxazosin, prazosin, and terazosin Metoprolol and propranolol
Antipsychotics	Clozapine, olanzapine, and quetiapine Lithium Perphenazine Risperidone
Contraceptives and hormones	Depo-medroxyprogesterone acetate Megestrol acetate
Steroids	Corticosteroids (eg, prednisone) Glucocorticoids Progestins

3.8. Physical disability

Approximately 53 million US adults (22% of adult population) are living with a disability. Disability in mobility is the most common type according to national statistics [94]. Data from epidemiologic studies indicate that individuals with physical disabilities have higher obesity prevalence than the general population [95,96]. Changes in body composition and energy expenditure as well as physical inactivity itself could explain the relationship [95]. In a longitudinal study, performed to assess body composition changes in patients with acute spinal cord injury, significant reductions in bone-mineral content, and lean body mass were observed during the first year of injury, along with an increase in adiposity [97]. Physical disability-driven obesity is also a concern among children with disabilities. A study reported that children and adolescents with spastic quadriplegic cerebral palsy had significantly lower measures of total energy expenditure and nonbasal energy expenditure when compared with healthy controls [98]. Hence, it is suggested that individuals with disabilities should be an emerging population of concern within public health efforts related to obesity [96].

3.9. Gut microbiome

Animal and human studies have associated the gut microbiota with body weight through its effects on energy metabolism and systemic inflammation [99-101]. The gut microbiota comprises 10-100 trillion microorganisms, indicating that there is up to 10-fold more microbial cells than human cells in the human

body [102]. It has long been known that indigestible polysaccharides are actually fermented by gut bacteria to produce sugars or short-chain fatty acids, which are in turn digestible and can play a role in energy metabolism in the host [103]. In fact, energy extracted from ingested but undigested food has been proposed as the mechanism resulting in adipose tissue hypertrophy observed in mice with normal gut microbiota when compared with germ-free mice [104]. Recent findings continue to indicate that metabolites produced through fermentation in the gastrointestinal tract by gut microbiota have important functions in metabolism [105]. For instance, a number of studies have reported that gut microbiota extracted from obese mice can transfer the obesity phenotype when transplanted into germ-free mice, a breakthrough finding seen in diet-induced obese mice as well as the genetic mouse models of obesity, *ob/ob* and toll-like receptor 5 (TLR5) knockout mice [106-108]. Shortly after these discoveries, human studies aimed at understanding the link between the gut microbiome and obesity reported marked differences in microbial diversity between subjects who have obesity and subjects who do not have obesity. However, there has been a disagreement regarding the bacterial species or genus associated with obesity [105]. Thus, further studies are clearly required to understand the role of microbiome in obesity.

3.10. Viruses

Despite the diverse etiology of obesity, obesity owing to an infection is often overlooked. In recent decades, it has been proven that animals can develop obesity because of certain viral infections [109,110]. Adenoviruses, namely Ad36 and Ad37, have particularly been implicated as adipogenic pathogens in animal models [109,111,112]. Some of these viruses have been associated with increased adiposity in humans, according to preliminary data [8,113]. In the first study to screen humans for Ad36 prevalence, it was reported that the virus was significantly more prevalent in people with obesity than in people without obesity (30% vs 11%, 502 US participants). Furthermore, the virus was detected in approximately 60% of participants with severe obesity (BMI $\geq$ 50) [114]. Hence, there is a possibility that certain infections may be risk factors for obesity in humans [113]. A wide range of human studies is required in this area to establish definitive causation.

4. Environmental factors

The environment is a crucial element in the etiology of obesity. As mentioned in previous sections, in most cases of obesity, a biological propensity for the development of obesity requires interaction with environmental factors for obesity to be expressed. These factors require serious attention from researchers, policy makers, and practitioners in the field. This section reviews the major environmental determinants of obesity: the obesogenic environment, society and culture, and environmental chemicals.

4.1. The obesogenic environment

Nowadays in the United States, food has rather become overly abundant and eating for pleasure and entertainment has taken over eating for survival. The food supply chain has created a favorable environment for overeating, consuming foods that are rich in calories, and hence gaining weight [115]. This environment has been a major contributing factor in the development of obesity. This may partly explain why, for instance, Arizona Pima Indians living on a reservation are significantly heavier with higher rates of diabetes than their counterparts across the border in a remote Mexican village [116]. Another aspect of modernization

that is considered one of the pillars of our obesogenic environment is the built environment. Because of urban sprawl, walking has become less favorable and residents of sprawling areas tend to be heavier than those in compact areas [117].

4.2. Society, culture, and obesity

There is an inverse relationship between socioeconomic status and obesity prevalence in the United States and elsewhere [118]. This association is postulated to arise from effects of socioeconomic factors such as the aforementioned food environments and the built environment, in addition to other social factors such as education, particularly nutrition education [119,120]. Obesity rates are also influenced by ethnicity, gender, and their interplay [121]. For example, morbid obesity is more prevalent in women than in men, and most prevalent among Black adults, followed by White, Asian, and Hispanic adults, respectively [122]. These differences bring about the concept of culture. Culture is merely the characteristics, beliefs, and behaviors of different social, ethnic, or age groups [123]. Hence, culture can shape the values and norms that in turn influence one's health behavior and body weight [124]. For instance, White women are more likely to experience body dissatisfaction and feel overweight than Black and Hispanic women [125].

Other social and environmental considerations play a pivotal role in the status of obesity. Individuals who have obesity are immensely affected by bias, stigma, and discrimination that they face in our society. Bias is commonly encountered in their daily lives in a wide range of settings, from health care to employment, not to forget weight bias in the media. Weight bias has emotional and psychological consequences that in turn affect the individual's physical well-being. For instance, overweight youth who encounter weight-based teasing have been shown to be more prone to poor weight control and unhealthy eating behavior, particularly binge eating, and less likely to be physically active [126].

4.3. Environmental chemicals and obesity

An emerging issue in environmental health is the role of environmental chemicals in obesity. Recent studies support the concept that certain endocrine-disrupting chemicals, or "obesogens," potentially increase the risk of obesity. For example, phthalates are among the recognized obesogens as they interact with peroxisome proliferator–activated receptors (*PPARs*), which are closely involved in fat development. Other obesogens have also been identified and they are being investigated [127].

5. Behavioral factors

With the exception of obesity subtypes originating from monogenic etiologies or factors that cause reduced energy expenditure, individual decisions and lifestyles are essential in precipitating the interplay between biological and environmental factors to generate a state of obesity. For example, although we are surrounded by an obesogenic food environment characterized by food abundance, affordability, variety, and convenience [128], individual decisions play a major role in the extent to which this environment will affect caloric intake. Similarly, other behaviors such as reduced physical activity, insufficient sleep, and smoking (thus smoking cessation) are self-inflicted behaviors despite being influenced by the environment.

5.1. Increased calorie intake and eating patterns

Per capita use of refined grains, sugar, and fats in the United States has increased dramatically since the 1970s particularly in processed and fast foods, resulting in a respective increase in calorie intake [129]. Research has consistently demonstrated that diets high in sugar and fat are associated with obesity. Between 1986 and 2006, Mozaffarian et al prospectively evaluated the relationships between lifestyle changes and weight change in 3 cohorts (120,877 healthy men and women) over 4-year periods. They reported that weight gain was markedly associated with the consumption of potato chips, potatoes, sugar-sweetened beverages, unprocessed red meats, and processed meats, while being inversely associated with the consumption of vegetables, whole grains, fruits, nuts, and yogurt [130]. Additionally, the intake of liquid calories has been increasingly recognized as an important risk factor for the development of obesity. Studies support the notion that the intake of sweetened beverages is associated with higher total caloric intake and in turn weight gain, and it has played a major role in the onset of the obesity epidemic [131]. In fact, about half the total added-sugar intake in the US population is sugar in liquid form [132] and it is projected that sweetened beverages are responsible for at least one-fifth of the weight that Americans have gained between 1977 and 2007 [131]. Furthermore, prevalence of binge drinking and heavy drinking among US adults in 2014 were estimated to be approximately 24.7% and 6.7%, respectively [133]. Consumption of alcoholic beverages is in turn associated with increased total calorie intake. In a prospective study of 7608 men aged 40-59 years conducted in the United Kingdom, it was shown that heavy alcohol consumption is directly associated with weight gain and obesity, after 5 years of follow-up [134].

Another issue worth discussing in the context of weight gain is eating patterns. Two eating disorders are linked with obesity: binge eating disorder (BED) and night eating syndrome (NES) [135]. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), BED is defined as "recurring episodes of eating significantly more food in a short period of time than most people would eat under similar circumstances, with episodes marked by feelings of lack of control" [136]. BED was found to be strongly associated with central obesity and generalized obesity in a study assessing the prevalence of BED and its relationship to obesity in a sample of 497 university students (male and female) between 2013 and 2014 [137]. On the contrary, NES is characterized by recurrent episodes of night eating, that is, eating after awakening from sleep, or excessive food consumption after the evening meal [136]. In studies investigating the relationship between NES and obesity, NES appears to be positively associated with indicators of obesity, such as BMI and weight gain or both [138,139].

In conclusion, excessive calorie consumption is the cornerstone of weight gain. This occurs because of various factors and in different ways. It is important to understand the unique contributors to excess calorie intake in an individual to better predict their determinants of obesity and individualize their treatment.

5.2. Sedentary lifestyle and physical inactivity

Physical activity comprises 20%-30% of total daily energy expenditure in the human body [140], accounting for a wide variation between individuals because of different levels of activity. Sedentary behaviors, such as prolonged TV watching, are associated with an increased risk of weight gain and obesity, independent of exercise and diet [141,142]. Similarly, the mere lack of physical activity is independently associated with higher BMI levels [142]. The influence on energy expenditure can explain this relationship. Physiologically, sedentary posture lowers energy

expenditure, and this in turn promotes weight gain [143]. For example, the use of energy-sparing equipment at home and at work has been shown to contribute to a reduction in energy expenditure and an increased propensity to gaining weight [144]. Conversely, there is a general consensus that an inverse relationship exists between physical activity and obesity risk. Multiple studies have shown that physically active children are less likely to become overweight and develop obesity in childhood and adolescence, and have a reduced risk of obesity in adulthood [145]. In a similar manner, physical activity appears to be protective against obesity among adults. Haapanen et al followed a large cohort of physically active and physically inactive women and men over a 10-year period and found that inactive individuals gained weight whereas their active counterparts maintained or lost weight, and the likelihood of gaining more than 5 kg throughout this period was significantly higher in the inactive group [14]. Unfortunately, in today's society that faces the most rapid technological advances in history, it is not uncommon for a person to spend an entire half of their waking day sitting and the other half of the day engaging in nonexercise physical activity [143]. Alarmingly, physical inactivity is a strong factor in propagating several chronic disease risks (eg, diabetes and heart disease) as well as overall mortality. Hence, promoting a physically active population will potentially assist in controlling the obesity epidemic and preventing other major health problems [146].

5.3. Insufficient sleep

The modern society trends of shift jobs, long work hours, and around-the-clock commercial accessibility of basic needs have been accompanied by reduced quantity of sleep and increased prevalence of reported exhaustion [147]. Meanwhile, research findings are in support of an association between hours of sleep and obesity, in both children and adults [148]. This was experimentally demonstrated in a study that evaluated the effect of sleep curtailment on appetite regulation in 12 healthy men with a mean BMI under 25. The subjects participated in 2 days of sleep deprivation and 2 days of sleep extension spaced 6 weeks apart, under controlled physical activity and food intake conditions. Sleep restriction was associated with a decrease in leptin levels and an increase in ghrelin levels and ratings of hunger and appetite [149,150]. Hence, epidemiologic findings suggest that insufficient sleep may induce excessive food intake and adiposity. However, more evidence is required to establish a causal link between short sleep and obesity [147].

5.4. Smoking cessation

The public perception that cigarette smoking helps with weight control has been around for many decades. The association is in fact supported by epidemiologic evidence. On average, adult smokers are 4-5 kg lighter than nonsmokers and are less likely to develop overweight or obesity [151]. Smokers have a tendency to gain weight on smoking cessation [152], an association that may be partly explained by nicotine withdrawal, which is usually accompanied by increased food intake and decreased energy expenditure [153]. In a cohort of adults weighed in the First National Health and Nutrition Examination Survey (NHANES I, 1971-1975) and weighed again between 1982 and 1984, the average weight gain attributable to smoking cessation (after adjusting for other factors) was 3.8 kg in women and 2.8 kg in men, and major weight gain (> 13 kg) was observed in 13.4% of the women and 9.8% of the men who quit smoking [152]. Other studies have reported a weight gain of 4-5 kg or more [153,154]. Diet and physical activity coaching may be a helpful strategy for preventing weight gain in individuals planning to quit smoking.
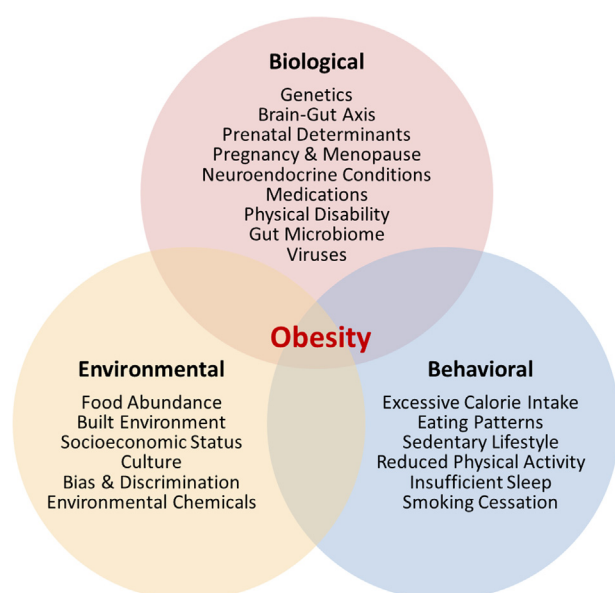
Fig. 3. Obesity, a multifactorial disease. Obesity is a complex disease that results from the interaction of multiple factors. This figure depicts the biological, environmental, and behavioral factors that contribute to positive energy balance, excess weight gain, and therefore obesity. (Color version of figure is available online.).

6. Conclusion

Many studies have suggested that body weight is maintained at a steady range, referred to as the "set-point" [155]. In this context, storage of energy in the form of body fat has been a vital adaptation for human survival, suggesting the likelihood that a number of genes have been selected during evolution to encourage energy storage. When met with an environment that provides food in excess and promotes sedentariness, these genes will likely flourish and favor the onset and sustenance of obesity [156]. Hence, obesity is a result of the intricate interaction between genes and the environment. The key biological factors that contribute to excessive adiposity include genetics, the brain-gut axis, prenatal determinants, pregnancy, menopause, neuroendocrine conditions, medications, physical disability, gut microbiome, and viral infections. Propensity to obesity owing to one or more of these elements is exacerbated by environmental and behavioral influences. Environmental factors include food abundance, built environments, socioeconomic status, culture, social bias, and environmental chemicals. Behavioral factors include excessive calorie intake, eating patterns, sedentary lifestyles, insufficient sleep, and smoking cessation. Figure 3 illustrates the development of obesity through the interplay of the reviewed factors. As clinicians and researchers, it is essential to identify the unique determinants of adiposity in an individual with obesity to tailor prevention and treatment techniques effectively.

Authors' contributions

Hoda C. Kadouh: drafting, writing, and critical revision of the manuscript.
Andres Acosta: drafting, writing, and critical revision of the manuscript.

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