

# **BODY WEIGHT REGULATION**

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#### ABSTRACT

Body weight reflects the chronic balance between energy intake and energy expenditure. The pathophysiology of weight loss and gain is complex with genetic, physiological, and environmental factors contributing to a person's ability to maintain, lose or gain weight. The inability for the body to counteract chronic caloric surplus leads to overweight and obesity. Among U.S. adults, overweight and obesity has dramatically increased over the last 60 years and, particularly within the past decade and more recently as a result of the COVID-19 global pandemic. The prevalence of children with obesity has also continued to rise, which is a major health concern for future generations. The objective of this chapter is to review of the current state of obesity in the United States, discuss mechanisms of body regulation in humans, and present key factors that may be contributing to its global epidemic.

#### INTRODUCTION

Body weight in the United States (US) has increased dramatically since the 1980s, with a steeper increase from 2011 to 2014 (Figure 1). Although controversial,

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to determine an individual's body weight status, body mass index (BMI) is calculated from weight in kilograms divided by height in meters squared. This results in a general classification for body weight ranges attributable to health risks, including normal weight (18.5 kg/m<sup>2</sup> > BMI < 24.9 kg/m<sup>2</sup>), overweight  $(25 \text{ kg/m}^2 > \text{BMI} < 29.9 \text{ kg/m}^2)$ , and obesity (BMI > 30  $kg/m^2$ ) (1). The National Health and Nutrition Examination Survey (NHANES) has been conducting BMI surveillance studies in the US since 1960. The first report (1971-1974) found that 44.9% of adults aged 20-74 years were living with overweight or obesity combined (2). The latest available survey 43 years later (2017-2018) reports that 31.0% of US adults are overweight and 42.8% are obese (3). Obesity prevalence is particularly high among American females, non-Hispanic Blacks, and individuals aged 60-69 years (3). Also, the prevalence of overweight and obesity in children (defined by weight for height above the 95<sup>th</sup> percentile for age) aged 2-20 years has increased from 14% to 19.2% and 3.9% to 6.1%, respectively, between 1992 and 2018. Hispanic, Mexican American, and Black children had a higher prevalence of developing obesity (26.9% and 24.2%, respectively) compared to non-Hispanic white children (16.1%) in 2017-2018 (4).



Figure 1. Prevalence of males and females aged 20-74 with overweight and obesity in the United States between 1988 and 2018. The table represents overweight and obesity trends overall. Values are ageadjusted by the direct method to the year 2000 U.S. Census Bureau estimates using the age groups 20-39, 40-59, and 60-74. Females who were pregnant were not included in the analysis. Source: CDC/NCHS, National Health Examination Survey and National Health and Nutrition Examination Survey.

The racial and ethnic disparities in overweight and obesity prevalence are a result of the effects of both social and environmental factors contributing to physiological changes over time (Figure 2). The growing health disparities following the COVID-19 pandemic encapsulate the interaction between social, environmental, and physiological components of health. Symptoms of COVID-19 were more severe in individuals with obesity, exposing them to greater risks of hospitalization, long-term comorbidities, and even death (5,6). Simultaneously, obesity prevalence increased at the height of the COVID-19 pandemic, most pointedly among children and individuals from marginalized backgrounds (7). During the pandemic, school shutdowns, limited access to exercise facilities and fresh foods, along with declining mental health rates culminated in increases in metabolic health risks including obesity, highlighting the importance of considering both biological and behavioral aspects of weight regulation (7,8). The worldwide acceleration in obesity prevalence is commonly explained by a gene-environment interaction. Overtime global populations have endured rapid socioeconomic shifts from their traditional environment where human manual labor was the primary driver of economic growth and sustainability, to a modern environment characterized by industrial and technological advances. This shift lessened the need for physical activity and changed the food supply, leading to physiological and behavioral adaptations among people. As illustrated in Figure 2, the "traditional" environment is defined by whole food consumption and high occupational physical activity levels entrained normal appetite regulation which was coupled with energy expenditure to result in maintained leanness (leptogenic) and a lower BMI. In contrast, the industrial revolution and technology boom promoted obesogenic behaviors, such as the consumption of abundant. sweetened. and inexpensive calorie-dense and ultra processed food sedentariness. (UPF) and In obesogenic environments, food intake is uncoupled from energy expenditure and the population has a higher BMI than compared to that of the leptogenic environment.



Figure 2. The potential effects of genetic and environmental drivers on adiposity are assessed by body mass index (BMI). Some concepts described in this figure were proposed by Bouchard et al. (9). This figure was reprinted with permission from Galgani & Ravussin (42).

The following sections review the physiological regulators of energy balance and weight loss and

maintenance to further understand the effects of changing environments on physiology and behaviors

that affect weight regulation. The chapter concludes with a discussion of physiological factors that are contributing to weight gain and obesity.

### ENERGY BALANCE

The balance between energy intake and energy expenditure determines the body energy stores (Figure 3). Energy intake is defined as the calories consumed and metabolized from food and drink, while energy expenditure consists of three components: 1) resting or basal metabolic rate - the energy required for basic organismal functions, 2) activity energy expenditure - the energy required for all nonsedentary activity, and 3) the thermic effects of food the energy needed to digest and metabolize food. The thermic effect of food makes up approximately 8-10% of the total energy expenditure, while activity energy expenditure and resting metabolic rates are highly variable depending on an individual's body composition and lifestyle. Fat free mass particularly is the largest determinant of energy expenditure (10). Energy is primarily stored in the body as fat. This renders the balance between energy intake and energy expenditure the main determinant of body fat acquisition and loss. For body weight to be maintained, a long-term energy balance with a possible variation of 100-250 calories per day (i.e., the energy imbalance gap) is required (11,12).

The energy balance equation (Energy Balance = Energy Intake - Energy Expenditure) is used to predict fluctuations in body weight when energy intake expenditure change. Despite or energy the intuitiveness of the energy balance equation, Alpert (13) elegantly demonstrated that it is inadequate for calculations on living organisms, given that it does not account for increasing or decreasing energy expenditure that ensues alongside weight gain or loss (14-16). Contrary to initial assumptions, small increases in energy intake sustained over several years do not lead to large weight gain. The more appropriate equation shown below incorporates the

use of rates by introducing time dependency and allowing the effect of changing energy stores (especially fat-free mass and weight) on energy expenditure into the calculation (13).

### Rate of Change of Energy Stores = Rate of Energy Intake - Rate of Energy Expenditure

This equation explains why a small initial positive energy balance (i.e., from an increased energy intake) will not lead to large weight increases over a number of years. After a short period of positive energy balance, the energy stores (fat mass and fat-free mass) will increase, in turn increasing energy expenditure thereby matching energy intake. These fluxes restore energy balance when there is a higher energy intake, greater energy expenditure, or larger energy stores compared to the initial energy balance state. Weight gain can therefore be viewed not only as the consequence of an initial positive energy balance, but also as the mechanism by which energy balance can eventually be re-established. This highlights the non-linear relationship between the changes in energy fluxes and the changes in energy stores.

To minimize fluxes in energy balance, it is important to calibrate energy intake with body weight. In January 2023. the National Academies of Science. Engineering, and Medicine published updated Dietary Reference Intake (DRI) providing the US and Canada populations with guidance on energy intake requirements to maintain a healthy weight status. The DRI includes estimated energy requirement equations for males and females in different age categories and separate DRI equations are provided for children, adolescents, and pregnant individuals. DRI equations account for factors contributing to energy expenditure such as gestational age, obesity category, and physical activity levels (17). In addition to providing energy intake estimates, the DRI also provides nutrient specific goals for maintaining a healthy weight and overall metabolic state. The following section will

explore the role of nutrient balance in body weight regulation.

### NUTRIENT BALANCE

Nutrition is a critical part of maintaining health and well-being and nutritional status affects clinical such as obesity. outcomes Nutrient intake requirements depend on various factors such as age, sex, and activity level. A classical approach to understanding how a chronic mismatch of intake and expenditure might occur is to examine dietary recommendations for macronutrients (i.e., carbohydrates, proteins, and fats) and their contribution to overall caloric intake.

An imbalance in nutritional intake can lead to malnutrition and hidden hunger (18,19). In the US, the Food and Nutrition Board of the Academy of Medicine issues nutrition recommendations for populations across the lifespan providing Acceptable Macronutrient Distribution Ranges (AMDR) that can be used to assess nutrient intake. The AMDR expresses intake recommendations as a percentage of total caloric intake for proteins (10-35%), carbohydrates (45-65%), and fats (20-35%) (20). These ranges are based on evidence from intervention trials, suggesting they provide the lowest relative risk for chronic diseases and should be tailored to the individual to ensure proper nutrient intake.

# **Protein Balance**

Protein stores constitute an important component of body composition, specifically lean body mass, and are vital for growth and development, physical functioning, and hormone balance. Protein stores respond to growth stimuli such as growth hormones, androgens, physical training, and weight gain. In addition, dietary protein intake is required to replace irreversibly oxidized amino acids that cannot be synthesized in the body (e.g., essential amino acids).

The AMDR for protein is 10-35% of caloric intake which is 1.05–3.67 g/kg of body weight/day when the reference body weights (57 and 70 kg for women and men, respectively) are used. This translates to an estimated energy requirement of 36.5 kcal/kg body weight/day (Figure 3) (21,22). The actual protein requirement of an individual depends on sex, body weight, lean body mass, activity level and other factors that influence the rate of protein synthesis and degradation (e.g., protein turnover). Protein stores are ~1% and therefore tightly controlled and physiological mechanisms exist to ensure protein balance is achieved in healthy individuals on a day-to-day basis (23). As such, protein imbalance is not a direct cause of obesity. The fate of excess protein is not in tissue storage, but excretion through urea or other metabolic pathways (24). In a controlled inpatient study, 25 healthy individuals were overfed diets that contained either low (5%), normal (15%), or high (25%) protein for 8 weeks (25). Individuals in the low protein group gained significantly less weight [3.16 kg (95% CI 1.88, 4.44)] compared to individuals in the normal [6.05 kg (95% CI 4.84, 7.26)] or high protein [6.17 kg (95% CI 5.23, 7.79)] groups (p=0.0016). Body fat increased similarly in all 3 groups and represented up to 90% of the excess stored calories implying that differences in body mass were due to differences in the accumulation of body protein or lean body mass [normal protein group: 2.86 kg (CI 2.11, 3.62); high protein group: 3.17 kg (CI 2.37, 3.98)]. To reconcile the contradicting understandings of the effects of protein imbalance on weight regulation, the protein leverage hypothesis suggests that a diet with a low protein to non-protein energy nutrients (i.e., carbohydrates and fats) ratio is compensated for by overfeeding and through increased energy intake (26). The idea is that the body [and brain] prioritizes protein intake to ensure a chronic protein deficit does not impact tissues and organs, and hence through signaling molecules such as FGF21 (fibroblast growth factor 21), energy intake is stimulated with the signal being inhibited when protein balance is achieved (27). In the modern obesogenic environment, an increase in caloric intake

for protein often accompanied is by an overconsumption of carbohydrate and fat. Prospective and cross-sectional studies have demonstrated that a smaller percentage of protein intake (e.g., <10%) can lead to excess energy intake (28). Compared to low carbohydrate and low fat diets, high-protein diets (>0.8 g/kg body weight/day) are often touted as robust nutritional strategies for weight management as protein increases satiety, reduces prospective food consumption and over time, leads to greater reductions in fat mass, supports lean mass growth, and increases thermic effect of food (25).

### **Carbohydrate Balance**

Dietary carbohydrates are eventually converted to glucose, which is the primary metabolic fuel for the body. Carbohydrates are stored as glycogen, yet the body storage capacity of glycogen is limited to 500-1000 g on average equating to ~2000-4000 kcals of energy stored as carbohydrates (500 g x 4kcal/g) (29). Dietary intake of carbohydrates corresponds to ~50-70% of carbohydrate stores, compared to ~1% for protein and fat (Figure 3). Because glucose is the main source of energy, the AMDR for carbohydrates is the highest of the macronutrients at 45-65% of caloric intake. The homeostatic regulatory mechanisms that euglycemia suggest that occur to maintain carbohydrate availability is important for energy balance. Intake of dietary carbohydrates stimulates both glycogen storage and glucose oxidation, thereby suppressing fat oxidation (30). However, a modern hypothesis to explain the increased prevalence of obesity is the carbohydrate-insulin model of obesity. Ludwig and colleagues postulate that diets with a large relative intake of carbohydrate elevate insulin section, thereby suppressing the release of fatty acids from adipose tissue (31). In turn, these decreases circulating fatty acid subsequently partitioning substrates away from fatty acid oxidation and directing them to adipose tissue storage. This metabolic dysregulation leads to a state of cellular 'internal starvation' triggering compensatory mechanisms of increasing hunger and decreasing energy expenditure (31,32). However, both animal models and human studies testing the carbohydrate-insulin model have mixed results, suggesting the important aspect of the model may relate to the relative intake of carbohydrate in the diet (31). Moreover, excess intake of carbohydrates during overall excess energy intake results in high levels of acetyl-CoA, which is eventually converted to malonyl-CoA, the precursor of de novo lipogenesis. During excess carbohydrate and energy intake, carbohydrate stores remain in balance while excess carbohydrates are converted to fat contributing to weight gain. This is supported by a large analysis of US dietary data that suggests the increased consumption of refined carbohydrates is positively associated with weight gain (33). While there is no clear evidence suggesting that altering the relative intake of total carbohydrate in the diet is an important determinant of energy intake (34), there is strong evidence that reducing total carbohydrate intake (e.g., < 45%) is effective for improving weight loss, highdensity lipoprotein cholesterol (HDL), and triglyceride profiles (35). Indeed, a large randomized controlled trial examining the effects of diets varying in carbohydrate to fat ratio on energy expenditure during weight loss found in participants consuming low carbohydrates (20%), energy expenditure was increased by an average of 209 kcal/day compared to a 91 kcal/day increase in the moderate carbohydrate group (40%). Therefore, lowering dietary carbohydrate increased energy expenditure during weight loss maintenance (36).

### Fat Balance

Dietary fat provides energy and essential fatty acids that cannot be synthesized in the body. Fatty acids, although often seen as harmful, are critical for life as they support membrane structure and function, cell signaling, steroid hormone production, and metabolism (37). The daily fat intake represents <1% of the total energy stored as fat (Figure 3), but the fat stores contain about 3 times the energy of the protein stores (38). The AMDR for dietary fats (20-35%) with the minimum recommendation ensuring there is adequate consumption of total energy and essential fatty acids to prevent atherogenic dyslipidemia that can occur with low fat, high carbohydrate diets (39,40). The maximum of 35% fat intake relies on limiting saturated fat and on the observation that higher fat diets lead to consumption of more calories often resulting in weight gain (39). Fat stores are the energy buffer for the body, and fat and energy balance are tightly positively associated (41). A deficit of 200 kcal of energy intake over 24 hours thus means that 200 kcal of energy expenditure comes from fat stores, and the same is assumed for an excess of 200 kcal of energy intake, which is stored as fat. As increased dietary fat intake leads to fat storage and, ultimately, to increased adipose tissue mass (42), a reduced fat oxidation that favors positive fat (and thus total) daily energy balance may indicate a greater predisposition to weight gain over time (43). This principal has been spontaneous demonstrated in conditions of overfeeding, where the entire excess fat intake was stored as body fat (44). One randomized controlled trial examining two 24-hr 200% overfeeding dietary intake (high carbohydrate and high fat) found a high fat overfeeding diet was linked to a decreased capacity to oxidize dietary fat, thereby leading to greater weight gain at 6 and 12 months (45). Interestingly, a 24-hour

fast also disrupted metabolic oxidation rates such that a lower (or higher) 24-h oxidation during fasting was associated with lower (or higher) 24-h oxidation during feeding and overfeeding, respectively (45).

In contrast to the other macronutrients, body fat stores are large and fat intake has little influence on fat oxidation (30,46). When a mixed meal is consumed, there is an increase in carbohydrate oxidation and a decrease in fat oxidation, demonstrating the macronutrient composition of a meal significantly affects metabolism. The addition of extra fat in a mixed meal does not alter the nutrient oxidation pattern (30,46). The amount of total body fat exerts a small, but significant, effect on fat oxidation, with higher body fat levels leading to higher fat oxidation. This may be a mechanism allowing for the attenuation of the rate of weight gain when high levels of dietary fat are consumed (47). Given that energy balance is the driving force for fat oxidation (41,47), fat oxidation increases when energy balance is negative (i.e., expenditure exceeds enerav energy intake). Additionally, the type of dietary fat consumed may have implications for metabolic health and weight balance, with recommendations encouraging the consumption of polyunsaturated fats over saturated fats for metabolic health (37).



Figure 3. The daily energy and nutrient balance in relationship to macronutrient intake, and oxidation for a 30-year-old female that is 90-kg and 165 cm tall with 35% body fat on a 2,400 kcal/day standard American diet (35% fat, 50% carbohydrate, 15% protein) (48). Energy stores were calculated using the energy coefficient for fat free mass (1.1 kcal/g) and fat mass (9.3 kcal/g) (49). Macronutrient intake and oxidation are based on individual energy requirements computed using the Dietary Reference Intake equations (17). Macronutrient percentage, equivalent to the USDA Dietary Guidelines for Americans (50), is shown on the left as absolute intake in kilocalories and on the right as a percentage of its respective nutrient store. Because carbohydrate and protein intake and oxidation rates are tightly regulated daily, any inherent differences between energy intake and energy expenditure therefore predominantly impact body fat stores. During chronic overfeeding (shown in red), the oxidation of carbohydrate and protein is increased to compensate for their increased intake and at the expense of fat intake and the increase in fat oxidation is not equally coupled with its intake. Thus, if sustained fat kilocalories are stored, fat stores expand, and body weight is gained. This figure was adapted with permission from Galgani & Ravussin (42).

### **Alcohol Balance**

Alcohol consumption is considered a risk factor for weight gain and obesity contributing to other noncommunicable diseases and early mortality (51). Alcohol, an energy dense diet component, provides 7 kcal/g. Evidence suggest there is a hierarchy in macronutrient oxidation rate during the postprandial state with the sequence alcohol > protein > carbohydrate > fat (52-54). Diet induced thermogenesis is increased after meals rich in alcohol (~20% of energy) (54), suggesting the body recognizes the caloric contribution of alcohol similar to the other macronutrients. The energy derived from alcohol consumption is additive to other energy sources, promoting positive energy balance and leading to weight gain (55). Alcohol consumed before or with meals induces an orexigenic effect, which increases appetite and reduces satiation via mediation of the rewarding perception of food leading to greater food intake (55). However, prospective studies demonstrate that light-to-moderate alcohol intake is not associated with adiposity gain while heavy drinking is more consistently related to weight gain (56). The differences interindividual between alcohol consumption habits and the types of alcohol (e.g. beer, wine, liquor) may have a differential impact on abdominal adiposity and weight gain (57). A population-based cross-sectional study found alcohol intake was inversely associated to relative body fat in women whereas spirits consumption was positively related to central and general obesity in men (57). This may reflect a variance effect by sex and the type of alcohol consumed on body weight regulation. While the imbalance between alcohol intake and oxidation may not be a direct cause of obesity, it may be linked to behavioral factors that are related to obesity.

### Energy Imbalance Is Buffered By Fat Stores

The intake of carbohydrates, protein, and alcohol, and subsequent oxidation rates, are tightly regulated. Amino acids, glucose, and alcohol oxidation rates adjust to the amount consumed. Fat oxidation, however, relies on various regulatory mechanisms such as leptin, peptide YY and ghrelin, to regulate energy expenditure, satiety, appetite and hence energy stores (58,59). Specifically, leptin, an adipose tissue derived hormone, controls adipose tissue mass by regulating energy intake and energy expenditure via negative feedback loop hormonal signaling to the hypothalamus (60). Lower leptin levels decrease energy expenditure and inhibit appetite regulation, which is an issue often observed in obesity (61). However, because fat provides a greater storage of energy, there may be a higher propensity for the body to store excess energy intake as fat, thus, directly contributing to the flux in adipose tissue mass and associated weight regulation (Figure 3). Another way energy imbalance is buffered by fat storage is through glucagon like peptide-1 [GLP-1], a gut hormone vital to glucose homeostasis, which acts through the GLP-1 receptor (62). GLP-1 decreases blood glucose levels by stimulating insulin secretion and by inhibiting glucagon secretion. These mechanisms decrease glucose production, endogenous subsequently reducing the need for energy intake and decreasing gastric emptying time (63,64). Obesity interferes with gut hormones' (e.g., GLP-1) ability to secret peptides (e.g. AgRP, peptide tyrosine tyrosine [PPY]), thereby interfering with the homeostatic control of body mass via energy intake (brain) and energy expenditure (metabolism) regulation (65).

### Is A Calorie Truly A Calorie?

Thermodynamically, а calorie is a unit of measurement that reflects the amount of energy needed to raise the temperature of 1 kg of water by 1°C. However, when evaluating the metabolizable energy content of calories from macronutrients, many factors influence the actual caloric value of food. For example, dietary fiber, often found in carbohydrate sources, has been shown to decrease transit time of food in the intestine, resulting in less time for digestion and absorption of energy (66). The thermic effect of food, the obligatory energy expenditure, increases with digestion and processing of ingested foods. Conversely, degradation of amino acids increases transit time of protein sources. Thus, diet composition has a strong effect on the thermic effect of foods with isocaloric amounts of protein having a greater thermic effect compared to carbohydrates and fat. Diets high in carbohydrates, fat, or both, produce a 4%-8% increase in energy expenditure (67), while meals high in protein cause an 11%-14% increase above resting metabolic rate due to the extra energy needed for amino acid degradation (68). One study comparing isocaloric low-fat and very low-carbohydrate diets found that total energy expenditure was approximately

300 kcal/day higher in the low-carbohydrate diet, an effect corresponding to the amount of energy typically expended in 1 h of moderate-intensity physical activity (69). As protein content was the same in both diets, the authors suggest the dietary composition differentially affected the availability of metabolic fuel types and efficiency, changes in hormone secretion, and skeletal muscle efficiency as regulated by leptin. As such, a calorie ingested does not necessarily correspond to a calorie absorbed, highlighting the importance of diet content on weight regulation. This is highlighted in an examination of a plantbased, low-fat diet versus an animal-based, ketogenic diet on ad libitum energy intake showing that the low-fat diet led to ~690 kcal/day less energy intake than the low-carbohydrate diet over 2 weeks (70). Furthermore, the same research group assessed the effects of UPF on energy intake finding an ultraprocessed diet increased calories (508 kcal/day), carbohydrates (280 kcal/day), and fat (230 kcal/day) when compared to an unprocessed diet (71). Notably, weight changes were highly correlated with energy intake with the ultra-processed diet leading to a ~1 kg weight gain in 2 weeks, whereas the unprocessed diet led to a loss of ~ 1 kg.

### DIETARY IMPLICATIONS FOR WEIGHT LOSS

Dietary modification is central for weight management and obesity treatment. A variety of approaches exist with weight loss diets including versions of energy restriction, manipulations of macronutrient composition, and dietary intake patterns (72). While caloric restriction is the most common method for weight loss, other methods such as time-restricted feeding, low-fat, and low-carbohydrate diets may be as effective. However, there are considerations with weight loss like weight cycling and disease status that should evaluated to ensure long-term success.

### **Calorie Restriction**

Calorie restriction followed by macronutrient modification are the primary non-surgical and nonpharmaceutical drivers of weight loss (73). Caloric restriction is the reduction of average daily caloric intake below what is typical or habitual without causing malnutrition or restricting the intake of essential nutrients allowing for the diet to provide sufficient micronutrients, fiber, and energy needed for metabolic homeostasis (74). Caloric restriction may be more successful than other dietary strategies because it is an eating pattern rather than a temporary weight loss plan. Several approaches can be taken to achieve caloric restriction. A prescribed eating plan that consists of 1,200-1,500 kcal/day for women and 1,500-1,800 kcal/day for men (75). Another approach is to determine baseline energy requirements, modify them to factor in an individual's level of physical activity, and create a 500 kcal/day (women) or 750 kcal (men) energy deficit. When caloric restriction is paired with behavioral changes (e.g., monitoring food intake, physical activity), an average weight loss of 8 kg by 6 months can be expected (75). Tools like the NIH Body Weight Planner that estimate energy intake required for the target weight loss can be useful for selfmanagement. Other options exist such as popular commercial diets such as Atkins, Weight Watchers, and Zone diets, which focus on macronutrient composition in addition to calorie reduction. These diets have shown modest long-term weight loss after 1 year (73). As discussed throughout this chapter, reducing daily calorie intake is the most important factor for weight loss and is outlined in the American College of Cardiology/American Heart Association Task Force on Practice Guidelines 2013 for the management of overweight and obesity in adults (76). Results from a systematic review and meta-analysis of 8 clinical trials concluded that 20-30% caloric restriction induced weight loss in overweight (-6.50 kg) and obese (-3.30 kg) adults, with greater weight loss in studies that were  $\geq$  6 to  $\leq$  11 months (-8.70 kg) and  $\geq$  12 months long (-7.90 kg) compared to studies of shorter duration of calorie restriction ( $\leq$  5 months; -4.26 kg). Further, 20-30% calorie restriction reduced fat mass in overweight (-3.64 kg) and obese adults (-2.40 kg), again, with greater losses with > 6 months of calorie restriction (-5.80 kg) compared to  $\leq$  6 months of duration (-1.91 kg) (77). However, more human clinical trials are needed to fully understand the longterm implications such as weight maintenance.

### **Time-Restricted Feeding**

In a fasting diet, an individual does not eat at all or severely limits dietary intake during certain times of the day, week, or month. Recently, intermittent fasting, limiting the number of hours (e.g., 6-8 h) each day food can is consumed, has become a popular and effective dietary pattern for weight loss, as the primary focus is on frequency of eating (78). This eating pattern may be a practical way to reduce caloric intake because there is less time for regular eating. Time-restricted feeding may improve body weight regulation through the extended fasting duration, which promotes the mobilization of free fatty acids and increases fat oxidation and the production of ketones (79). While there is no calorie goal for time-restricted feeding, there is about a 3-5% caloric reduction as a result of having less time to eat during the day (80). Currently, there are only a few human trials examining timerestricted feeding (eating window  $\leq$  8-10 h for  $\geq$  8 weeks). One study demonstrated weight loss of 3.3 kg (95% Cl -5.6 to -0.9 kg) with a self-selected 20% reduction in daily caloric intake estimates (81). Another study examining restricted feeding (without calorie counting) to an 8 h window (10:00 to 18:00) for 12 weeks demonstrated a 2.6  $\pm$  0.5% weight loss compared to control (82). Restricting energy intake to a short window during waking hours and extending the length of the overnight fast appears to provide metabolic and potential health benefits, but more human research is needed. Additionally, for timerestricted feeding to be effective, a reduced calorie intake relative to energy expenditure must be achieved. Compared to a traditional caloric restriction diet, time-restricted feeding may pose unique barriers to weight loss such as diet quality, scheduling conflicts, and social influences (80).

### Low-Carbohydrate vs Low-Fat

The most common adjustment to macronutrients for weight loss has been a reduction in fat intake since, in comparison to both carbohydrate and protein, fat contains more than twice as much energy per gram and fat tends to be overconsumed compared to dietary recommendations. Dietary macronutrient composition has been studied extensively regarding weight loss efficacy. The results of these studies were combined in a recent meta-analysis (83) where a total of 53 randomized controlled trials that imposed a low-fat diet or an alternative dietary intervention for 1 year. Collectively, these studies showed that dietary interventions targeting reduced fat intake do not lead to significantly greater weight loss than dietary interventions targeting reduced carbohydrate intake, which produced an average long-term weight loss of 1.15 kg (83). The reported weight loss with a low carbohydrate diet should be cautioned. It may be illadvised to tout low-carbohydrate higher-fat diets as superior to low-fat diets since only 1 extra kg of weight was lost, which can be considered irrelevant and even indicative of weight maintenance in clinical settings.

Low-carbohydrate diets have had positive effects on health: however. the reduction of refined carbohydrates can induce weight loss through a decrease in the insulin-induced action for lipogenesis (storage of excess carbohydrates in adipose tissue) and the action to inhibit lipolysis (84). Since refined carbohydrates are strong stimulators of insulin, the unintentional reduction in refined carbohydrates as a result of improved overall diet quality in lowcarbohydrate diets could be the reason for weight loss success (34). Furthermore, carbohydrates that are higher in fiber may reduce the metabolizable energy content leading to lower total calorie consumption. The low-fat versus low-carbohydrate diet debate for weight loss was recently put to the test in an elegant study conducted at the NIH (85). Individuals with obesity were randomized into 2 groups in an in-patient clinical setting where one group received 30% fewer calories from fat (~800 kcal/day) while keeping carbohydrates comparable to the baseline diet and the other group received 30% fewer calories from carbohydrates (~800 kcal/day) while keeping fat comparable to the diet. Interestingly, baseline only the reduced

carbohydrate group had an increase in fat oxidation, whereas the reduced fat group did not. However, the reduced fat group astonishingly had a greater rate of body fat loss even though fat oxidation was unchanged (85). The reduced carbohydrate group, however, saw a reduction in insulin secretion. The mathematical model that was used to simulate the effects of these 2 diets on weight and fat suggests that the reduced fat diet group would continue to show enhanced fat loss for up to 6 months (85). Although as energy balance is reached again with weight loss, differences in fat loss between groups will likely diminish over time. Additionally, systematic review and meta-analysis comparing 14 dietary macronutrient patterns demonstrated that most macronutrient diets resulted in modest weight loss over 6 months, but reduction and weight improvements in cardiometabolic factors largely disappeared after 12 months (86). This suggests that caloric restriction, regardless of whether the diet is low fat or low carbohydrate, can lead to weight loss.

Recently, the focus on intra-individuality surrounding carbohydrate and fat oxidation has gained momentum. In a 12-week weight loss study, 145 participants with overweight/obesity were identified as fat-responders or carbohydrate-responders based on their combined genotypes at 10 genetic variants, and then randomized to a high-fat or high-carbohydrate diet. However, weight loss did not differ between the genotypes (87). Another randomized control trial examining whether a low-fat diet compared to a lowcarbohydrate diet related to genotype patterns or insulin secretion found no significant differences in weight loss over 12 months between the low fat and low carbohydrate diets, and neither genotype pattern nor baseline insulin secretion was associated with the dietary effects on weight loss. Taken together, it appears that understanding who may benefit from a low-carbohydrate diet remains low-fat versus convoluted (88).

### Weight Cycling

Weight regain following weight loss is a common issue that people with obesity encounter. Common mechanisms of action that spur weight regain are related to gut hormone secretion profiles, changes in appetite and reward centers related to food, decreases in energy expenditure, and changes in composition (89). Indeed. body research demonstrates that the ratio of fat mass to fat-free mass in an individual can predict food and macronutrient intake impacting energy homeostasis (90). Even with assisted weight loss (e.g., anti-obesity medications, bariatric surgery), weight regain can occur. Repeated episodes of weight loss and regain is popularly known as 'weight cycling' (91). Although a standardized definition is lacking (92), a 5% weight loss and regain is a common clinical definition of weight cycling (93). Weight cycling is thought to have an adverse impact on metabolism and increase the likelihood of increased fat regain. The weight-reduced state elicits a complex response of hunger, increased metabolic efficiency, and reduced energy expenditure, which together favor weight regain (94). Specifically, weight regain can lead to collateral fattening, the process where excess fat is deposited because of the body's attempt to counter a deficit in lean mass through overeating. Under the weight regain conditions post weight loss, persistent hyperphagia driven by the need to complete the recovery of lean tissue will result in the excess fat deposition (hence collateral fattening) and fat overshooting (95). Achieving long-term weight requires overcoming neuroendocrine reduction systems that favor restoration of one's initial weight (96).

Population-based studies have shown that individuals who reported a history of large weight fluctuations over adulthood (besides pregnancy) had an increased risk for cardiovascular and all-cause morbidity and mortality (97-100). In 441,199 participants, body-

weight fluctuation was associated with increased risk for all-cause mortality (RR, 1.41; 95% confidence interval (CI): 1.27-1.57), CVD mortality (RR, 1.36; 95% CI 1.22-1.52), and morbidity of CVD (RR, 1.49, 95% CI 1.26–1.76) and hypertension (RR, 1.35, 95%) CI 1.14-1.61) (98). A weight fluctuation of 4.5 kg between the ages of 40 and 60 y significantly increased the relative risk for diabetes by 1.7, even more so than a weight gain by the same amount (101). Furthermore, larger fluctuations in weight were associated with higher fasting insulin (102), impaired glucose tolerance (103) and greater risk for metabolic syndrome (104) independently of BMI. An inherent issue with these data is separating the contribution of pre-existing conditions, unintentional weight loss, and BMI to the outcomes (105-109). Therefore, individuals should be counselled on weight loss and the importance of weight loss maintenance because subsequent weight regain might be worse for longterm health than maintaining the original obese state.

### Personalization of Weight Loss and Weight Loss Maintenance Interventions

The concept of precision medicine is rapidly gaining attention as an innovative approach for the management of obesity. Within this concept, individual differences in genes, demographics, environments, and lifestyles are considered for nutrition, exercise, and medical prescriptions. Individual-specific diet and physical activity components are identified and used for tailoring weight loss or weight maintenance strategies (110). By evaluating an individual's cardiometabolic profile and other risk factors associated with obesity, precision health directly targets the disease. Laboratory tests for the assessment of metabolic profiles, metabolomics, and nutritional status are recommended along with the assessment of diet quality.

Better understanding the differing phenotypes of obesity may aid in addressing anti-obesity treatment response heterogeneity among individuals. Obesityrelated cardiometabolic complications and metabolic disorders are often liked to a proinflammatory state (111). Yet, the occurrence of these obesity-related morbidities is not present in all individuals with obesity. Consequently, the terms "metabolically unhealthy obese" and "metabolically healthy obese", have been introduced to define individuals with obesity who have cardiometabolic risk factors or those who do not, respectively (112). While there is no standard definition of these obesity phenotypes, the most common criteria to define metabolically unhealthy obese are based on the presence of  $\geq$  2 of the 4 diagnostic criteria for metabolic syndrome (112). Other proposed criteria to identify obesity phenotypes are the presence of insulin resistance, high-sensitivity Creactive protein levels, and indices of visceral adiposity and fatty liver. Identifying the phenotype of obesity can provide a tailored approach to clinical care for those with overweight and obesity. Recent work by Acosta and colleagues suggests obesity presents in 4 distinct ways: hungry brain (abnormal satiation), emotional hunger (hedonic eating), hungry gut (abnormal satiety), and slow burn (decreased metabolic rate) (113). In a 12-month pragmatic weight management trial with 450 adults, 32% of patients were presented with hungry brain, 32% with hungry gut, 21% with emotional hunger, and 21% with slow burn. Addressing hedonic eating behavior (energy intake), homeostatic eating behavior (hunger, satiation, and satiety), and energy expenditure (resting metabolic rate) separately was shown by Acosta to deeper assessment of provide а potential mechanisms for precision health for obesity (113). Understanding the key determinants to an individual's eating behavior and energy expenditure is the first step in addressing weight management with behavioral counseling.

### FACTORS OF WEIGHT GAIN AND OBESITY

### Sedentary Lifestyle and Energy Intake

A NHANES analysis on physical activity in adults  $\geq$  18 years old reported that sitting time has increased 19 minutes in 2007-2008 to 2017-2018 (from 332 min/day to 351 min/day, respectively) (114), with the highest point of sitting time being in 2013-2014 (426 min/day) (114). In 2007-2008, 33.6% adults (n = 5838) reporting sitting < 4 h/day, 23.6% 4-6 h/day, 24.8% 6-8 h/day, and 18.0% > 8 h/day (same as above). Sitting time increased in 2017-2018, with 26.9% adults (n = 5350) were sitting < 4 h/day, 26.3% 4-6 h/day, 27.2% 6-8 h/day, and 19.7% > 8 h/day (same citation as above).

Increased sitting time contributes to a sedentary lifestyle due to factors such as limited availability/feasibility to exercise facilities, occupation (e.g., office/desk job), television, video games, and smartphones and devices. Exercise facilities may be too expensive or too far commute for some people and households to get to. Sedentary occupational activities and the associated drop in energy expenditure have been related to the gradual increase in bodyweight in the US population (115). There is also growing evidence for a strong association between hours/day spent watching television and obesity in adults (116) and children (117). The iPhone was first released in 2007 exposing the world to easy access to the internet, applications, and games, and it has been shown that smartphone use is associated with obesity in children and adolescents (118). Lastly, according to NHANES, the average energy intake for adults aged 20 to 64 years is approximately 2,093 kcals/day from 2017-2018, only increasing slightly from 2,044 kcals/day in 2007-2010 (119). Based on the Dietary Guidelines for Americans 2020-2025 (120), the average calorie needs for adults ranges from 1,600 to 2,400 kcals/day for females and 2,000 to 3,200 for males (website above) depending on activity level and exact age (website above). Although US adults have not necessarily increased overall mean energy intake over the past 10-15 years, adults may be consuming more than the recommended number of calories per day which combined with increased sedentary behavior (e.g., sitting time) is likely contributing to weight gain and obesity.

### **Diet Quality and Ultra-Processed Foods**

Overall diet quality is shown to contribute to weight gain and obesity (121). Increasing consumption of whole foods such as whole grains, vegetables, fruits, and fibers have been associated with weight loss and reduction of caloric intake (122) as well as lower rates of long-term weight gain (123,124). However, the opposite is found with the typical Westernized diet, which is known to be high in sugar, calories, and portion sizes (122,124). Diet index scores classify the quality of the diet, such as the NIH Healthy Eating Index (HEI). HEI score is widely used to assess diet quality based on the US Department of Agriculture 2015-202 Dietary Guidelines for Americans (125). Calculated on a scale of 0 (lowest quality) to 100 (highest quality), the HEI contains 13 components, 9 of which are classified as beneficial (total fruits, whole fruits, greens and beans, total vegetables, whole grains, seafood and plant proteins, fatty acids, total protein foods, and dairy) and 4 as harmful (sodium, refined grains, added sugar, and saturated fats) (125). A higher HEI score is indicative of a healthier diet and associated with lower BMI (126). NHANES analysis of 24-h food recall showed that a 1-point increase in HEI score was associated with a 0.8% decreased risk for abdominal obesity in adult women and 1.4% decreased risk in adult men (126,127). From 2001-2002 to 2017-2018, HEI-2015 decreased 47.82 to 45.25 (of 100 result in lower than the 50<sup>th</sup> percentile for diet quality) in adults 65 years and older who completed the NHANES 24-h dietary recall (125). Furthermore, another NHANES analysis of 24-h recalls in adults 20 years of age and older indicated that HEI-2015 for the overall population significantly decreased from 2011 to 2018 (128).

A possible reason for diet quality decreasing in the US could be due to the increase of UPF (129). UPF have

become a large source of dietary food intake in highincome countries, including the US (130), and such foods have become increasingly available around the world due to the globalization of food systems (i.e., post 1970s). UPF are foods that have 5 or more ingredients, including chemically synthesized ingredients that are not found in unprocessed or minimally processed foods, such as artificial sweeteners, hydrogenated oils, and colorants (131,132). UPF are cheaper for consumers as they are mostly produced from high yielding crops such as soy, wheat, and maize. Data indicates that sales of UPF, but not ultra-processed beverages, per capita have been steadily increasing since 2012 in the US (130). A NHANES cross-sectional analysis in US adults age >19 years indicates that UPF consumption increased from 2001-2002 to 2017-2018 (129). Further, consumption of UPF has been positively associated with obesity possibly due to being energy dense and containing higher levels of trans- and saturated fatty acids, sodium, sugar, and refined carbohydrates (132). A randomized controlled clinical trial showed that energy intake was significantly increased in weight-stable adults during the UPF diet compared to the unprocessed food diet, with increased consumption of carbohydrates and fat (71). Weight gain was also correlated with UPF diet while losing weight was correlated with the unprocessed food diet (71).

# Intrauterine and Intergenerational Effects

As obesity is continuously rising, the prevalence of obesity in pregnant women has also increased (133). In addition to the interrelated physiological and environmental components affecting metabolism, recent work shows that obesity (and other disorders) may be the result of genetic and epigenetic programming that occurs *in utero* and can be traced back up to two generations (Figure 4). Genetics alone are unlikely to be causing the ballooning of obesity observed the past decades, as genetic mutations are the result of evolutionary pressures occurring over

multiple generations (134,135). Instead, environmental factors contributing to physiological changes can have implications for health and weight regulation in future generations. Rodent studies show that overfeeding results in increased body weight and adiposity both in sample animals and also in their offspring across 3 generations (136). Environmental changes, such as the shift towards predominantly obesogenic environments promote the expression of so-called "mal-adaptive" genes, predisposing the offspring to greater metabolic health risks (137). Accumulating evidence suggests that predisposition to obesity starts in utero if not earlier. Epigenetic factors such as the intrauterine environment affect health and phenotype outcomes in the offspring. Pregnant individuals with obesity are at risk for having infants born large for gestational age, which increases the infant's risk for adult-onset obesity (138). Furthermore, pregnant individuals with obesity are also at higher risk of having overweight or obesity during postpartum and entering a subsequent pregnancy with obesity, perpetuating a cycle of weight gain, putting both parent and child at risk of adverse health outcomes. Lifestyle interventions during pregnancy focusing on altering the maternal milieu through increased physical activity, time-restricted eating, and individual feedback are likely to lead to healthy pregnancies and outcomes (139-142).

# **Obesogenics (Endocrine Disrupting Chemicals)**

Obesogens, ingested or internalized environmental chemicals, interfere with endocrine signaling leading to adiposity and weight gain (143). Increased exposure to endocrine disrupting chemicals (EDCs) in the past half-century is both an ecological and a health concern. EDCs can be naturally occurring or manmade chemicals, with the most common including bisphenol A (BPA; used in plastic manufacturing), pesticides, phthalates (liquid plasticizers common in food packaging, cosmetics, and fragrances), and perand polyfluoroalkyl substances (PFAS; chemicals common in paper, non-stick pans, and clothing) (144). All of these substances affect numerous metabolic outcomes, including adipocyte differentiation, number, size, and function, lipid profiles, energy intake, energy expenditure, the gut microbiome, basal inflammation, and insulin resistance (145). The most common methods of exposure include in utero, environmental exposures, food and beverages, cosmetics. household products, pollution, drugs, medical devices, and toys. Early exposure leads to higher risk for subsequent disease development later in life, as the umbilical cord, placenta, and breast milk are primary accumulation locations of EDCs and routes of exposure to developing young at their most susceptible (146). Given the abundance of obesogens in our everyday lives, it is imperative the obesogen hypothesis/model of obesity receive greater attention by the broader scientific community as a potential contributor to the increased prevalence of obesity.

#### SUMMARY

In the US, overweight and obesity among adults and children has dramatically increased in the last 50 years. While body weight is ultimately regulated by the interplay between energy intake and energy expenditure over the long term, it is likely that the drastic environmental changes that have occurred over the past decades have dramatically contributed to the epidemic of obesity. Changes in our environment not only directly influence the mechanisms regulating energy intake and energy expenditure, but also may indirectly reprogram the genetic and epigenetic background of human beings predisposing future generations to weight gain and adiposity. The obesity epidemic can be considered a predictable adaptation to changes in the pathogenic environment. In addition, more emphasis is being placed on the macronutrient content of diets. Not only are low-carbohydrate and low-fat diets showing differences in substrate use and fat loss, but lowprotein diets may have a new place in the regulation of body weight due to the activation of FGF21. Although these various effects of each macronutrient are intriguing, it may still be the case that all calories are equal, and that weight loss follows a negative energy balance. Weight cycling resulting from repetitive intentional fluctuations in weight loss and regain is becoming more prevalent as well and could have negative implications on health. Furthermore, other factors that could be contributing to the consistent rise in obesity include increased sitting time, energy intake, consumption of ultra-processed food (UPF) and obesogens. This is something that must be addressed appropriately because it could add to an increased prevalence of cardiovascular episodes and other morbidities in upcoming decades.

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