REGULATION OF BODY WEIGHT IN HUMANS

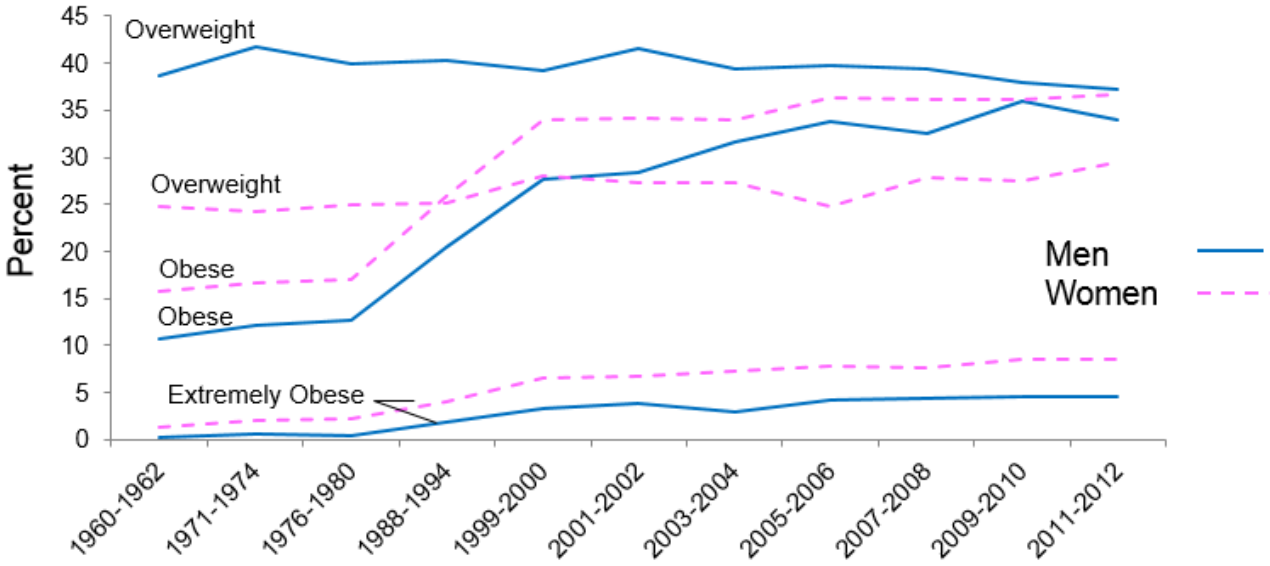
Nicholas T. Broskey, PhD Postdoctoral Fellow, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808
Darcy Johannsen, PhD Assistant Professor, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808
Leanne Redman, PhD Associate Professor, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808

Revised February 2016

ABSTRACT
Overweight and obesity among adults has dramatically increased in the last 50 years in the United States, although more recently the trend being that of a slight plateau. However, the rise of obesity in children has continued to increase, which is a major health concern for future generations. Body weight regulation is typically thought of as a balance between energy intake and energy expenditure, but other physiological and environmental factors likely contribute to the epidemic of obesity. These factors may influence the mechanisms regulating energy intake and energy expenditure but also indirectly reprogram the genetic and epigenetic background of human beings predisposing future generations to weight gain and adiposity. The environments that we reside in and how we adapt can also influence the obesity epidemic. In addition, more emphasis is being placed on the macronutrient content of diets. Not only are the typical low-carbohydrate and low-fat diets playing a role, but low-protein diets may have a new place in the regulation of body weight. Although the effects of each macronutrient may be slightly different, it seems be the case that weight loss still follows a simple negative energy balance. Weight cycling resulting from repetitive intentional fluctuations in weight loss and weight regain is becoming more prevalent as well and could have negative implications on health. This chapter will begin with a brief overview of the current state of obesity in the United States, discuss how body weight is regulated in humans and will follow with discussion of some of the key environmental and physiological factors proposed to contribute to epidemic of obesity.

INTRODUCTION
Body weight in the United States has increased dramatically since 1980 (Figure 1). In epidemiological studies, the body mass index (BMI) calculated as weight in kilograms divided by height in meters squared is used to classify body weight. Body weight is considered to be healthy when the BMI is between 18.5-24.9 kg/m^2. An individual is classified overweight with a BMI of 25-29.9 kg/m^2 and obese with a BMI >30 kg/m^2. The National Health and Nutrition Examination Survey (NHANES) has been collating data for BMI in the United States since 1960. The first report (NHANES I) found that 44.9% of adults aged 20-74 years were overweight or obese [1]. Data from the NHANES 2007-2008 report indicate a dramatic increase in the prevalence rates of overweight and obesity in adults (Figure 1). A staggering 68% of the population studied was overweight or obese [2]. While the prevalence of overweight increased by only ~4% in forty years, the prevalence of obesity almost tripled from 13.3% in 1960-62 to 33.8% in 2007-2008 [2]. Data from the 2009-2010 census do not suggest any further marked increase in the prevalence of obesity (Figure 1). As for gender, the prevalence of obesity has leveled off in women, while it still appears to be rising in men [2, 3]. Similar trends indicating stability were also described in other Westernized Countries in a comprehensive analysis of 52 national surveys [4]. The most recent data from 2011-2012 is in line with the previous report from 2009-2010 in that 35%, or more than 78 million, adults are obese with the highest amount being in middle-aged adults and not differing by gender. Over the last decades, body weight also increased dramatically in children and adolescents. The prevalence of overweight (defined by weight for height above the 95th percentile for age) more than tripled from 5% in 1971-74 to ~17% in 2007-08 and remained stable at ~17% in 2011-2012 [5]. However, the prevalence of young children (age 2-5) has shown a decrease in obesity from 13.9 in 2003-2004 to now 8.4%.

Despite this encouraging plateau, the overall prevalence in children and adolescents remains very high and represents a major public health concern, particularly in children aged 6-11 and 12-19. The highest percentage of obese children was made up by the Hispanic population (22.4%) and followed closely behind by African Americans (20.2%).



	Overweight (25<BMI<30)	Obese (BMI ≥30)	Extremely Obese (BMI≥40)
1976-1980	32.1%	15.0%	1.4%
1999-2000	34.0%	30.5%	4.7%
2007-2008	34.2%	33.8%	5.7%
2009-2010	33.0%	35.7%	6.3%
2011-2012	33.9%	34.9%	6.4%

Figure 1

The secular rise in overweight and obesity can be explained by physiological and behavioral factors as well as changes in social and environmental cues (Figure 2). The coming sections will describe the physiological regulators of energy balance and hence body weight, as well discuss the growing list of putative environmental and behavioral changes over the last 40 years that probably play a role in the epidemic of obesity of the new millennium.

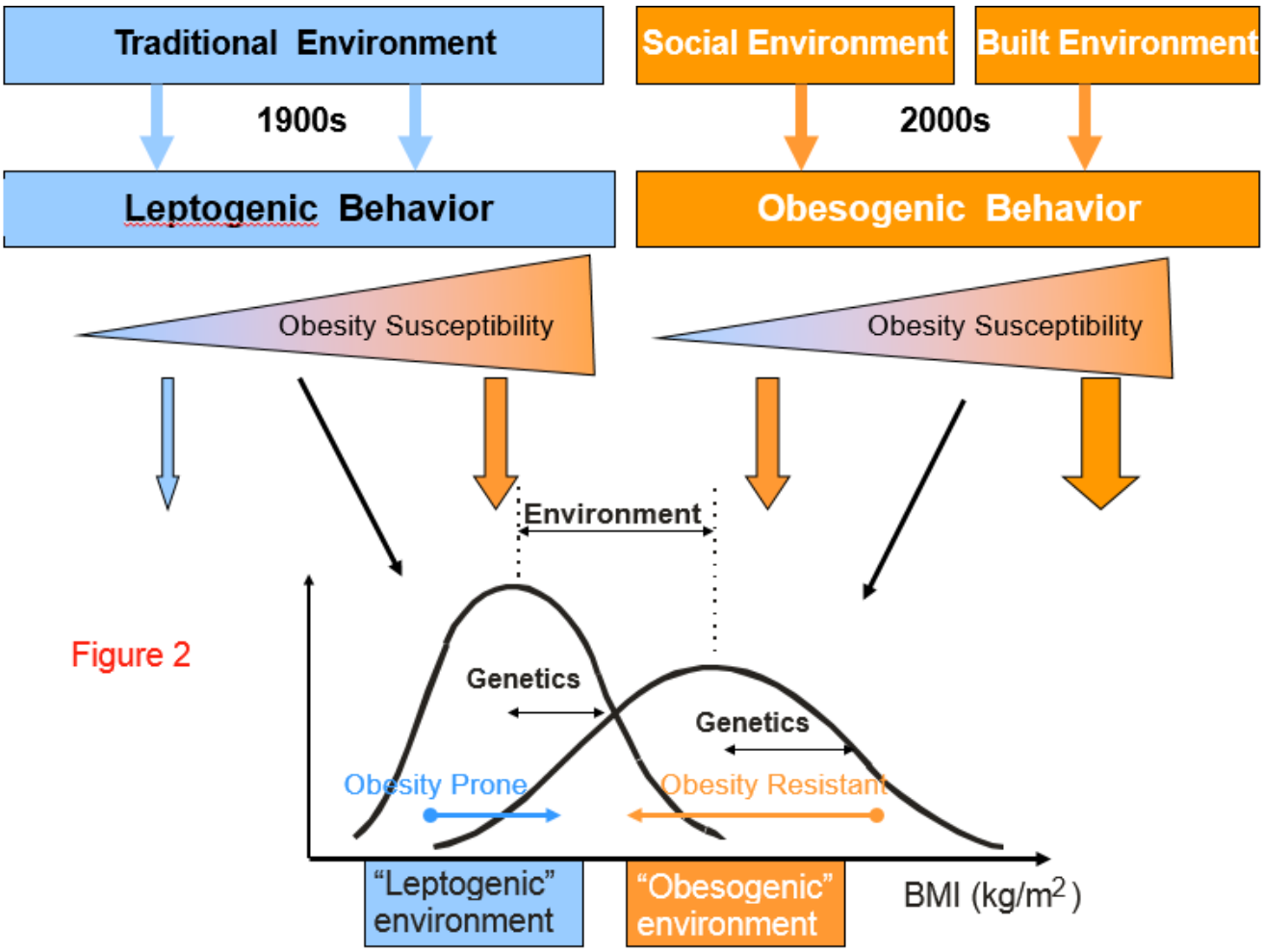


Figure 2

ENERGY BALANCE

The balance between energy intake (calories consumed) and energy expenditure (calories burned) determines body energy stores (Figure 3). The majority of the energy is stored in the body as fat; therefore, the balance between energy intake and energy expenditure primarily determines whether body fat and hence body weight, is gained or lost.

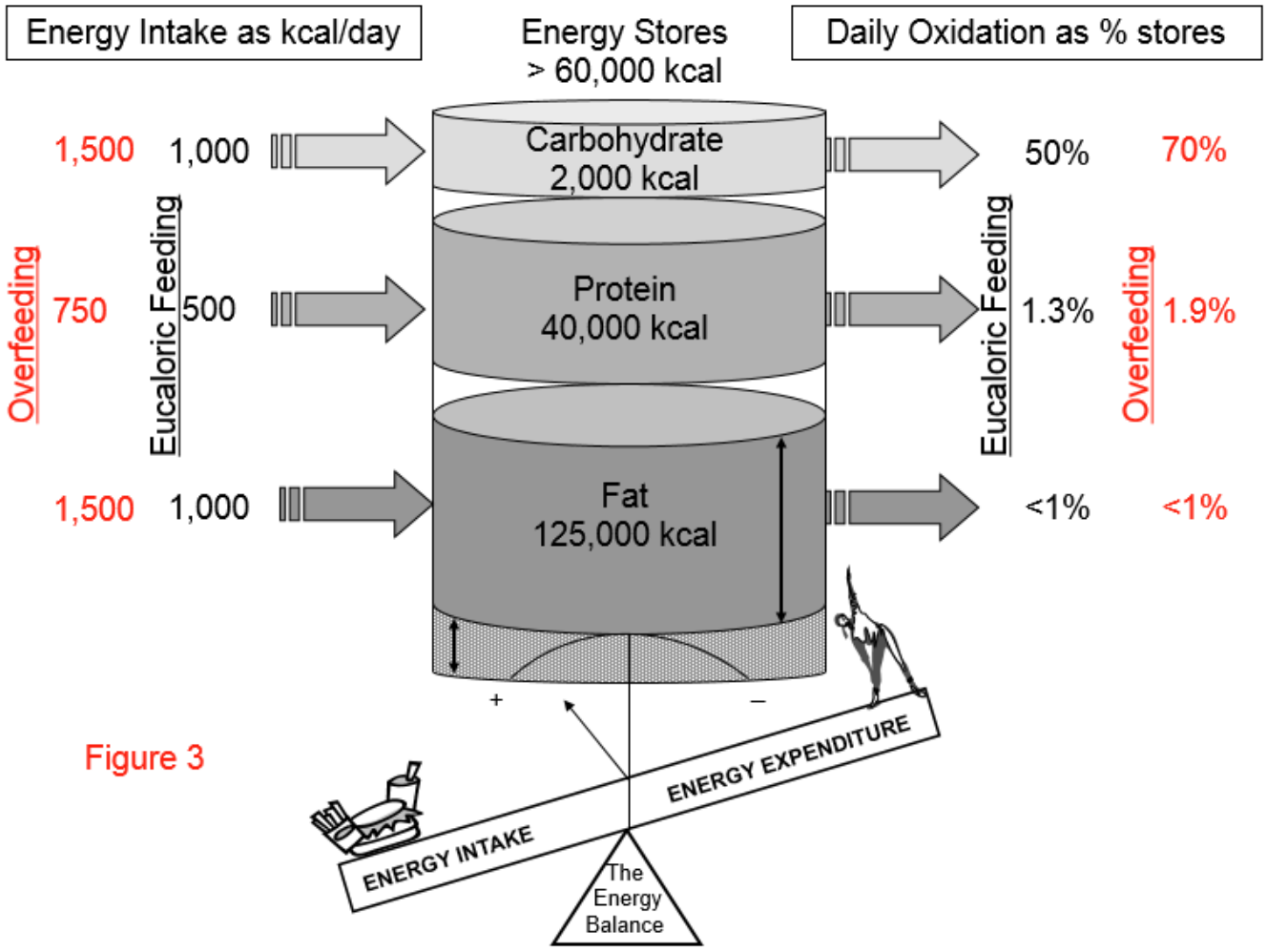


Figure 3

Given that all living organisms comply with the first law of thermodynamics, the energy balance equation has been used to predict changes in body weight when energy intake or expenditure is changed. However, the classic equation of energy balance, which states that the body energy store is equal to energy intake minus energy expenditure, has provided both insight and confusion in the understanding of energy balance in humans. Much of the confusion comes from inappropriate energy calculations using a static equation of energy balance. This equation is self-evident and reasonably accurate when body weight is maintained. Therefore if body weight and hence energy stores are stable it is likely that the energy flux is balanced between what is consumed and what is expended (Energy Intake = Energy Expenditure).

The most common equation used in discussions and calculations of energy balance is referred to as the static energy balance equation (below).

Change in Energy Stores = Energy Intake - Energy Expenditure

Intuitively, the equation appears valid, but Alpert [6] elegantly demonstrated that it is inadequate for calculations on living organisms, because it does not take into account the increasing energy expenditure that ensues as a result of the increasing weight [7-9]. A small initial increase in energy intake sustained over a number of years therefore cannot lead to a large weight gain, as is often claimed.

The more appropriate equation shown below incorporates the use of "rates" because it introduces time dependency thereby allowing the effect of changing energy stores (especially fat-free mass and weight) on energy expenditure to enter into the calculation [6].

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

This equation explains why a small initial positive energy balance (for example, from an increased energy intake or a lower thermic effect of food) 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 and cause an increase in energy expenditure which will balance the increased energy intake. The individual will then once again be in energy balance, but now with a higher energy intake, greater energy expenditure, and larger energy stores. 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 is eventually re-established. This highlights the non-linear relationship between the changes in energy fluxes and the changes in energy stores.

Recently, mathematical models capable of capturing this complex relationship were developed and validated from complex clinical and population-based studies. When applied to individuals and populations, changes in energy intake and/or changes in energy expenditure or body energy stores can be estimated. These models thereby can be used to simulate the effect of manipulating dietary intake (dietary restriction or overfeeding) on bodyweight and composition changes for an individual, and also to evaluate the efficacy of changes to public health policy, such as taxing sugar-sweetened beverages or subsidizing “healthy foods” [10]. Moreover, these models shed some light into the dynamics of the relationship between the changes in energy intake and changes in energy stores [11, 12] and the role of physical activity in modulating this relationship [13].

NUTRIENT BALANCE

A more classical but fruitful approach to understand how energy intake is balanced against energy expenditure and how a chronic mismatch might occur, is to dissect the energy balance equation into its various macronutrient components.

If the origins of a positive energy balance lie in the chronic imbalance of energy intake and expenditure, an appropriate question is: "What conditions allow a long-lasting imbalance between intake and expenditure to occur?” An examination of each nutrient balance equation to determine if a chronic imbalance between nutrient intake and oxidation exists is only valid if each nutrient has a separate balance equation, implying separate regulation. In practical terms: Is each nutrient (protein, carbohydrate, fat and alcohol) either oxidized or stored in its own compartment (separate regulation), or does it get converted into another compartment for storage?

Protein Balance

Protein intake is usually about 15% of calories and the protein stores in the body represent about one-third of the total stored calories in a 70 kg man. The daily protein intake amounts to a little over 1% of the total protein stores [14, 15] (Figure 3). The protein stores increase in size in response to growth stimuli such as growth hormone, androgens, physical training, and weight gain, but do not simply increase from increased intake of dietary protein. Protein stores are, therefore, tightly controlled and on a day-to-day basis protein balance is achieved [16]. Protein imbalance is therefore, not implicated as a direct cause of obesity although, as with the other non-fat nutrients, protein intake may affect fat balance [15]. However, in a controlled inpatient study where 25 healthy individuals were overfed diets that contained either low (5%), normal (15%) or high (25%) protein for 8 weeks [17], 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). Interestingly, body fat increased similarly in all 3 groups and represented up to 90% of the excess stored calories,

which implies that differences in body mass were due to differences in the accumulation of body protein or lean body mass [LBM, NPD: 2.86 kg (CI 2.11, 3.62); HPD 3.17 kg (CI 2.37, 3.98)].

Carbohydrate Balance

Carbohydrate is usually the main source of dietary calories, yet body stores of glycogen are very limited: 500-1000 grams on average [18]. Daily intake of carbohydrate corresponds to about 50-70% of the carbohydrate stores compared to about 1% for protein and fat [19] (Figure 3), so that over a period of hours and days, the carbohydrate stores fluctuate markedly compared with those of protein and fat. However, as with protein stores, carbohydrate stores are tightly regulated [20]. Even if all the details of this regulation remain to be established, the control is based on humoral and/or neural signals exchanged between the muscle, the liver and the brain. Dietary carbohydrate stimulates both glycogen storage and glucose oxidation and suppresses fat oxidation [21]. Carbohydrate which is not stored as glycogen is oxidized (not converted to fat), and carbohydrate balance is achieved [19, 21]. Therefore, as with the other non-fat nutrients, a chronic imbalance between carbohydrate intake and oxidation cannot be the basis of weight gain because storage capacity is limited and controlled, conversion to fat is an option which only occurs under extreme conditions in humans, and oxidation is increased to match intake. However there is one exception to this rule. In situations of high acetyl-CoA (excess intake of carbohydrate in the face of excess energy intake overall), acetyl-CoA will be converted to citrate, and an accumulation of citrate will cause it to be transported out of the mitochondria into the cytosol where it is converted back to acetyl-CoA and acetylated to form malonyl-CoA – which the first step in de novo lipogenesis. Therefore in situations of excess carbohydrate and energy intake, carbohydrate store remain in balance and excess carbohydrates are converted to fat which can contribute to weight gain.

Fat Balance

In marked contrast to the other nutrients, body fat stores are large and fat intake has no influence on fat oxidation [19, 21]. As with protein, the daily fat intake represents less than 1% of the total energy stored as fat, but the fat stores contain about three times the energy of the protein stores [14] (Figure 3). These fat stores are the energy buffer for the body and the slope of the relationship between energy balance and fat balance is equal to one in conditions of small day-to-day positive or negative energy balances [16]. A deficit of 200 kcal of energy over 24 hours means 200 kcal comes from the fat stores, and the same holds true for an excess of 200 kcal of energy which ends up in the fat stores. Even in conditions of spontaneous overfeeding the entire excess fat intake is stored as body fat [20].

Ingestion of a mixed meal is followed by an increase in carbohydrate oxidation and a decrease in fat oxidation and the addition of extra fat does not alter that mix of nutrient oxidation [19, 21]. What promotes fat oxidation if it is not dietary fat intake? The amount of total body fat exerts a small, but significant, effect on fat oxidation and this promotion of fat oxidation at higher body fat levels may represent a mechanism for attenuating the rate of weight gain [22]. Energy balance is the driving force for fat oxidation [16, 22]: when it is negative (i.e., energy expenditure exceeding intake), fat oxidation increases. After a few days, some individuals can however increase their fat oxidation in response to an increase in dietary fat under eucaloric conditions [23].

Alcohol Balance

There is an inconsistent relationship between reported alcohol intake and body mass index, with many studies showing a negative relationship [24, 25]. However, it has been shown that in healthy individuals the fate of ingested alcohol is oxidation and not storage (as fat), and therefore perfect alcohol balance is achieved [26]. In the same manner as dietary carbohydrate and protein, alcohol diverts dietary fat away from oxidation and towards storage and inhibits lipolysis. Therefore a chronic imbalance between alcohol intake and oxidation cannot be a direct cause of obesity, although by contributing to overall energy balance, it may indirectly influence fat balance [27].

Energy imbalance is buffered by fat stores

The concept that the imbalance between energy intake and energy expenditure is buffered by changes in fat stores was introduced by Flatt [28]. As a consequence of the fact that amino acids, glucose and alcohol oxidation rates adjust themselves to the amount consumed, fat oxidation ends up to be determined primarily by the 'gap' between total energy expenditure and energy ingested in the form of carbohydrates, protein and alcohol rather than just the amount of fat consumed on a given day. Therefore under physiological conditions, fat is the only nutrient capable of maintaining a chronic imbalance between intake and oxidation; thus, directly contributing to the flux in adipose tissue mass. The other macronutrients influence adiposity indirectly given their contribution to overall energy balance and thus fat balance as emphasized by Frayn [29]. The use of the fat balance equation instead of the energy balance equation offers a new framework for understanding the pathogenesis of obesity (Figure 3).

Is a calorie a calorie for body weight loss?

As explained above, the long-term prevention of weight gain is accomplished by an effective balance of energy intake to energy expenditure, with the former being some type of manipulation of macronutrient composition to create a deficit in energy balance. 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. Dietary macronutrient composition has been studied extensively in regards to weight loss efficacy. The results of these studies were combined in a recent meta-analysis [30] where a total of 53 randomized controlled trials that imposed a low-fat diet or an alternative dietary intervention for one 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 1.15kg. The reported weight loss with a low carbohydrate diet should be cautioned. It may be ill-advised to tout low-carbohydrate higher-fat diets as superior to low-fat diets since only 1 extra kilogram of weight was lost, which can be considered irrelevant and even indicative of weight maintenance in clinical settings.

When low-fat diets are successful in achieving weight loss, it is not known if the majority of the success can be owed to the unintentional elimination of refined carbohydrates from the diet or from the intentional elimination of fat. It is hypothesized that a reduction of refined carbohydrates can induce weight loss through a reduction in the insulin-induced action for lipogenesis (storage of excess carbohydrates in adipose tissue) and the action to inhibit lipolysis. Since refined carbohydrates are strong stimulators of insulin, the unintentional reduction in refined carbohydrates as a result of improved overall diet quality in low-fat diets could be the reason for weight loss success. The low-fat versus low-carbohydrate diet debate for weight loss recently tested in an elegant study conducted at the National Institutes of Health [31]. Obese individuals were randomized into two 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 baseline diet. Interestingly, 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. This leads one to question whether there is a difference between a calorie from carbohydrate or a calorie from fat. As stated above, the lowering of refined carbohydrates in a diet can reduce insulin secretion and the reduced carbohydrate group indeed had a reduction in insulin secretion. The mathematical model that was used to simulate the effects of these two diets on weight and fat suggests that the reduced fat diet group would continue to show enhanced fat loss for up to 6 months. Although this would eventually be minimized by the body to show little differences between the two groups in regards to fat loss over a longer term. More research is necessary to better understand how varying macronutrient consumption can alter body composition.

DETERMINANTS OF WEIGHT GAIN AT THE TURN OF MILLENIUM

Over the past several decades, humans living in industrialized countries have been challenged with relatively sudden and momentous changes in the environment. Agricultural and technological revolutions have coincided to allow significant changes to occur in both energy intake and energy expenditure [32]. The current Western environment supports sedentary behavior by allowing for profound reductions in the amount of physical activity necessary to exist and function successfully. One of the most remarkable occurrences of the past 50 years is that humans have devised methods for producing mass quantities of low-cost, energy dense foods with very minimal input of physical labor needed to produce these foods. The excess food availability and physical inactivity combined have created an "obesogenic" environment that promotes energy imbalance and weight gain in everyone, but more in those genetically susceptible (Figure 2). Other significant trends in energy intake and expenditure that have occurred over the past 20 – 50 years and coincided with the significant increase in weight gain and the prevalence of obesity are:

Changes in Energy Intake

According to food supply data (which provides an estimate of food availability) and results from large-scale dietary surveys, American adults are consuming more calories today than they were in the 1970s [33-35]. In particular, a large increase in caloric intake occurred between 1985 and 2000. In 2000, the average daily calorie consumption was 12 percent, or approximately 300 kcal, more than that consumed in 1985 [36]. Of that 300 kcal increase, grains (mostly refined) accounted for 46%; added fats, 24%; added sugars, 23%; fruits and vegetables, 8%; and meat and dairy consumption declined 1%. Between 1997 and 2000, consumption of added fats increased dramatically by 16%, from 56 to 64 g per day on average [36]. The increase in fat consumption is suggested to be a major player in the obesity epidemic, since consuming a high fat diet is associated with dysregulation of normal satiety mechanisms meant to regulate energy balance (i.e., humans overcompensate energy requirements when eating foods high in fat) [37].

Another major change in the American diet over the past 30 years is the consumption of refined sugars. In the United States, the per capita consumption of all refined sugars was 55.5 kg in 1970, and by 2000 this number rose to 69.1 kg, a staggering 25% [38]. The Dietary Guidelines for Americans 2010 recommend that consumers limit added sugars to 12-32 g/day for a 2,000 kcal diet, whereas it is estimated that approximately 115 g of total added sugars per day were consumed in 2009 [39]. The quality of added sugars has also changed in recent years with the invention of high-fructose corn syrup in the 1970's [38]. This invention stimulated the 22% increase in average consumption of added sugars between 1980 and 2000, since the intake of high-fructose corn syrup rose from practically zero in the 1970s to 55 g per capita per day in 2000 [36], the majority of which is being consumed as sugar-sweetened beverages. A recent study indicates that the intake of added sugars peaked in the early 2000's and is now declining, and that this decline is concomitant with the leveling off of the prevalence in obesity [40]. The existence of abundant carbohydrates and fats in a highly refined form has increased the energy density of the U.S. diet and has also decreased the satiety index [14, 32].

A change in the portion size of foods appears to have contributed to the increase in obesity rates. Compared with similar older data, current portions of restaurant foods, grocery products, and cookbook recipes have increased in size in every food category except bread [41]. Portions started to expand in the 1970s, increased sharply in the 1980s, and continue to rise today. Recent analyses of nationally representative survey data show that self-reported portion sizes of foods consumed has increased between 1977 and 1998 [42, 43] and this has occurred both inside and outside of the home, with the largest increase in portion size occurring at fast-food establishments [42]. Indeed, the increase in obesity prevalence has coincided with an increase in the number of meals eaten outside of the home [33], and the frequency of eating out is associated with increased energy and fat intake [44] and higher BMI [45]. Frequent snacking is thought to be another likely culprit of the obesity epidemic. Although consumption of snack foods and snacking (consumption of calories between meals) has increased substantially from 1977 to 2006, many RCT studies have shown no association between body weight and snacking [46].

Food deserts, or regions in the United States that have scarce access to grocery stores that sell healthy and fresh affordable foods, are a relatively new concept that is thought to contribute to obesity prevalence in particular areas of the country. More specifically a food desert is defined as a region that has a poverty rate of >20% and at least one-third of the population reside >1 mile from a large grocery store [47]. Although it is true that low income communities reside in these food deserts, it is hard to dissect whether these deserts are a cause of obesity by providing foods higher in fat and sugar content or more so, the stores choose to reside in lucrative areas where fast-food is desired [48]. There is currently little support of the notion that food deserts independently increase obesity.

Another driver for an increased energy intake may be the decrease in protein content in the diet. The 'Protein Leverage Hypothesis' states that humans and other species prioritize intake to maintain protein intake at a targeted level at the expense of the other macronutrients [49]. Experimentally, decreasing the protein content of a diet from 15 to 10% increased energy intake by 12% [50]. Accordingly, a decreased percentage of kilocalories that come from protein in the diet, as it occurred from the 1970's to 2005 in the U.S., was associated with increased overall energy intake [51]. One proposed mechanism for this is through an endocrine signal called fibroblast growth factor 21 (FGF21). Secreted by the liver, FGF21 is better described for its role in stimulating insulin sensitivity [52]. However, FGF21 was recently shown to be a signal of protein balance in man and studies in both mice and humans have showed that FGF21 increases in response to low-protein diets and in rodents was a powerful stimulator of food intake [53].

Changes in Energy Expenditure

Historical observations suggest that regulatory systems for maintaining body weight evolved against a backdrop of high physical activity and energy expenditure [54]. Technological advancements within the past century including mechanized equipment have shifted the majority of the population away from work that demands physical labor to occupations that encourage mostly sedentary behavior (i.e. office jobs) [55]. Furthermore affluence is associated with significant reductions in work-related energy expenditure. Compounding the sedentary nature of work is the development of power-assisted domestic appliances and tools that have allowed for significant reductions in the amount of energy expended in daily living and those conducted during leisure time. Further reductions in the propensity to expend energy during leisure time can be owed to devices such as television viewing, computer games and the Internet, all of which generally require minimal movement and low energy expenditure. In some opinions, modern obesity can be viewed as a normal and predictable physiological response to a new, pathogenic and "obesogenic" environment (Figure 2).

Despite the changing environment, nationally-representative survey data indicate that the number of adults achieving the recommended physical activity levels increased between 1990 and 2005 [56] [57]. Although in the last decade, less than 50% of the adult population met the recommended levels of physical activity [57]. Vigorous physical activity during leisure time (LTPA), reported as metabolic equivalents (METs), increased by ~60 MET min/day in men between the 1960s and 1990s, which represented an average increase of approximately 10 min of high intensity LTPA per day. No change in vigorous LTPA during this time was found in women, and there were no changes in moderate LTPA in either men or women during this time period [58]. Accordingly, the percentage of adults who were sedentary in their leisure time decreased from the 1960s to 1990s in both men (24% to 14%) and women (26% to 17%) [58]. In children and adolescents, 30% to 40% of youth meet the recommended levels of physical activity, a level that remained stable over the last 20 years [59]. There is even a hint that physical activity increased in children 6-11 years in the U.S., at least in some ethnic groups, whereas it declined in others [60]. Although physical education that is implemented in schools is thought to show a reduction or prevention in obesity it is not yet certain if the feasibility of using a school environment to promote increased physical activity is achievable [48].

The major change in activity patterns appears to have occurred in physical activity related to occupation [55]. Over the last 50 years, the structure and characteristics of the U.S. workforce was transformed, with the total number of adults employed more than doubling from 62.2 million in 1950 to 142.5 million in 2000. Another significant change has been in the percentage of adults employed in agricultural work, typically associated with high physical activity levels, which declined from 12.2% in 1950 to less than 2% in 2000 [56]. Overall, the percentage of adults who worked in low physical activity occupations increased by almost 83% from 1950 to 2000 and those employed in high activity jobs decreased by 25.2% [56]. Thus, a steady decline in physically active occupations and an increase in sedentary activity occupations concurred, and as a consequence, the estimated occupational energy expenditure dropped by 140 and 124 kcal/day in men and women, respectively [55]. This change was also observed in other countries and, in 1992, it was estimated that only 20% of men and 10% of women were employed in active occupations ([61], U.K. data). The shift in occupational physical activity towards more sedentary occupational activities and the associated drop in energy expenditure have been related to the gradual increase in bodyweight in the US population [55].

Despite the suggestion that LTPA has increased over the past 50 years, there is reason to believe that changes in our physical environment have influenced leisure-time energy expenditure. For example, car ownership has increased significantly over the past 30 years and as of 2001, U.S. households on average had more vehicles than available drivers [39]. The likelihood of walking or biking is inversely related to the number of automobiles per household, and this is independent of income level [56]. Another influential change has been the television. In 1950, only about 10% of U.S. households owned a TV, whereas now, approximately 98% of households have at least one television set [56]. This increase is associated with a doubling of average viewing hours per day; daily television viewing increased by 61.4% from 1950 to 2000 [56]. There is growing evidence for a strong association between hours per day spent watching TV and obesity, in adults [62] and children [63]. Overall, proxy measures of inactivity, such as automobile ownership and TV viewing, may be more closely related to overweight and obesity than purposeful physical activity [64].

Is the overall increase in body weight the result of increased food intake, reduced physical activity, or both? A growing number of mathematical and statistical models suggest that the main driver of the dramatic increase in body weight is due to changes in energy intake that occurred over the last 40 years. Examining the U.S. food supply data, Swinburn *et al.* showed that although reductions in overall physical activity may contribute to the change in average body weight in the U.S., the increase in energy supply - and thus intake – is more than sufficient to explain the increase in body weight and obesity epidemic [34, 35]. Moreover, the biphasic trends in physical activity and energy intake over the last century, which are characterized by reduced physical activity and energy intake during the first half of the 20th century followed by an increase in energy intake only thereafter, lends support to this explanation: total daily energy expenditure declined steadily over the last century, and as a consequence energy intake followed a similar trend, at least until the 1960's. This explains – at least partly - why the prevalence of obesity did not change substantially during the first half of the 20th century. During the second phase however, the prevalence of obesity increased dramatically in parallel with the increase in the availability of energy-dense foods in the 1970's, without compensatory increases in energy expenditure [65].

Other Recent Developments

Recently, evidence has been collated to support other potential contributors to the obesity epidemic [67]. That is besides the 'Big Two' (diet and physical activity), these other factors can increase adiposity and the frequency distribution has changed in the direction that would support an "obesogenic" response. Here we briefly discuss these potential, but controversial, contributors to the rapid rise in obesity.

Ambient Temperature

The reduction in variability in ambient temperature may have a significant impact on energy balance regulation. Greater use of central air conditioning and heating has increased the amount of time that U.S. adults spend in the thermoneutral zone, which is defined as the range of ambient temperature at which energy expenditure is not required for maintaining homeothermy [67]. For example the number of homes in the U.S. without air conditioning has decreased by almost 20% to a low 28% and is estimated to be as low as 7% in the Southern States where the obesity rates are at the highest levels in the country. Exposure to temperatures above the thermoneutral zone increases energy expenditure [68] and may significantly decrease food intake [69], while exposure to temperature below thermoneutrality induces a thermogenic response, and thus, increases energy expenditure.

Brown Adipose Tissue

An important player in thermogenesis and a possible contributor to energy expenditure in humans is brown adipose tissue (BAT). The majority of body fat is white adipose tissue. The abundance of white adipose tissue is essential for its roles as an energy store depot and as an active endocrine organ. BAT is found in much smaller depots located in the supraclavicular and axillary regions of the neck, the paravertebral and perirenal/adrenal regions, and around the major vessels. Brown adipose tissue is characterized by its high level of mitochondria that express energy "uncouplers" such as uncoupling protein 1, which give rise to the regulation of BAT, and subsequently increases in energy expenditure, by the sympathetic nervous system and thyroid hormones [70] in response to cold exposure or excessive energy intake.

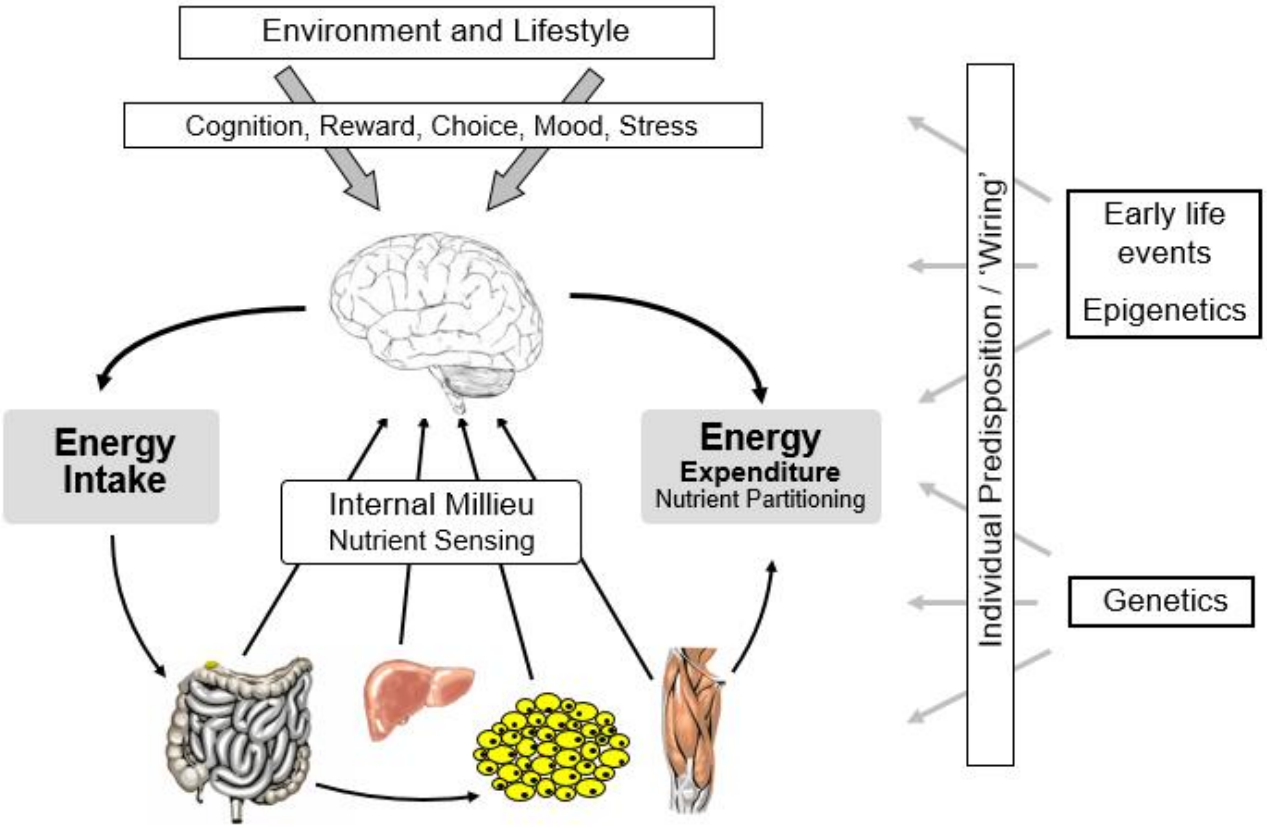
Although BAT was thought to have a negligible role in metabolism in adults, an increasing number of studies have identified metabolically active amounts of BAT in adult humans [71-75]. Evidence of a role for BAT in regulating body weight may be found in reports showing an inverse relationship between BAT and measures of adiposity such as BMI or body fat content [72, 76]. How can as little as 100 cm^3 (averaged from ref. [74]) of BAT influence body weight by increasing energy expenditure? Extrapolating data of the thermogenic capacity of BAT in rodents to humans suggests that 40-50 grams of BAT could account for up to 20% of daily energy expenditure [77]. However, more recent calculations indicate that the thermogenic capacity of BAT is much lower in humans, but could still account for up to 5% of basal metabolic rate, and thus, exert a substantial impact on energy expenditure [78]. In addition to its thermoregulatory role, BAT may be involved in the thermogenic response to food intake, i.e. diet-induced thermogenesis. Although this phenomenon is debated [79], a close relationship exist between cold-induced and diet-induced thermogenesis, suggesting that BAT is involved in both mechanisms [80]. As a very plastic tissue, BAT volume expands in pheochromocitoma [81], a disease characterized by chronic catecholamine content or with chronic exposure to cold as observed in lumberjacks in Finland [82]. Exposure to less extreme environmental conditions also appear to induce BAT activity and volume since numerous studies report an association between BAT activity and outdoor temperature [71, 72, 76, 83]. To what extent the homogenization of indoor temperature throughout the year influences body weight regulation by impeding the thermogenic capacity and activity of BAT is unknown, but BAT is considered as a contributor to the obesity epidemic [84].

Intrauterine and Intergenerational Effects

A recent hypothesis that is gaining momentum in the scientific community is that obesity (and others disorders) may be the result of genetic and epigenetic programming that occurs *in utero* up to two generations earlier (Figure 4). Some believe that genetics are extremely unlikely to be causing the ballooning of obesity over the past 30 years because mutations in genes can take up to thousands of years to divulge [46]. Although it is possible by mate choice that parents with high BMI's produce more offspring, a term referred to as *differential realized fertility [46]*. Therefore, researchers have looked more to environmental changes (epigenetics) that occurred during the lifetime of our grandparents that could be implicated in the obesity epidemic today. In support of this hypothesis, studies in rodents have shown that overfeeding results in increased body weight and adiposity in the offspring which continues for more

than 3 generations [85]. In humans, an infant born small for gestational age (SGA) is considered to be at risk for adult onset obesity [86]. A low birth weight and the subsequent catch-up growth is associated with adult BMI and interestingly the incidence of low birth weight babies has increased in the US reaching ~8% in 2002 [87].

Figure 4



Reduced smoking

Nicotine suppresses appetite and increases thermogenesis. It is frequently reported that smokers have a lower body weight compared to non-smokers and that weight gain coincides with smoking cessation. Cigarette smoking has declined steadily over the past several decades and together with the change in overweight during the 12 years to 1990, smoking was estimated to account for approximately 25% of the increase in men and approximately 10% of the increase in women [88].

Sleep debt

Average hours of sleep per night has decreased from over 9 to around 7 hours per night [89] and this has been proposed to stimulate hyperphagia via endocrine changes including increased ghrelin and decreased leptin concentrations [90]. Hours of sleep per night is inversely associated with BMI and obesity in cross-sectional studies of children [91] and adults [92]. A more recent longitudinal study following large cohorts (>120,000 participants) for over two decades, reported greater weight gain in individuals sleeping less than 6 hours or more than 8 hours per night [66].

Increased obesity in predisposed genotypes

The number of individuals from racial minorities at high susceptibility for the development of obesity has increased in the Western world. BMI and hence obesity is clearly heritable as shown in twins in whom up to 65% of BMI has been shown to be heritable [93]. The second component of this hypothesis is that individuals with a higher BMI have an increased potential to reproduce. Supporting evidence suggests that the number of offspring is positively associated with BMI [94] in women and one explanation could be that obesity can lead to increased fertility. Certainly a low BMI in women is associated with infertility [95] and for men leanness too leads to a greater reduction in sperm count [96].

WEIGHT CYCLING

Repeated episodes of weight loss and regain is popularly known as 'weight cycling' or yoyo dieting [97]. Although a standardized definition is lacking [98], a 5% weight loss and regain is one clinical definition of weight cycling [99], and this type of dieting pattern is highly prevalent among individuals who are either normal weight, overweight or obese [100-102]. Among health professionals and laypeople alike, weight cycling is anecdotally thought to have an adverse impact on metabolism and therefore increase the likelihood of weight regain; however, this has not been shown by a randomized clinical trial. Population-based studies have shown that individuals who reported a history of large weight fluctuations over adulthood (besides for pregnancy) had an increased risk for cardiovascular (and all-cause) morbidity and mortality [103-110] even after adjusting for current body weight [111, 112]. In 33,834 females from the Iowa Women's Health Study, weight cycling was associated with a higher relative risk for myocardial infarction (1.89), stroke (1.71) and diabetes (1.72) [113]. Women who reported intentional weight loss followed by regain of ≥4.5 kg at least 3 times had 7% lower HDL, an amount known to increase risk for cardiac events [114]. Weight variability was associated with hypertriglyceridemia, low HDL-C, hypertension and insulin resistance in a group of Japanese men [115] and other studies support a link with T2DM [116, 117]. A weight fluctuation of 4.5 kg between the ages of 40 and 60 years significantly increased the relative risk (RR) for diabetes by 1.7, even more so than a weight gain by the same amount [118]. Furthermore, larger fluctuations in weight were associated with higher fasting insulin [119], impaired glucose tolerance [120] and greater risk for metabolic syndrome [121] 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 [122-126]. Therefore, individuals should be counselled on weight loss and the importance of weight loss maintenance because subsequent weight regain might be worse for long-term health than maintaining the original obese state.

SUMMARY

In the United States 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 indirectly may reprogram the genetic and epigenetic background of human beings predisposing future generations to weight gain and adiposity (Figure 4). 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 low-protein 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. 'Yo-yo dieting' or weight cycling resulting from repetitive intentional fluctuations in weight loss and weight regain is becoming more prevalent as well and could have negative implications on health. 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.

Figure Legends.

Figure 1

Prevalence of overweight, obesity, and extreme obesity among men and women aged 20-74 in the United States between 1960 and 2012. The table represents obesity trends overall. Overweight is classified as a body mass index (BMI) of 25 or greater but less than 30, obesity is classified as a BMI greater than or equal to 30, and extreme obesity is classified as a BMI greater than or equal to 40. Age-adjusted by the direct method to the year 2000 U.S. Census Bureau estimates using the age groups 20-39, 40-59, and 60-74. NHES 1960-1962 included adults aged 18-79, and NHANES 1971-1974 and 1976-1980 did not include individuals over age 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.

Figure 2

This figure depicts the potential effect of genes and environment on adiposity assessed here by body mass index (BMI). Some of the concepts described in this figure were recently proposed by Bouchard et al [127]. Our environment has evolved over the past century from a "traditional" environment to a new "westernized" environment. The left side of the figure represents the "traditional" environment in which food was rather scarce and energy expenditure was high mostly related to occupational physical activity. Such an environment leads to "leptogenic" (an environment in which one is more prone to being leaner) behaviors in which the variability of BMI is dependent upon the genetic propensity for weight gain. The right side of the figure depicts the more recent modern "social" and "built" environment which promotes "obesogenic" behaviors characterized by abundant and inexpensive calorie-dense food and little need to be physically active, in which the variability in BMI also depends upon the genetic propensity for weight gain. Compared to the "obesogenic" environment, the distribution of BMI will be shifted to the right and therefore the population will have a higher mean and higher standard error than the distribution in the "leptogenic" environment. Such a paradigm can be applied to populations with similar genetic background living in drastically different environment like the Pima Indians in Arizona and in Mexico [19].

Figure 3

The daily energy and nutrient balance of a 70-kg man (20% body fat) in relationship to macronutrient energy stores, intake and oxidation. Each macronutrient intake and oxidation on a 2,500 kcal/day standard American diet (composition 40% fat, 40% carbohydrate, 20% protein) 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 on a daily basis any inherent differences between energy intake and energy expenditure therefore predominantly impact body fat stores. During overfeeding (shown in red) the oxidation of carbohydrate and protein is increased to compensate for the increased intake at the expense of fat intake where the increase in oxidation is not equally coupled with intake. Thus, if sustained fat kilocalories are stored, fat stores expand and body weight is gained.

Figure 4

Principle components of body weight regulation in an "obesogenic" environment. Body weight in adulthood is most likely to be the result of two key components; (a) changes in the environment of subsequent generations that influence genetic and epigenetic propensity for weight gain and (b) the current habitual lifestyle that promotes sedentary behaviors and provides an oversupply of energy dense foods.

REFERENCES:

1. Ogden, C.L., et al., *The epidemiology of obesity.* Gastroenterology, 2007. **132**(6): p. 2087-102.
2. Flegal, K.M., et al., *Prevalence and trends in obesity among US adults, 1999-2008.* JAMA, 2010. **303**(3): p. 235-41.
3. Ogden, C.L., et al., *Prevalence of overweight and obesity in the United States, 1999-2004.* Jama, 2006. **295**(13): p. 1549-55.
4. Rokholm, B., J.L. Baker, and T.I. Sorensen, *The levelling off of the obesity epidemic since the year 1999--a review of evidence and perspectives.* Obesity reviews : an official journal of the International Association for the Study of Obesity, 2010. **11**(12): p. 835-46.
5. Ogden, C.L., et al., *Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010.* JAMA, 2012. **307**(5): p. 483-90.
6. Alpert, S.S., *Growth, thermogenesis, and hyperphagia.* Am J Clin Nutr, 1990(552): p. 784-92.
7. Jequier, E. and Y. Schutz, *Long-term measurements of energy expenditure in humans using a respiration chamber.* Am J Clin Nutr, 1983. **38**(6): p. 989-98.
8. Ravussin, E., et al., *Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber.* J Clin Invest, 1986. **78**(6): p. 1568-78.
9. Weyer, C., et al., *Determinants of energy expenditure and fuel utilization in man: effects of body composition, age, sex, ethnicity and glucose tolerance in 916 subjects.* Int J Obes Relat Metab Disord, 1999. **23**(7): p. 715-22.
10. Hall, K.D., et al., *Quantification of the effect of energy imbalance on bodyweight.* Lancet, 2011. **378**(9793): p. 826-37.
11. Hall, K.D., *Predicting metabolic adaptation, body weight change, and energy intake in humans.* American journal of physiology. Endocrinology and metabolism, 2010. **298**(3): p. E449-66.
12. Thomas, D.M., et al., *A computational model to determine energy intake during weight loss.* The American journal of clinical nutrition, 2010. **92**(6): p. 1326-31.
13. Thomas, D.M., et al., *Why do individuals not lose more weight from an exercise intervention at a defined dose? An energy balance analysis.* Obesity reviews : an official journal of the International Association for the Study of Obesity, 2012. **13**(10): p. 835-47.
14. Bray, G.A., *Treatment for obesity: a nutrient balance/nutrient partition approach.* Nutr Rev, 1991(249): p. 33-45.
15. Snyder, W.S., et al., *Report of the task group on reference man.* The International Commission on Radiological Protection, no. 23 ed. The International Commission on Radiological Protection, no. 231974, New York: Pergamon Press.
16. Abbott, W.G., et al., *Short-term energy balance: relationship with protein, carbohydrate, and fat balances.* Am J Physiol, 1988(3 Pt 1255): p. E332-7.
17. Bray, G.A., et al., *Effect of dietary protein content on weight gain, energy expenditure, and body composition during overeating: a randomized controlled trial.* JAMA, 2012. **307**(1): p. 47-55.
18. Acheson, K.J., et al., *Glycogen storage capacity and de novo lipogenesis during massive carbohydrate overfeeding in man.* Am J Clin Nutr, 1988(248): p. 240-7.
19. Schutz, Y., J.P. Flatt, and E. Jequier, *Failure of dietary fat intake to promote fat oxidation: a factor favoring the development of obesity.* Am J Clin Nutr, 1989(250): p. 307-14.
20. Rising, R., et al., *Food intake measured by an automated food-selection system: relationship to energy expenditure.* Am J Clin Nutr, 1992(255): p. 343-9.
21. Flatt, J.P., et al., *Effects of dietary fat on postprandial substrate oxidation and on carbohydrate and fat balances.* J Clin Invest, 1985(376): p. 1019-24.
22. Zurlo, F., et al., *Low ratio of fat to carbohydrate oxidation as predictor of weight gain: study of 24-h RQ.* Am J Physiol, 1990(5 Pt 1259): p. E650-7.
23. Smith, S.R., et al., *Fat and carbohydrate balances during adaptation to a high-fat.* Am J Clin Nutr, 2000(271): p. 450-7.
24. Colditz, G.A., et al., *Alcohol intake in relation to diet and obesity in women and men.* Am J Clin Nutr, 1991(154): p. 49-55.

25. Hellerstedt, W.L., R.W. Jeffery, and D.M. Murray, *The association between alcohol intake and adiposity in the general population.* Am J Epidemiol, 1990(4132): p. 594-611.
26. Shelmet, J.J., et al., *Ethanol causes acute inhibition of carbohydrate, fat, and protein oxidation and insulin resistance.* J Clin Invest, 1988(481): p. 1137-45.
27. Suter, P.M., Y. Schutz, and E. Jequier, *The effect of ethanol on fat storage in healthy subjects.* N Engl J Med, 1992. **326**(15): p. 983-7.
28. Flatt, J.P., *McCollum Award Lecture, 1995: diet, lifestyle, and weight maintenance.* The American journal of clinical nutrition, 1995. **62**(4): p. 820-36.
29. Frayn, K.N., *Physiological regulation of macronutrient balance.* Int J Obes Relat Metab Disord, 1995(19 Suppl 5): p. S4-10.
30. Tobias, D.K., et al., *Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis.* The lancet. Diabetes & endocrinology, 2015. **3**(12): p. 968-79.
31. Hall, K.D., et al., *Calorie for Calorie, Dietary Fat Restriction Results in More Body Fat Loss than Carbohydrate Restriction in People with Obesity.* Cell metabolism, 2015. **22**(3): p. 427-36.
32. Prentice, A. and S. Jebb, *Energy intake/physical activity interactions in the homeostasis of body weight regulation.* Nutr Rev, 2004. **62**(7 Pt 2): p. S98-104.
33. Harnack, L.J., R.W. Jeffery, and K.N. Boutelle, *Temporal trends in energy intake in the United States: an ecologic perspective.* Am J Clin Nutr, 2000. **71**(6): p. 1478-84.
34. Swinburn, B., G. Sacks, and E. Ravussin, *Increased food energy supply is more than sufficient to explain the US epidemic of obesity.* The American journal of clinical nutrition, 2009. **90**(6): p. 1453-6.
35. Swinburn, B.A., et al., *Estimating the changes in energy flux that characterize the rise in obesity prevalence.* The American journal of clinical nutrition, 2009. **89**(6): p. 1723-8.
36. Putnam J, A.J., Kantor LS, *U.S. per capita food supply trends: more calories, refined carbohydrates, and fats.* FoodReview, 2002. **25**(3): p. 2-15.
37. Blundell, J.E., et al., *Dietary fat and the control of energy intake: evaluating the effects of fat on meal size and postmeal satiety.* Am J Clin Nutr, 1993. **57**(5 Suppl): p. 772S-777S; discussion 777S-778S.
38. Cordain, L., et al., *Origins and evolution of the Western diet: health implications for the 21st century.* Am J Clin Nutr, 2005. **81**(2): p. 341-54.
39. Stat., U.D.T.B.T., *NHTS 2001 Highlights Report.*, 2003, US Dep. Transp. Bur. Transp. Stat.: Washington, DC.
40. Welsh, J.A., et al., *Consumption of added sugars is decreasing in the United States.* The American journal of clinical nutrition, 2011. **94**(3): p. 726-34.
41. Young, L.R. and M. Nestle, *The contribution of expanding portion sizes to the US obesity epidemic.* Am J Public Health, 2002. **92**(2): p. 246-9.
42. Nielsen, S.J. and B.M. Popkin, *Patterns and trends in food portion sizes, 1977-1998.* Jama, 2003. **289**(4): p. 450-3.
43. Smiciklas-Wright, H., et al., *Foods commonly eaten in the United States, 1989-1991 and 1994-1996: are portion sizes changing?* J Am Diet Assoc, 2003. **103**(1): p. 41-7.
44. Clemens, L.H., D.L. Slawson, and R.C. Klesges, *The effect of eating out on quality of diet in premenopausal women.* J Am Diet Assoc, 1999. **99**(4): p. 442-4.
45. Binkley, J.K., J. Eales, and M. Jekanowski, *The relation between dietary change and rising US obesity.* Int J Obes Relat Metab Disord, 2000. **24**(8): p. 1032-9.
46. Casazza, K., et al., *Weighing the Evidence of Common Beliefs in Obesity Research.* Critical reviews in food science and nutrition, 2015. **55**(14): p. 2014-53.
47. Jiao, J., et al., *How to identify food deserts: measuring physical and economic access to supermarkets in King County, Washington.* American journal of public health, 2012. **102**(10): p. e32-9.

48. Casazza, K., R. Pate, and D.B. Allison, *Myths, presumptions, and facts about obesity.* The New England journal of medicine, 2013. **368**(23): p. 2236-7.
49. Simpson, S.J. and D. Raubenheimer, *Obesity: the protein leverage hypothesis.* Obesity reviews : an official journal of the International Association for the Study of Obesity, 2005. **6**(2): p. 133-42.
50. Gosby, A.K., et al., *Testing protein leverage in lean humans: a randomised controlled experimental study.* PloS one, 2011. **6**(10): p. e25929.
51. Austin, G.L., L.G. Ogden, and J.O. Hill, *Trends in carbohydrate, fat, and protein intakes and association with energy intake in normal-weight, overweight, and obese individuals: 1971-2006.* The American journal of clinical nutrition, 2011. **93**(4): p. 836-43.
52. Kharitonenkov, A., et al., *FGF-21 as a novel metabolic regulator.* The Journal of clinical investigation, 2005. **115**(6): p. 1627-35.
53. Laeger, T., et al., *FGF21 is an endocrine signal of protein restriction.* The Journal of clinical investigation, 2014. **124**(9): p. 3913-22.
54. Hayes, M., et al., *Low physical activity levels of modern Homo sapiens among free-ranging mammals.* Int J Obes (Lond), 2005. **29**(1): p. 151-6.
55. Church, T.S., et al., *Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity.* PloS one, 2011. **6**(5): p. e19657.
56. Brownson, R.C., T.K. Boehmer, and D.A. Luke, *Declining rates of physical activity in the United States: what are the contributors?* Annu Rev Public Health, 2005. **26**: p. 421-43.
57. CDC, *Prevalence of regular physical activity among adults--United States, 2001 and 2005.* MMWR Morb Mortal Wkly Rep, 2007. **56**(46): p. 1209-12.
58. Talbot, L.A., J.L. Fleg, and E.J. Metter, *Secular trends in leisure-time physical activity in men and women across four decades.* Prev Med, 2003. **37**(1): p. 52-60.
59. Ekelund, U., G. Tomkinson, and N. Armstrong, *What proportion of youth are physically active? Measurement issues, levels and recent time trends.* British journal of sports medicine, 2011. **45**(11): p. 859-65.
60. Gortmaker, S.L., et al., *Disparities in youth physical activity in the United States: 2003-2006.* Medicine and science in sports and exercise, 2012. **44**(5): p. 888-93.
61. Survey, A.D.N.F., *A report on activity patterns and fitness levels., in London*, L.S.C.a.H.E. Authority, Editor 1992.
62. Bowman, S., *Television-viewing characteristics of adults: correlations to eating practices and overweight and health status.* Prev Chronic Dis, 2006. **3**(2): p. 1-11.
63. Gortmaker, S.L., et al., *Television viewing as a cause of increasing obesity among children in the United States, 1986-1990.* Arch Pediatr Adolesc Med, 1996. **150**(4): p. 356-62.
64. Prentice, A.M. and S.A. Jebb, *Obesity in Britain: gluttony or sloth?* Bmj, 1995. **311**(7002): p. 437-9.
65. Swinburn, B.A., et al., *The global obesity pandemic: shaped by global drivers and local environments.* Lancet, 2011. **378**(9793): p. 804-14.
66. Mozaffarian, D., et al., *Changes in diet and lifestyle and long-term weight gain in women and men.* The New England journal of medicine, 2011. **364**(25): p. 2392-404.
67. Keith, S.W., et al., *Putative contributors to the secular increase in obesity: exploring the roads less traveled.* Int J Obes (Lond), 2006. **30**(11): p. 1585-94.
68. Westerterp-Plantenga, M.S., et al., *Energy metabolism in women during short exposure to the thermoneutral zone.* Physiol Behav, 2002. **75**(1-2): p. 227-35.
69. Herman, C., *Effects of heat on appetite.* Nutritional Needs in Hot Environments: Applications for Military Personnel in Field Operations., ed. M. BM1993, Washington, DC: National Academy Press. 187-214.
70. Cannon, B. and J. Nedergaard, *Brown adipose tissue: function and physiological significance.* Physiological reviews, 2004. **84**(1): p. 277-359.
71. Cypess, A.M., et al., *Identification and importance of brown adipose tissue in adult humans.* The New England journal of medicine, 2009. **360**(15): p. 1509-17.

72. Saito, M., et al., *High incidence of metabolically active brown adipose tissue in healthy adult humans: effects of cold exposure and adiposity.* Diabetes, 2009. **58**(7): p. 1526-31.
73. van Marken Lichtenbelt, W.D., et al., *Cold-activated brown adipose tissue in healthy men.* The New England journal of medicine, 2009. **360**(15): p. 1500-8.
74. Virtanen, K.A., et al., *Functional brown adipose tissue in healthy adults.* The New England journal of medicine, 2009. **360**(15): p. 1518-25.
75. Yoneshiro, T., et al., *Brown adipose tissue, whole-body energy expenditure, and thermogenesis in healthy adult men.* Obesity, 2011. **19**(1): p. 13-6.
76. Ouellet, V., et al., *Outdoor temperature, age, sex, body mass index, and diabetic status determine the prevalence, mass, and glucose-uptake activity of 18F-FDG-detected BAT in humans.* The Journal of clinical endocrinology and metabolism, 2011. **96**(1): p. 192-9.
77. Rothwell, N.J. and M.J. Stock, *A role for brown adipose tissue in diet-induced thermogenesis.* Nature, 1979. **281**(5726): p. 31-5.
78. van Marken Lichtenbelt, W.D. and P. Schrauwen, *Implications of nonshivering thermogenesis for energy balance regulation in humans.* American journal of physiology. Regulatory, integrative and comparative physiology, 2011. **301**(2): p. R285-96.
79. Kozak, L.P., *Brown fat and the myth of diet-induced thermogenesis.* Cell metabolism, 2010. **11**(4): p. 263-7.
80. Wijers, S.L., W.H. Saris, and W.D. van Marken Lichtenbelt, *Individual thermogenic responses to mild cold and overfeeding are closely related.* The Journal of clinical endocrinology and metabolism, 2007. **92**(11): p. 4299-305.
81. Wang, Q., et al., *Brown adipose tissue in humans is activated by elevated plasma catecholamines levels and is inversely related to central obesity.* PloS one, 2011. **6**(6): p. e21006.
82. Huttunen, P., J. Hirvonen, and V. Kinnula, *The occurrence of brown adipose tissue in outdoor workers.* European journal of applied physiology and occupational physiology, 1981. **46**(4): p. 339-45.
83. Au-Yong, I.T., et al., *Brown adipose tissue and seasonal variation in humans.* Diabetes, 2009. **58**(11): p. 2583-7.
84. Johnson, F., et al., *Could increased time spent in a thermal comfort zone contribute to population increases in obesity?* Obesity reviews : an official journal of the International Association for the Study of Obesity, 2011. **12**(7): p. 543-51.
85. Diaz, J. and E.M. Taylor, *Abnormally high nourishment during sensitive periods results in body weight changes across generations.* Obes Res, 1998. **6**(5): p. 368-74.
86. Silverman, B.L., et al., *Long-term effects of the intrauterine environment. The Northwestern University Diabetes in Pregnancy Center.* Diabetes Care, 1998. **21 Suppl 2**: p. B142-9.
87. Hamilton, B.E., J.A. Martin, and P.D. Sutton, *Births: preliminary data for 2003.* Natl Vital Stat Rep, 2004. **53**(9): p. 1-17.
88. Flegal, K.M., et al., *The influence of smoking cessation on the prevalence of overweight in the United States.* N Engl J Med, 1995. **333**(18): p. 1165-70.
89. Bonnet, M.H. and D.L. Arand, *We are chronically sleep deprived.* Sleep, 1995. **18**(10): p. 908-11.
90. Taheri, S., et al., *Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index.* PLoS Med, 2004. **1**(3): p. e62.
91. von Kries, R., et al., *Reduced risk for overweight and obesity in 5- and 6-y-old children by duration of sleep--a cross-sectional study.* Int J Obes Relat Metab Disord, 2002. **26**(5): p. 710-6.
92. Gangwisch, J.E., et al., *Inadequate sleep as a risk factor for obesity: analyses of the NHANES I.* Sleep, 2005. **28**(10): p. 1289-96.
93. Segal, N.L. and D.B. Allison, *Twins and virtual twins: bases of relative body weight revisited.* Int J Obes Relat Metab Disord, 2002. **26**(4): p. 437-41.
94. Weng, H.H., et al., *Number of children associated with obesity in middle-aged women and men: results from the health and retirement study.* J Womens Health (Larchmt), 2004. **13**(1): p. 85-91.
95. Frisch, R.E., *Body fat, menarche, fitness and fertility.* Hum Reprod, 1987. **2**(6): p. 521-33.

96. Jensen, T.K., et al., *Body mass index in relation to semen quality and reproductive hormones among 1,558 Danish men.* Fertil Steril, 2004. **82**(4): p. 863-70.
97. Blackburn, G.L., et al., *Weight cycling: the experience of human dieters.* The American journal of clinical nutrition, 1989. **49**(5 Suppl): p. 1105-9.
98. *Weight cycling. National Task Force on the Prevention and Treatment of Obesity.* JAMA, 1994. **272**(15): p. 1196-202.
99. Taing, K.Y., C.I. Ardern, and J.L. Kuk, *Effect of the timing of weight cycling during adulthood on mortality risk in overweight and obese postmenopausal women.* Obesity, 2012. **20**(2): p. 407-13.
100. Tsai, C.J., et al., *Weight cycling and risk of gallstone disease in men.* Archives of internal medicine, 2006. **166**(21): p. 2369-74.
101. Syngal, S., et al., *Long-term weight patterns and risk for cholecystectomy in women.* Annals of internal medicine, 1999. **130**(6): p. 471-7.
102. Brownell, K.D. and J. Rodin, *Medical, metabolic, and psychological effects of weight cycling.* Archives of internal medicine, 1994. **154**(12): p. 1325-30.
103. Blair, S.N., et al., *Body weight change, all-cause mortality, and cause-specific mortality in the Multiple Risk Factor Intervention Trial.* Annals of internal medicine, 1993. **119**(7 Pt 2): p. 749-57.
104. Hamm, P., R.B. Shekelle, and J. Stamler, *Large fluctuations in body weight during young adulthood and twenty-five-year risk of coronary death in men.* American journal of epidemiology, 1989. **129**(2): p. 312-8.
105. Lissner, L., et al., *Variability of body weight and health outcomes in the Framingham population.* The New England journal of medicine, 1991. **324**(26): p. 1839-44.
106. Folsom, A.R., et al., *Weight variability and mortality: the Iowa Women's Health Study.* International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity, 1996. **20**(8): p. 704-9.
107. Lee, I.M. and R.S. Paffenbarger, Jr., *Change in body weight and longevity.* JAMA, 1992. **268**(15): p. 2045-9.
108. Rzehak, P., et al., *Weight change, weight cycling and mortality in the ERFORT Male Cohort Study.* European journal of epidemiology, 2007. **22**(10): p. 665-73.
109. Reynolds, M.W., et al., *Weight, weight change, mortality in a random sample of older community-dwelling women.* Journal of the American Geriatrics Society, 1999. **47**(12): p. 1409-14.
110. Diaz, V.A., A.G. Mainous, 3rd, and C.J. Everett, *The association between weight fluctuation and mortality: results from a population-based cohort study.* Journal of community health, 2005. **30**(3): p. 153-65.
111. Iribarren, C., et al., *Association of weight loss and weight fluctuation with mortality among Japanese American men.* The New England journal of medicine, 1995. **333**(11): p. 686-92.
112. Peters, E.T., et al., *Changes in body weight in relation to mortality in 6441 European middle-aged men: the Seven Countries Study.* International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity, 1995. **19**(12): p. 862-8.
113. French, S.A., et al., *Weight variability and incident disease in older women: the Iowa Women's Health Study.* International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity, 1997. **21**(3): p. 217-23.
114. Rubins, H.B., et al., *Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group.* The New England journal of medicine, 1999. **341**(6): p. 410-8.
115. Zhang, H., et al., *Long-term body weight fluctuation is associated with metabolic syndrome independent of current body mass index among Japanese men.* Circulation journal : official journal of the Japanese Circulation Society, 2005. **69**(1): p. 13-8.
116. Brancati, F.L., et al., *Body weight patterns from 20 to 49 years of age and subsequent risk for diabetes mellitus: the Johns Hopkins Precursors Study.* Archives of internal medicine, 1999. **159**(9): p. 957-63.

117. Waring, M.E., et al., *Incident diabetes in relation to weight patterns during middle age.* American journal of epidemiology, 2010. **171**(5): p. 550-6.
118. Holbrook, T.L., E. Barrett-Connor, and D.L. Wingard, *The association of lifetime weight and weight control patterns with diabetes among men and women in an adult community.* International journal of obesity, 1989. **13**(5): p. 723-9.
119. Yatsuya, H., et al., *Association between weight fluctuation and fasting insulin concentration in Japanese men.* International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity, 2003. **27**(4): p. 478-83.
120. Lissner, L., et al., *Body weight variability in men: metabolic rate, health and longevity.* International journal of obesity, 1990. **14**(4): p. 373-83.
121. Vergnaud, A.C., et al., *Weight fluctuations and risk for metabolic syndrome in an adult cohort.* International journal of obesity, 2008. **32**(2): p. 315-21.
122. Field, A.E., S. Malspeis, and W.C. Willett, *Weight cycling and mortality among middle-aged or older women.* Archives of internal medicine, 2009. **169**(9): p. 881-6.
123. Stevens, V.L., et al., *Weight cycling and mortality in a large prospective US study.* American journal of epidemiology, 2012. **175**(8): p. 785-92.
124. Wannamethee, S.G., A.G. Shaper, and M. Walker, *Weight change, weight fluctuation, and mortality.* Archives of internal medicine, 2002. **162**(22): p. 2575-80.
125. Field, A.E., et al., *Weight cycling and the risk of developing type 2 diabetes among adult women in the United States.* Obesity research, 2004. **12**(2): p. 267-74.
126. Schienkiewitz, A., et al., *Body mass index history and risk of type 2 diabetes: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study.* The American journal of clinical nutrition, 2006. **84**(2): p. 427-33.
127. Bouchard, C., *The biological predisposition to obesity: beyond the thrifty genotype scenario.* International journal of obesity, 2007. **31**(9): p. 1337-9.