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Health Professional's Guide *to* Treatment of Overweight and Obesity

Weight Management Dietetic Practice Group

Editors

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Health Professional's Guide to Treatment of Overweight and Obesity

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Preface

The treatment of overweight and obesity is a relatively new practice area in the health care field. While the incidence of overweight and obesity increased in the 1980s and 1990s, and the National Institutes of Health recognized obesity as a chronic disease in 1998, it was not until 2013 that the American Medical Association classified obesity as a chronic disease. For too long the health risks associated with excess adipose tissue were ignored. Obesity was attributed to individual choices and lack of self-control, and the focus of care was on changing body shape. Historically, the expectation was that calorie restriction would cure the problem of extra pounds. The landscape is still evolving today as we continue to learn about the complex nature of this chronic disease, its associated health concerns, and its management.

The *Health Professional's Guide to Treatment of Overweight and Obesity* provides a resource for clinicians involved in the care of adults with overweight and obesity. (Treatment of children and adolescents with overweight and obesity is a separate and highly nuanced topic—a subspecialty in its own right—and is not included in the scope of this book.) We begin by looking at the "big picture." Chapter 1 describes the physiological components of weight regulation, addressing genetics and life stages associated with the risk of increased adiposity. Chapters 2 and 3 incorporate the human element, describing social determinants of health, bias, and stigma, which can impact our perceptions of the disease and the care that is provided. With greater recognition of obesity as a disease, evidence-based standards for treatment have emerged, as outlined in Chapter 4. While the similarities in the guidelines outline a clearer direction for treatment, Chapter 5 reminds us that the patient is a member of the team. It is important to acknowledge the individual's goals and include them in the decision-making process; this can include whether treatment should even occur, and if it does, what it should look like.

Given the complexity of overweight and obesity, it is understandable that an interprofessional approach is now associated with comprehensive treatment. Clinicians generally tend to first look at the conditions through the lens of their own professional orientation. Chapters 6 through 14 review assessment, followed by interventions from the perspectives of medicine, nutrition, physical activity, and behavioral health. Chapter 10 highlights the strength of multicomponent lifestyle interventions, which are also part of the more intensive medical and surgical interventions described in Chapter 14. Personalized nutrition therapy from a registered dietitian nutritionist is a vital part of comprehensive obesity care, whether the approach includes lifestyle intervention, antiobesity medication, metabolic and bariatric surgery, or a combination of approaches to lose weight or maintain weight loss. As we develop greater appreciation for obesity as a chronic condition, it is important to acknowledge that it requires ongoing intervention and attention, as discussed in Chapter 15. Because obesity treatment is sometimes criticized for triggering eating disorders, Chapter 16 discusses the evidence between obesity treatment and eating pathology.

Several factors will affect how we implement interventions for overweight and obesity. We no longer rely solely on face-to-face interactions with our clients. Telehealth, remote monitoring, apps, and other technologies offer advantages—and disadvantages—for treatment plans, as discussed in Chapter 17. Chapter 18 identifies health care disciplines that may be part of an interprofessional team

involved in weight management practice; each team member brings skills and expertise to the team while respecting the boundaries of their scope of practice. Though we recognize obesity as a disease and significant progress has been made to develop interventions to manage health-related risks, payment structures remain barriers to many services. Chapter 19 summarizes current health care policies and payment structures, with insight on how to advocate for enhanced policies.

The Health Professional's Guide to Treatment of Overweight and Obesity is intended for registered dietitian nutritionists; nutrition and dietetic technicians, registered; diabetes care and education specialists; physicians; nurses; pharmacists; and other allied health professionals. While obesity medicine is now recognized as a specialty practice area, given the prevalence of overweight and obesity, most of us will work with clients with overweight and obesity regardless of our area of practice. Irrespective of where one practices or who one works with, understanding the key concepts about obesity, its assessment, and its management will provide a practice foundation that is crucial for all health professionals.

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CHAPTER

1

Obesity as a Disease

Daniel Bessesen, MD

CHAPTER OBJECTIVES

- Define obesity as a chronic progressive disease.
- Summarize the physiological components of body weight regulation.
- Describe the prevalence of overweight and obesity, including the life stages during which people are at the greatest risk for increased adiposity.
- Discuss adverse health consequences of being overweight or obese.

Introduction

Obesity: A Disease of Body Weight Regulation

Many health care providers and patients believe that body weight is the product of lifestyle choices independent of any physiological regulation. On the contrary, over the last 20 years, it has become increasingly clear that body weight is carefully regulated by complex integrated physiological systems involving appetite, metabolism, the autonomic nervous system, endocrine systems, and several important brain regions.[1] This understanding has led medical professionals to conclude that obesity is a disease of body weight regulation, much the way diabetes is a disease of glucose homeostasis and hypertension is a disorder of blood pressure regulation.[2] Like these other chronic metabolic conditions, obesity is the product of a genetic predisposition to weight gain combined with an environment that promotes positive energy balance. An appreciation of the regulation of body weight and the challenges that individuals face when trying to lose weight provides health care workers and patients with a more realistic view, and better understanding, of the condition. This framework also informs key aspects of treatment. This chapter discusses body weight regulation, the adaptive responses to weight loss that promote weight regain, the definition of obesity, the prevalence of obesity, and weight changes throughout the life span.

Obesity Defined

Obesity is a level of excess adiposity associated with adverse health consequences. The most commonly used method for quantifying excess body fat is BMI calculated as a person's height, in meters squared, divided by their weight in kilograms.[3] The categories of weight based on BMI per the Centers for Disease Control and Prevention (CDC) are: overweight (BMI 25–29.9), class 1 obesity (BMI 30–34.9), class 2 obesity (BMI 35–39.9), and class 3 (severe) obesity (BMI of 40 or higher). BMI was initially developed as a population metric for estimating the risk of morbidity and mortality. Actual health risks for individuals vary substantially, independent of BMI, according to factors such as genetics, habitual physical activity levels, dietary quality, and others. BMI also has its limitations for categorizing weight, because some individuals may weigh more than others due to their having a greater lean body mass. BMI is not a direct measure of body fat but correlates well with percent body fat in populations. Because metabolic complications of obesity are related to regional fat deposition—with increased fat in the abdominal region being more associated with adverse health consequences—waist circumference can supplement BMI in the

assessment of obesity-related health risks. BMI cutoff points to categorize individuals as overweight or obese differ among the various ethnic groups, as seen in Figure 1.1.[4]

The Regulation of Body Weight

Central to the understanding of obesity as a disease is the idea that body weight is regulated the same way as other important physiological variables, such as blood glucose or blood pressure. To maintain a stable body weight, energy intake must be balanced over time against energy expenditure. Stored nutrients within the body—including fat, glucose, and protein—buffer metabolic and energetic needs against hour-to-hour and day-to-day changes in energy balance. When one considers the amount of energy a person consumes and burns over the course of a lifetime, it becomes clear that body weight must be physiologically regulated. From age 20 years to age 60 years, a hypothetical cisgender male of average size might consume almost 30 million kcal of food. With certain assumptions being made about dietary composition, this represents more than 5,100 kg (11,220 lb) of food. Because of the long period of time (40 years) and the degree of daily energy flux, an increase in body weight from 66 kg (145 lb) at age 20 years to 100 kg (220 lb) at age 60 reflects an energy imbalance of only 13 kcal/d. Because energy expenditure declines with age, even in this hypothetical individual who gains 34 kg (75 lb) over 40 years, his predicted energy intake will actually decline from 2,911 kcal/d at age 20 years to 2,500 kcal/d at age 60 years, despite the increase in weight. Although people have the subjective experience that they choose what they eat and select their habitual level of physical activity, consideration of the energetics of weight balance quickly reveals how choice alone cannot produce the level of precision observed in this regulatory system, even when an individual gains weight.

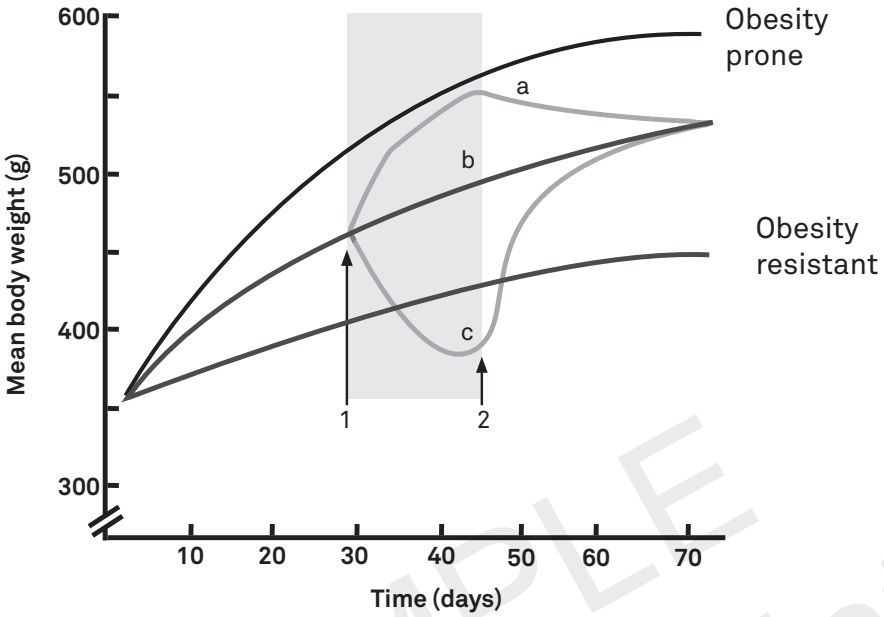
Studies in animals also support the idea that body weight is physiologically regulated. Rats living in an environment with palatable food and reduced access to physical activity will gradually gain weight throughout their lives. If a researcher places a feeding tube into the rat's stomach and overfeeds it, the rat will gradually gain weight if the overfeeding is continued. When the overfeeding stops, the rat's weight will gradually decline, not to where it was but to where it would have been had the overfeeding not occurred. This is shown in Figure 1.2 on page 4.[5]

FIGURE 1.1 Defining obesity using BMI and waist circumference[4]

Populations	Classification	BMI, kg/m^2	Co-morbidity risk	Waist circumference, cm	
				males < 94; females < 80	males ≥ 94; females ≥ 80
General population (Caucasian, Europid, Middle-Eastern, Sub-Saharan African)	underweight	<18.5	low but with other problems	–	–
	normal weight	18.5–24.9	average	–	–
	overweight	25.0–29.9	increased	increased	high
	obese class I	30.0–34.9	moderate	high	very high
	obese class II	35.0–39.9	severe	very high	very high
	obese class III	≥40	very severe	extremely high	extremely high
				Waist circumference, cm	
				males < 85; females < 74	males ≥ 85; females ≥ 74
East Asian, South Asian and Southeast Asian populations	normal weight	<23	–	–	–
	overweight	≥23	increased	increased	high
	obese	≥27.5	high	high	very high

Reproduced with permission from Abusnana S, Fargaly M, Alfardan SH, et al. Clinical practice recommendations for the management of obesity in the United Arab Emirates. *Obes Facts*. 2018;11(5):413-428. doi:10.1159/000491796.[4]

FIGURE 1.2 Regulation of body weight in animal studies[5]



Animals tend to adjust their food intake to achieve a normal body weight. The graph shows a schematized growth curve for three groups of rats that were either force-fed (a), allowed free access to food (b), or food-restricted (c) for the period of time between the arrows. Note that the animals slowly returned to normal weight when allowed free access to food.
Reproduced with permission from Bessesen DH. Regulation of body weight: what is the regulated parameter? *Physiol Behav*. 2011;104(4):599-607. doi:10.1016/j.physbeh.2011.05.006.[5]

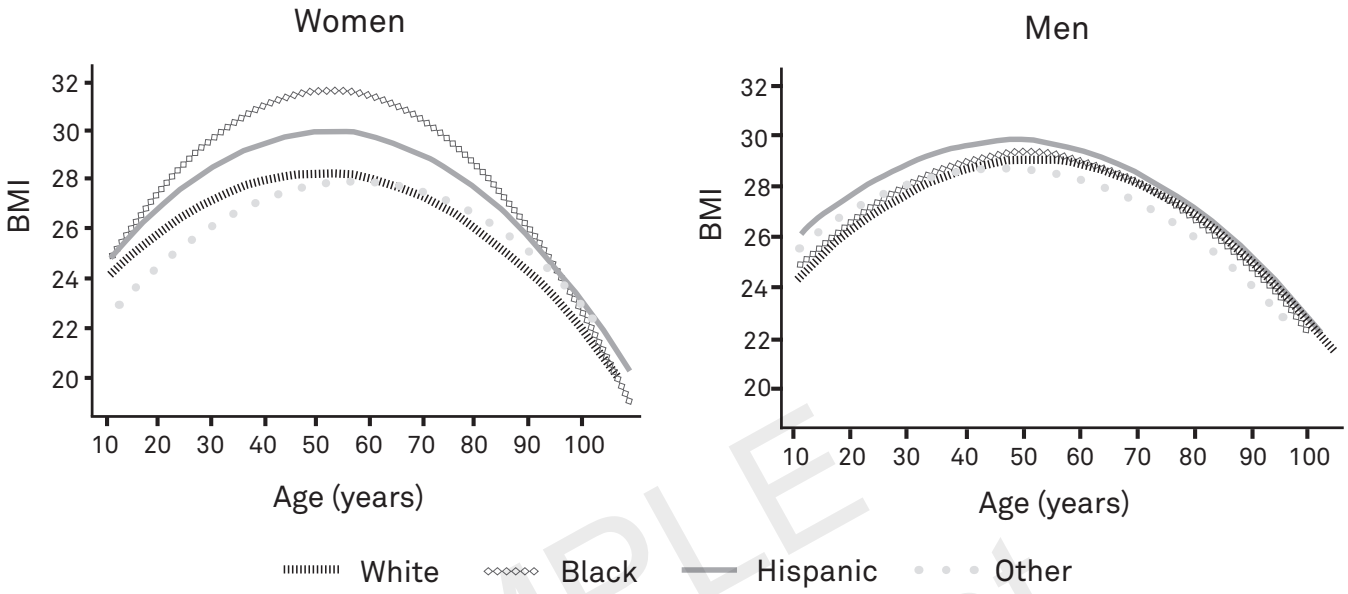
Alternatively, the researcher can restrict energy intake in an adult rat, and the rat's weight will gradually fall until it reaches a new plateau. If energy restriction is stopped, the rat's weight will increase, not to where it was but to where it would have been if energy restriction had not been imposed. These results suggest that weight is not regulated around a "set point" but rather around a trajectory of gradual weight gain across the life span.

Is this also true for human beings? Epidemiological data suggest that body weight gradually increases over the life span in human beings until roughly age 65 years, after which body weight gradually declines, as illustrated in Figure 1.3.[6]

Clinicians frequently see patients who experience progressive weight gain over their lifetime. When these patients adopt new lifestyle habits that produce weight loss, if the lifestyle habits are not sustained, their weight increases—not to where it was, but to an even higher level; this is consistent with what has been seen in animal studies (refer to Figure 1.4).[5] Even when an individual maintains consistent lifestyle habits or continues the use of an anti-obesity medication, weight often gradually increases over time. This increase in weight may reflect adaptive responses to weight loss that promote weight regain, but it may also reflect the natural tendency of body weight to increase over time.

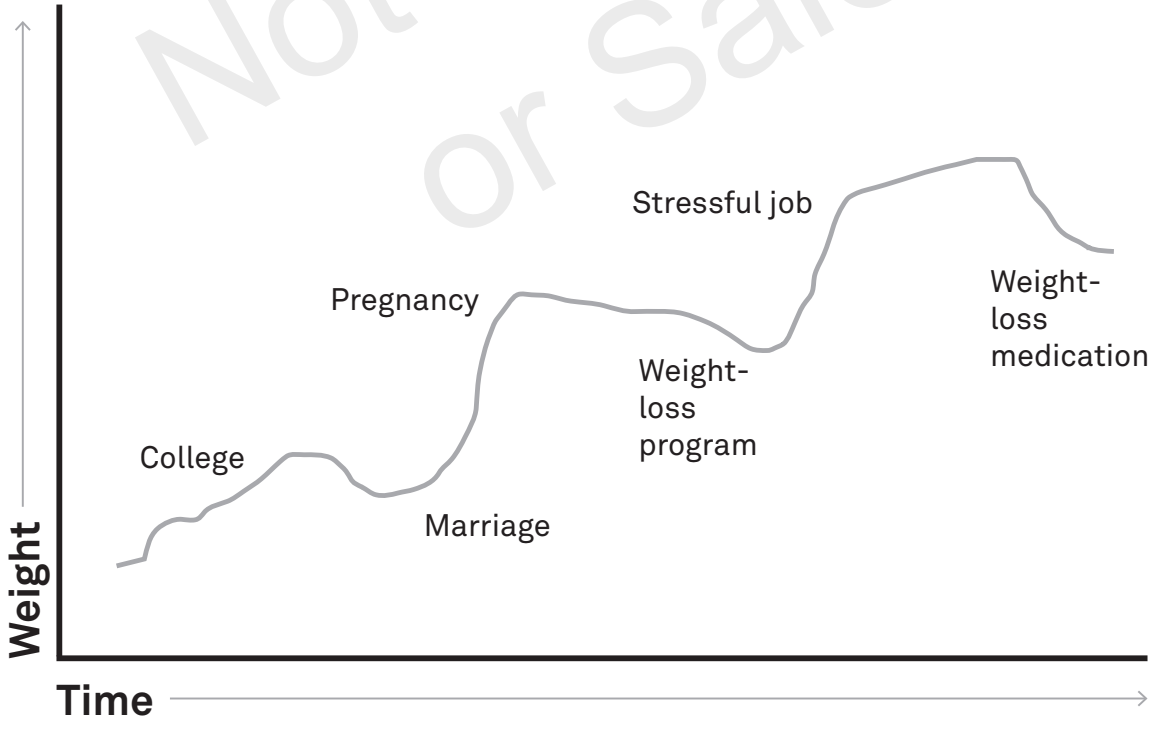
This type of regulation is called *homeorhesis*.[5] Unlike a system regulated by homeostasis, where the system maintains stability in a particular physiological parameter, a system regulated by homeorhesis is regulated around a trajectory rather than a steady state. In animal studies, the trajectory of weight gain over the life span reflects both genetics and the environment. Rats that are genetically prone to weight gain display a steeper trajectory of weight gain over the course of their lives. Alternatively, rats or mice that are genetically resistant to obesity

FIGURE 1.3 Predicted BMI trajectories by race and ethnicity[a,6]



[a] Study participants were described as men and women. Gender was not further specified.
Adapted with permission from Yang YC, Walsh CE, Johnson MP, et al. Life-course trajectories of body mass index from adolescence to old age: racial and educational disparities. *Proc Natl Acad Sci U S A*. 2021;118(17):e2020167118. doi:10.1073/pnas.2020167118.[6]

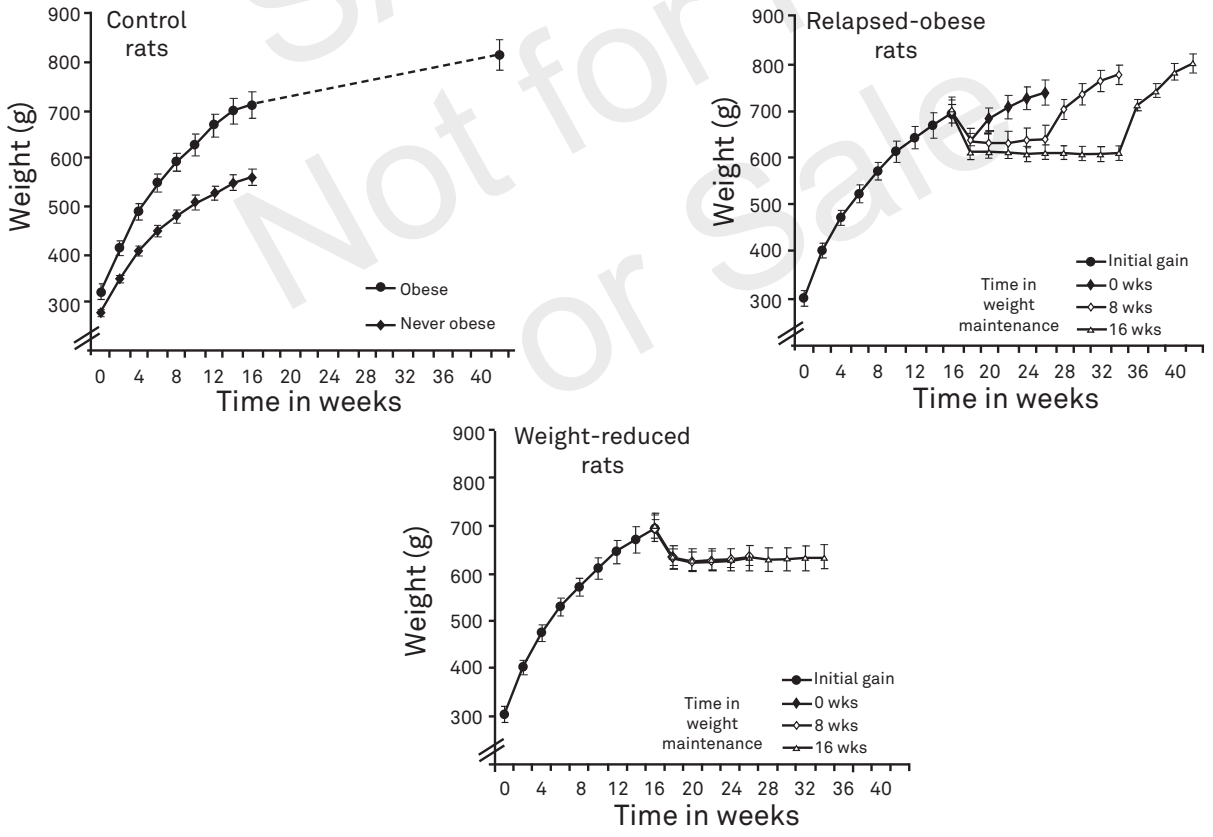
FIGURE 1.4 Weight regulation in humans[5]



gain less weight over their lives. An animal living in an environment where food is constantly available and highly palatable will gain more weight than the same animal living in an environment in which food is less available or less appetizing. The opportunity to exercise, made possible by the availability of a running wheel, reduces the rate of weight gain over time. All rodent models show weight gain over time; they just vary in the rate and degree of weight gain. This is similar to the situation with human beings, who vary in their weight gain based on genetic predisposition and environmental factors.

One might ask whether the trajectory of weight gain can be modified by long-term changes in lifestyle. Animal studies in which rats were placed on a hypocaloric diet for varying lengths of time and then were allowed to consume an ad libitum diet showed that the longer the animal was subjected to energy restriction, the more rapid and substantial their weight regain. Weight inevitably returned to where it would have been in control animals, not to where it was prior to energy restriction.[7] Because an animal's "defended weight" (the natural weight seen in the absence of an energy-restricted diet) continues to increase as time passes, the weight of rats subjected to prolonged energy restriction was farther away from the defended weight, resulting in a larger increase in weight when free choice of dietary intake was reintroduced (Figure 1.5).[8]

FIGURE 1.5 Does the body get used to the reduced obese state? Body weights and the rate of weight regain in animal studies[8]



Reproduced with permission from MacLean PS, Higgins JA, Johnson GC, et al. Enhanced metabolic efficiency contributes to weight regain after weight loss in obesity-prone rats. *Am J Physiol Regul Integr Comp Physiol*. 2004;287(6):R1306-R1315. doi:10.1152/ajpregu.00463.2004.[8]

Body weight, then, is a reflection of long-term energy balance, with weight gain occurring when intake exceeds expenditure, weight loss occurring when expenditure exceeds intake, and weight stability occurring when intake equals expenditure. To gain a deeper understanding of energy balance, one must understand its components—energy expenditure and energy intake.

Energy Expenditure

Total daily energy expenditure (TDEE) is equal to the amount of energy (in kilocalories) per day that a person can consume to maintain energy balance. The three main components of TDEE are:

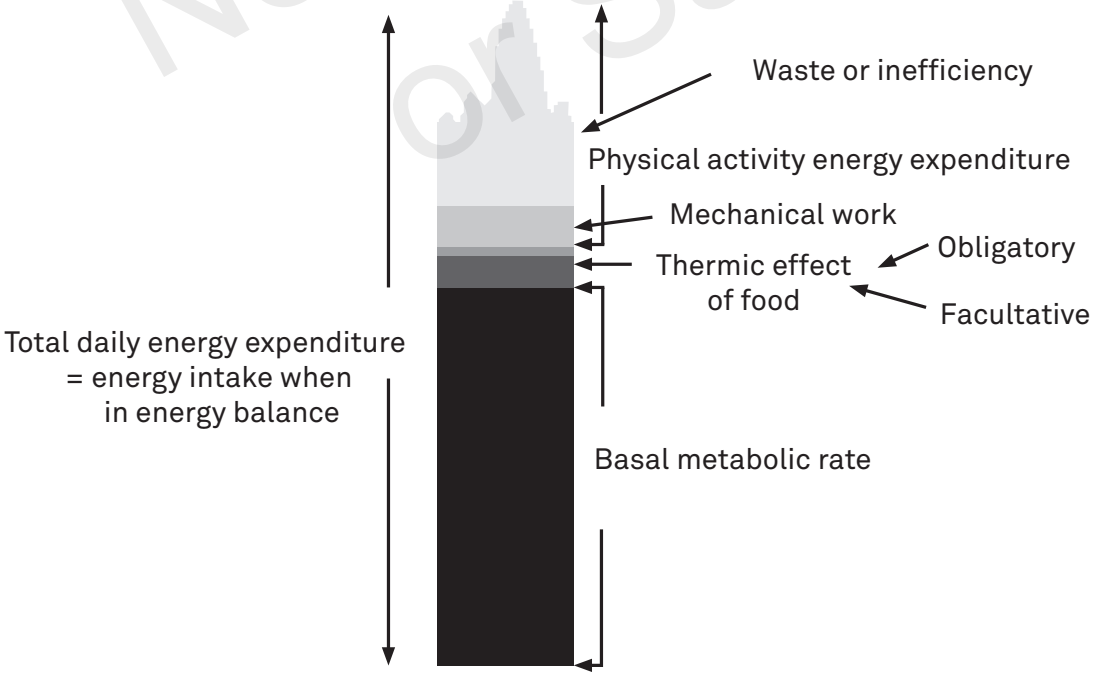
- basal metabolic rate (BMR),
- thermic effect of food (TEF), and
- physical activity energy expenditure (PAEE).

These are illustrated in Figure 1.6.

BMR is the largest component of TDEE, accounting for roughly 70% of TDEE in most individuals. It reflects the amount of energy consumed per day to maintain body temperature, electrolyte gradients across cell membranes, kidney function, and other vital bodily functions. BMR can be determined by measuring oxygen consumption with indirect calorimetry while an individual is awake but at rest. BMR can also be estimated using formulas, such as the Mifflin-St Jeor equation[9]:

Male: (10 × weight [kg]) + (6.25 × height [cm]) − (5 × age [y]) + 5
Female: (10 × weight [kg]) + (6.25 × height [cm]) − (5 × age [y]) − 161

FIGURE 1.6 Components of energy expenditure



These equations reflect the observed effect of body size, sex, and age on BMR. The formula predicts that BMR will fall with age, and as a result, so will TDEE. This fall in TDEE was recently demonstrated by a large study of more than 12,000 individuals as part of the Framingham Heart Study.[10] Because of this decline, people gain weight as they age unless they reduce their energy intake or increase their physical activity over time.

BMR is linearly related to lean body mass with a nonzero intercept.[11] That is, TDEE increases linearly as lean body mass increases, but if this relationship is extrapolated to a lean body mass of zero, there will still be some level of energy expenditure. This demonstrates that a certain minimal level of energy expenditure is associated with the energy requirements of core organs such as the brain, heart, and kidneys. There is some variability in the energy expended by people with the same lean body mass. Interestingly, though, recent evidence suggests that people with slightly elevated energy expenditure are at risk for weight gain. This somewhat counterintuitive idea will need confirmation by ongoing research, but it reflects what has been called a "thrifty phenotype."

TEF is the second component of energy expenditure. It is the energy required to digest food and distribute nutrients to tissues. The portion of TEF that represents the actual chemical energy involved in these biochemical reactions is called obligatory TEF. The other portion, called the facultative TEF, reflects the inefficiency of the system; in other words, more energy is expended in the process of assimilating dietary nutrients than would be predicted simply by the chemical reactions. TEF represents 8% to 10% of TDEE and varies between individuals. Some researchers have hypothesized that people with more efficient TEF might be predisposed to weight gain, yet the evidence for this is not conclusive.

The third and most variable component of TDEE is the PAEE. As was true for TEF, some of the energy expended in physical activity is the result of the actual mechanical work done during the activity, and some of the energy expended in physical activity is wasted due to the inefficiencies of movement. That is, it takes more energy to execute the activity than is needed just for the mechanical work of the activity. People vary in their exercise efficiency, and a person can become more efficient with experience. For example, suppose an amateur swimmer and an elite swimmer swim the same 100 m at the same speed. If both swimmers weigh the same, one might expect them to burn the same amount of energy because each must move the same amount of weight through the water for the same distance at the same speed. However, the elite athlete is a highly efficient swimmer and so burns less energy at the same workload compared to the amateur (of course the amateur is not able to generate the workload that the elite swimmer can). PAEE is a function of the intensity of the activity, the duration of the activity, and the size of the person if the activity is weight-bearing.

Physical Activity

Physical activity can occur in planned bouts or might occur through the activities of daily living. Energy generated by the latter is called nonexercise activity thermogenesis, or NEAT. There is evidence that, with overfeeding, some individuals increase their NEAT, leading to increased PAEE and a protection against weight gain.[12] The implications of this finding are that physical activity levels are biologically regulated. Most people can understand how food intake might be biologically regulated, because they experience hunger and satiety. However, people do not generally think of exercise bouts in the same way they think about meals. They understand hunger as stimulating food intake, satiety as promoting meal termination, and rising hunger as

affecting the length of time between meals. In contrast, what makes a person want to initiate an exercise bout? What makes them end the bout? What physiological parameters determine the interval between bouts of exercise? Ongoing research suggests that areas of the hypothalamus are involved in the regulation of physical activity in much the same way this region of the brain regulates appetite.

The observed relationship between TDEE and body size means that larger individuals have higher levels of TDEE than smaller individuals. This makes sense, as it would require more energy to sustain a larger body than a smaller body. This means that larger people who are maintaining weight must be eating more than smaller people. However, many people with obesity report very low levels of energy intake. These individuals wonder if they might have a "metabolic disorder" causing their obesity. This issue has been addressed in studies examining energy expenditure and food intake in people who are obese but report low levels of energy intake. These studies have demonstrated that energy expenditure in these people is what would be predicted based on their age, sex, and body size. These studies show that, although there is some variability in TDEE between individuals of a particular body size, the primary explanation for the discrepancy between reported energy intake and predicted TDEE is substantial underreporting of dietary intake.[13] These studies do not support the idea that very low levels of energy expenditure are a primary cause of weight gain.

While experimental evidence is firm on this point, it is rarely productive to discuss this data with patients in a clinical setting. Although it might be easy to think that the person with obesity who reports eating very little is not being entirely truthful, another view is that the basic pathophysiological problem leading to weight gain is a malfunction of the system that should allow them to get a realistic view of how much they are eating. The frequently heard comment "I'm eating almost nothing" may be more a reflection of the person's cognitive effort to restrict energy intake than an accurate assessment of what they are eating. In these situations, it may be more productive to say something such as, "It sounds like you're working hard to limit how much you are eating and trying your best to consume a good diet." In fact, this inability to accurately assess energy intake is one of the greatest barriers to effective lifestyle treatment of obesity and is the reason dietary self-monitoring is so important for those embarking on dietary restriction for weight loss.

Energy Intake

The brain is the primary regulator of energy homeostasis. Since the 1950s, following observations in human beings with tumors of the hypothalamus and studies in rodents in which brain regions were lesioned, scientists have known that the hypothalamus plays an important role in regulating body weight. To maintain body weight, the brain must receive information about energy consumed, energy expended, and nutrient stores within the body (refer to Figure 1.7 on page 10). For many years, the dominant theory of body weight regulation was the lipostatic theory, which posited that the brain regulated adipose tissue mass. It was not clear, however, how the brain knew what total-body adipose-tissue energy storage was.

In 1994, leptin was discovered as the likely hormone from adipose tissue signaling the brain on the status of total-body lipid stores. Ten years of experiments followed that revealed the underlying mechanisms by which leptin signaling in the hypothalamus affects energy balance.

It has become clear that the hypothalamus regulates energy intake through two parallel pathways: an anabolic pathway that promotes food intake and reduces

FIGURE 1.7 Overview of energy homeostasis

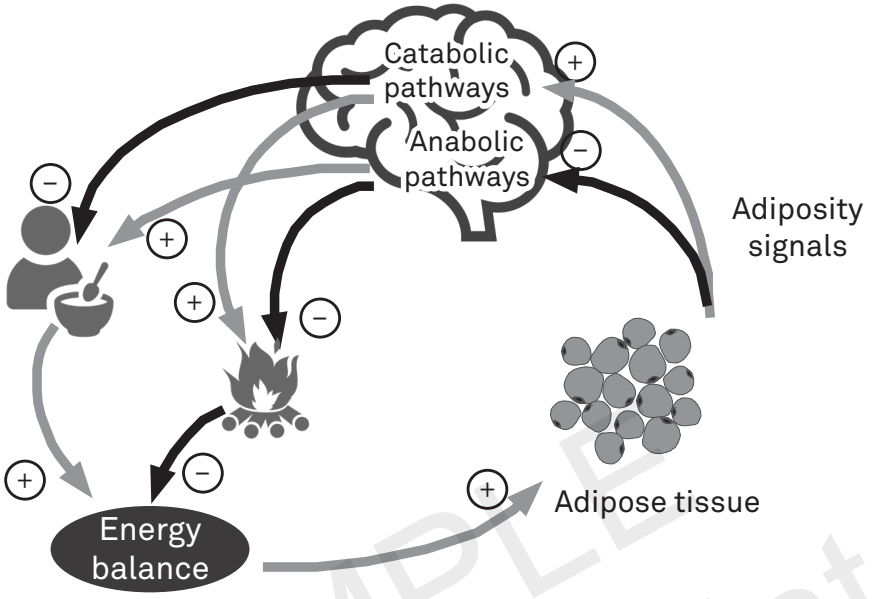
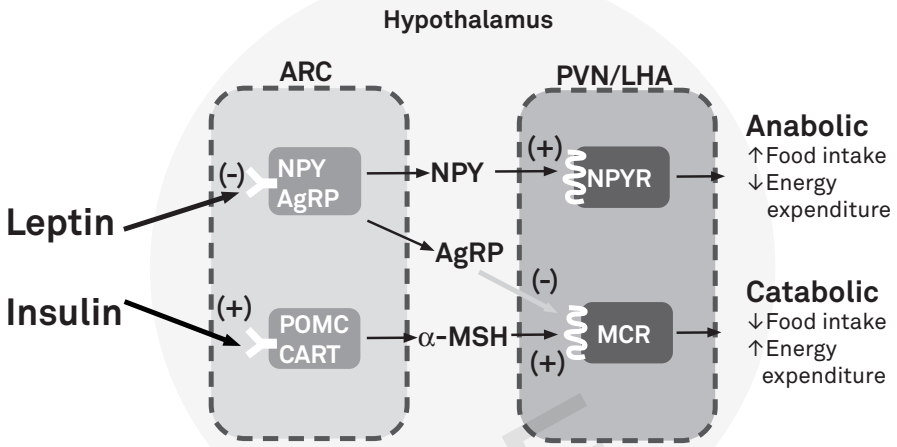


Figure 1.7 depicts the hypothalamic regulation of energy balance. The catabolic pathway from the hypothalamus inhibits food intake and stimulates energy expenditure when the body is in positive energy balance (increased fat mass). Conversely, the anabolic pathways stimulate food intake and inhibit energy expenditure when the body is in negative energy balance (decrease in fat mass). These systems work coordinately to help maintain energy homeostasis.

energy expenditure, and a catabolic pathway that reduces food intake and increases energy expenditure.[14] Changes in leptin and insulin levels signal these two pathways in a coordinate manner, stimulating the anabolic pathway in states of negative energy balance, and stimulating the catabolic pathway in states of energy excess. These two pathways live within the arcuate nucleus of the hypothalamus, as illustrated in Figure 1.8.

Cells expressing neuropeptide Y and agouti-related peptide are the first step in the anabolic pathway. Another population of cells in the arcuate nucleus express pro-opiomelanocortin and cocaine and amphetamine–regulated transcript. These cells are the first step in the catabolic pathway. Both populations of cells have receptors for leptin and insulin, although the effects of these hormones on the two cell populations are opposite. Leptin and insulin, which are increased in states of positive energy balance, stimulate the catabolic pathway and inhibit the anabolic pathway. The neurons that are downstream from these two cell populations are in the paraventricular nucleus and the lateral hypothalamus. Neuropeptide Y from the arcuate nucleus binds to receptors on cells in the paraventricular nucleus to stimulate food intake and reduce energy expenditure. A fragment of pro-opiomelanocortin, α-melanocyte-stimulating hormone, binds to downstream neurons, which express melanocortin receptors to reduce food intake and increase energy expenditure. Interestingly, agouti-related peptide made by cells in the anabolic pathway inhibits the catabolic pathway.

FIGURE 1.8 Regions of the hypothalamus that regulate energy balance



Abbreviations: AgRP, agouti-related peptide; α-MSH, α-melanocyte-stimulating hormone; ARC, arcuate nucleus; CART, cocaine and amphetamine–regulated transcript; MCR, melanocortin receptor; NPY, neuropeptide Y; NPYR, neuropeptide Y receptor; POMC, pro-opiomelanocortin; PVN/LHA, paraventricular nucleus/lateral hypothalamic area.

The Role of Appetite in Energy Intake

On closer consideration, the task of regulating appetite over time is incredibly complex. Although energy balance is generally depicted as a scale, balancing intake with expenditure, the body is rarely in energy balance. When a person wakes up in the morning, that person will not have eaten for, perhaps, 10 hours. The body is in negative energy balance and is using stored nutrients. Insulin level is low, appetite is increased, and satiety is reduced—all of which prompt the person to eat. In the hour after eating, the gastrointestinal tract is in a state of positive energy balance, but the nutrients consumed have not yet been delivered to peripheral tissues, such as skeletal muscle and adipose tissue, which remain in a state of negative energy balance. Over the course of the day, the body gradually moves into a state of positive energy balance through the ingestion of multiple meals and subsequent rising insulin levels, assimilation of ingested nutrients, and refilling of glycogen stores in the liver and muscle. Then, overnight during sleep, the body uses those stored nutrients as it transitions back to a state of negative energy balance. Thus, the body must make adjustments in energy intake on timescales shorter than what is needed for changes in levels of total body fat. The gastrointestinal tract sends out several signals that provide information on these shorter timescales. Ghrelin is a hormone made by the stomach and proximal intestine that increases with fasting and stimulates appetite. Peptide YY and glucagon-like peptide 1 are intestinal hormones whose levels increase after meal ingestion and that stimulate satiety. Many hormones are involved with regulation of hunger. The impact of these major hormones is summarized in Box 1.1 on page 12. The previously discussed cells in the hypothalamus also have receptors for and respond to these hormones. In this manner, both short-term and long-term signals of energy balance are conveyed to the hypothalamus to precisely regulate energy intake and expenditure. This system has come to be known as the *homeostatic regulatory system*.

BOX 1.1

Effect of Select Hormones and Neurotransmitters on Hunger

Hormone/neurotransmitter	Source	Effect on hunger
Leptin	Adipose tissue	Reduces
Ghrelin	Stomach	Increases
Peptide YY	Ileum and colon	Reduces
Glucagon-like peptide 1	Small intestine	Reduces

It is clear, however, that people eat not only because they are hungry. Food is a pleasurable stimulus, and brain regions that are involved in reward and pleasure are also involved in regulating food intake. The ventral striatum is one such region, and the neurotransmitter dopamine plays an important role in the process of reward and pleasure in relation to food. Some investigators have wondered whether alterations in dopamine signaling in brain regions associated with reward might be involved in the development of obesity. Studies have suggested that the density of dopamine receptors in these brain regions in people with obesity may differ from receptor density in people without obesity.[15] Whether these changes are the cause of, or the result of, obesity is not clear.

Although reward plays an important role in behavior, human beings do not always respond to rewarding stimuli. Certain regions of the brain, including the prefrontal cortex, modulate responses to rewarding stimuli in the environment. These brain regions modulate impulsivity and facilitate long-term planning. Activity in these regions has been found to be dramatically increased in individuals with eating disorders, such as anorexia nervosa, and reduced in individuals with obesity.[16] It is unclear whether these alterations in brain functioning are a cause of, or a consequence of, obesity.

Social and Cultural Influences on Intake

Food intake, physical activity, and other lifestyle behaviors are also subject to myriad social and cultural influences, which likely work through the cerebral cortex to modify behavior. Many people find that they overeat in social settings where it is encouraged, such as at holiday gatherings with family and friends. And individuals respond to a range of environmental stimuli—from the promotion of fast-food consumption to the praise of organic or natural food—that shape their behaviors. In addition, the importance of social relationships in body weight regulation has been demonstrated in studies of social networks. One such study, of people who were monitored over many years as part of the Framingham Heart Study, evaluated the available data on body weight measured longitudinally, as well as the data on the social relationships among people living in Framingham, MA.[17] The study found that social connections were strongly correlated with longitudinally measured weight gain. People in some groups gained weight together over time, and people in other groups maintained a normal weight over time. It is likely that social groups facilitated lifestyle behaviors that promoted weight gain or weight

maintenance. It is not clear whether social networks can be leveraged to alter body weight; however, it is certain that social support is important in helping people adhere to a lifestyle program.

Genetics

Studies of twins raised in different households suggest that 40% to 70% of BMI is genetically determined.[18] There are several rare conditions in which single gene mutations cause obesity. Examples are mutations of leptin, the leptin receptor, proopiomelanocortin, and the melanocortin receptor. There are also syndromic forms of obesity, the most common of which is the Prader-Willi syndrome. These monogenic and syndromic forms of obesity are characterized by early-onset severe obesity and are often associated with other findings, such as developmental delay, short stature, and hypogonadism. Currently, genetic testing is available to make specific diagnoses for many of these conditions.[19] The development of newer therapeutic approaches to some of these genetic and syndromic conditions means that knowledge of a specific genetic problem in an individual with early-onset severe obesity may allow for specific treatment to be delivered, resulting in an improved outcome.[20]

Common obesity is explained by not one but many genes. Genome-wide association studies have identified more than 100 genetic loci that are associated with obesity. However, together these genes only explain 3% to 5% of the variance in BMI in a population. A number of gene panels have been developed that allow for the prediction of weight-gain risk, but these tests are not yet precise enough to advocate for their use in clinical practice. The most common gene associated with obesity is the fat mass and obesity associated (*FTO*) gene.[21] Variants of *FTO* appear to be associated with differences in appetite and differences in the development of thermogenic fat (beige fat). Although the *FTO* gene is the most common gene variant associated with weight gain, the effect size is small. Individuals who are homozygous for the risk allele weigh, on average, only a few more pounds than those with low-risk alleles.

Implications of Thinking of Obesity as a Disease of Body Weight Regulation

Thinking about obesity as a chronic, often progressive metabolic disease rather than as a problem of lifestyle choices changes the way health care professionals communicate with patients about it and how they treat it. First, people who undertake a lifestyle change with the goal of losing weight often become frustrated when, despite continuing the new lifestyle program, their rate of weight loss—while initially rapid—slows and reaches a new plateau. Many people become discouraged with this plateau and feel that treatment plan is no longer working. This frustration can lead to discontinuation of the lifestyle intervention and weight regain. It is important to explain to patients that TDEE declines with weight loss for a number of reasons and, as a result, a new steady state is reached in which the reduced energy intake becomes equal to a reduced TDEE. What causes the reduction in TDEE with weight loss? The most important factor is the weight loss itself. Recall that energy expenditure is linearly related to lean body mass. As a person loses weight, that person's basal metabolic rate declines. In addition, energy expended in physical activity declines because the person weighs less. Walking a mile at a body weight of 68 kg (150 lb) uses less energy than walking a mile at a weight of 102 kg (225 lb). When discussing lifestyle interventions, clinicians should make clear to patients that, while continuing the lifestyle program, they can expect their

weight to plateau at a new level, and that continued adherence to the program will be required to maintain their new weight over time.

Adaptive Responses to Weight Loss That Promote Weight Regain

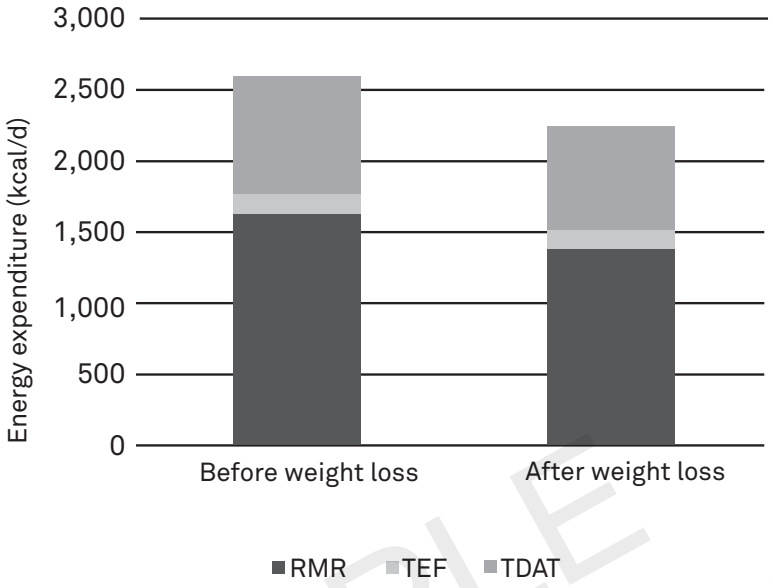
If weight is a physiologically regulated parameter, then when a person loses weight, it would stand to reason that the body would recruit regulatory systems to try to restore body weight to the defended (natural) trajectory. Evidence supports this hypothesis. Accumulating evidence in studies of people who have lost weight demonstrates that a person's energy expenditure falls more than one would expect based simply on the amount of weight lost, and that the person's appetite increases.[22] These responses to weight loss reduce energy needs and increase the drive for energy intake, predisposing the individual to positive energy balance and weight regain.

As noted previously, energy expenditure is linearly related to body mass. With weight loss, a person's energy expenditure would be expected to fall as a result of the reduction in body size. But studies measuring energy expenditure before and after weight loss have shown that the fall in energy expenditure is greater than what would be predicted simply by the loss in body weight.[22] This means that someone who has lost weight needs to consume less energy than a person of the same body size who has not lost weight. This disproportionate reduction in energy expenditure in relation to weight loss occurs both in the BMR and the PAEE. It is associated with a fall in leptin and thyroid hormone levels and a fall in sympathetic nervous system activity.[23] Studies examining work efficiency during low-level exercise have shown that, after weight loss, the amount of energy expended during a fixed exercise workload is lower than the amount expended at the same workload before weight loss. There is some evidence that replacing leptin to levels before weight loss restores exercise efficiency to levels before weight loss.[24] Several long-term follow-up studies have been done to see whether this reduction in energy expenditure persists over time. These studies have consistently shown that, indeed, the reduction in energy expenditure persists for years following weight loss, with no evidence that it goes into remission.[25] This means that energy intake needs to remain at a low level in order to sustain a reduced-weight state unless habitual levels of physical activity are increased to close the "energy gap." See the example in Figure 1.9.

Appetite increases with weight reduction. Studies have measured hunger and satiety in people before and after weight loss and shown, not surprisingly, that hunger increases and postmeal satiety falls. Appetite is regulated in part by levels of hormones, as discussed earlier. Levels of leptin and insulin, both satiety hormones, fall as fat mass declines with weight loss. Levels of ghrelin, the intestinal hormone that is associated with increased hunger, rise with weight loss. Levels of peptide YY, a satiety hormone from the intestine, fall with weight loss. These changes in appetite and hormonal modulators of eating behavior persist for at least a year after weight loss, the longest anyone has monitored patients for these changes (refer to Figure 1.10).[26]

Other studies have examined regional brain activity in response to food-related stimuli before and after weight loss. A wide variety of brain regions show increased blood flow in response to pictures of highly palatable food when these images are presented to patients during magnetic resonance imaging. When a normal-weight person is overfed for 3 days, these brain responses to palatable food images are markedly attenuated. However, when individuals who were previously obese and lost weight are overfed for 3 days, they continue to show robust

FIGURE 1.9 Energy expenditure before and after weight loss



Example: A 91-kg (200-lb) female losing 11 kg (25 lb) would experience a 350 kcal/d reduction in TDEE as a result of weight loss.
Abbreviations: TDAT, total daily activity thermogenesis; TDEE, total daily energy expenditure; TEF, thermic effect of food; RMR, resting metabolic rate.

FIGURE 1.10 Mean (±SE) fasting and postprandial levels of ghrelin, peptide YY, amylin, and cholecystokinin at baseline, 10 weeks, and 62 weeks[26]

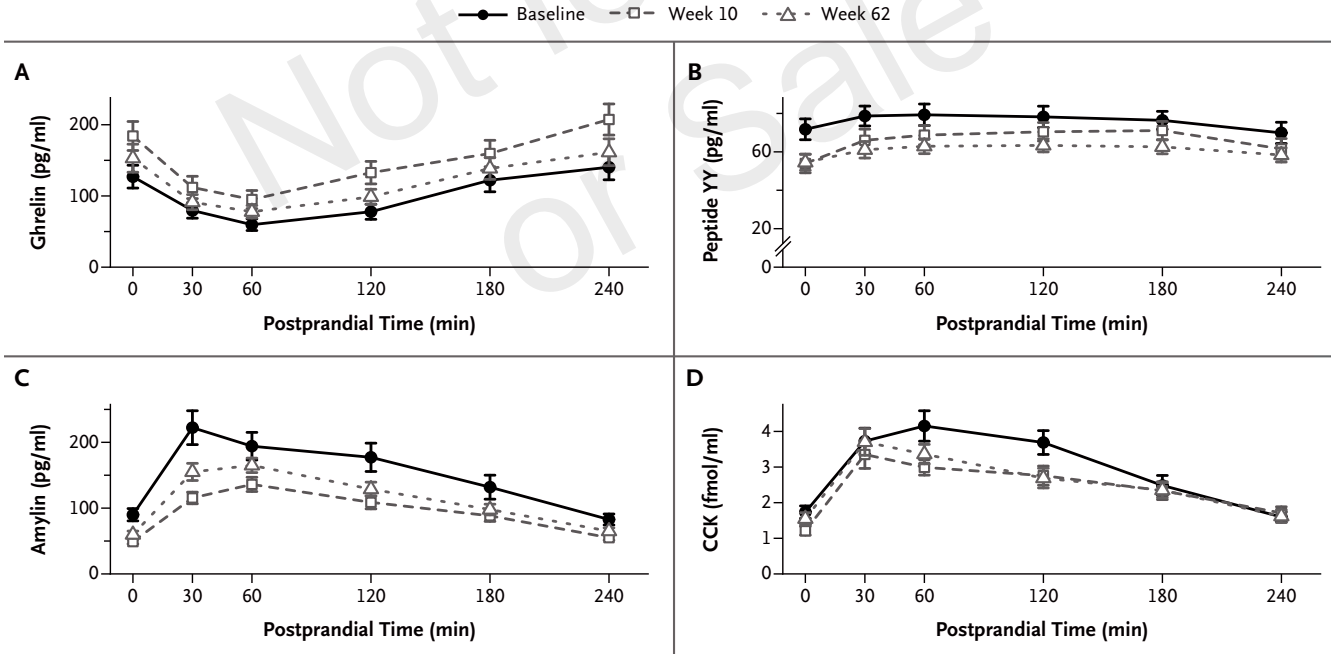


Figure 1.10 depicts levels of hormones that promote satiety (peptide YY, amylin, and cholecystokinin) and the hormone that promotes hunger (ghrelin) over 4 hours following a test meal delivered to people with obesity and consumed either before weight loss (baseline), at week 10 following weight loss, or at week 62 following weight loss.
Abbreviation: CCK, cholecystokinin.
Reproduced with permission from Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med*. 2011;365(17):1597-1604. doi:10.1056/NEJMoa1105816.[26]

increases in regional brain activity in response to images of palatable food.[27] These results support the notion that the drive to eat is increased in people who have lost weight, and their perception of food-related stimuli is different from that of people of normal weight. These findings emphasize the biological nature of weight regulation and the challenges facing people who have lost weight.

Is Weight Maintenance Possible?

How, then, can anyone maintain a reduced state in the face of all the biological mechanisms that promote weight regain? Despite what could be considered the depressing message conveyed by the data related here, many people are successful at losing weight and at maintaining that weight loss over time. The National Weight Control Registry is a group of more than 10,000 people who have lost more than 23 kg (50 lb) and maintained that weight loss for more than 5 years.[28] These individuals have been successful at pushing back against the physiologic mechanisms that drive weight regain in most people. They use cognitive strategies to counteract the biological drive for weight regain, including frequent self-weighing, high levels of physical activity, and the consumption of an energy-restricted, low-fat diet.

The Prevalence of Obesity

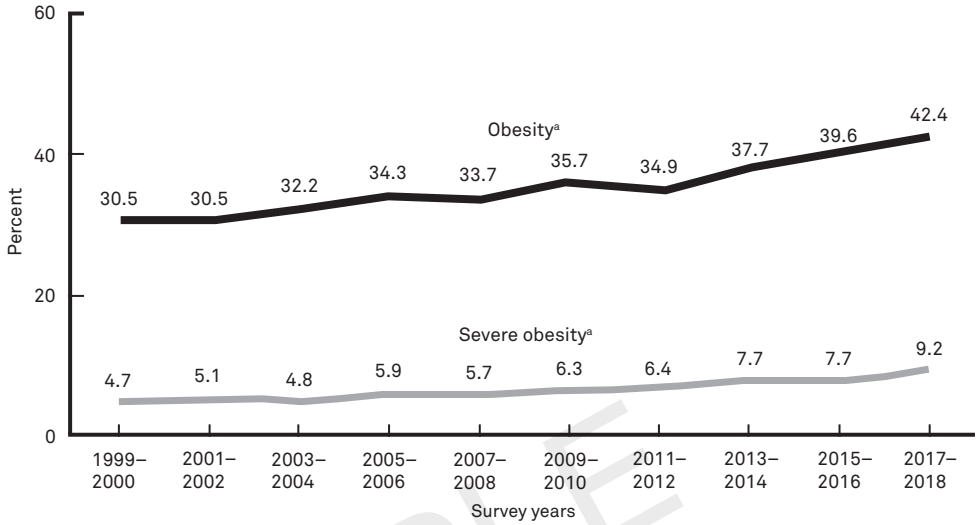
In the United States, two large epidemiologic studies have followed the prevalence of obesity over time. One, the Behavioral Risk Factor Surveillance System (BRFSS), is a health survey system that collects data from a large, geographically representative sample of US residents regarding their health-related risk behaviors and chronic health conditions, including obesity. BRFSS uses self-reported height and weight data to calculate BMI. Because these data are self-reported, the actual prevalence of obesity is likely underestimated. The advantage of the BRFSS data set is that it provides detailed geographic estimates of obesity prevalence over time. The second data set comes from the National Health and Nutrition Examination Survey (NHANES), which uses directly measured heights and weights from a smaller sample of people that is statistically representative but not as geographically comprehensive as the BRFSS sample.

Although some experts thought that the rising prevalence of obesity had plateaued, the most recent data suggest that the prevalence of obesity continues to rise across the United States. The most recent data from NHANES (2017–2018) showed that the prevalence of obesity among all children and adolescents aged 2 to 19 years in 2018 was 19.3%.[29] This was up from 5.2% in 1974 and from 17.2% in 2014. Among adults, the prevalence of obesity was 42.4% in 2018. From 1999–2000 to 2017–2018, the prevalence of obesity in adults increased from 30.5% to 42.4%. During the same interval, the prevalence of severe obesity increased from 4.7% to 9.2% (refer to Figure 1.11).[30]

Obesity disproportionately affects certain racial and ethnic groups. In 2017–2018, the prevalence of obesity was 49.6% in non-Hispanic Black adults and 44.8% among Hispanic adults, as shown in Figure 1.12.[30] These differences in prevalence are due in part to a number of social and environmental factors including food insecurity, aspects of the food environment, differential access to health care, financial and housing challenges, and neighborhood factors that result in barriers to physical activity. While women have more body fat at any given level of BMI, there was no difference in the prevalence of obesity in 2017–2018 between men and women.†

† Report identified participants as men and women. Gender was not further specified.

FIGURE 1.11 Trends in age-adjusted obesity and severe obesity prevalence among adults aged 20 years and older from 1999–2000 through 2017–2018 in the United States[30]

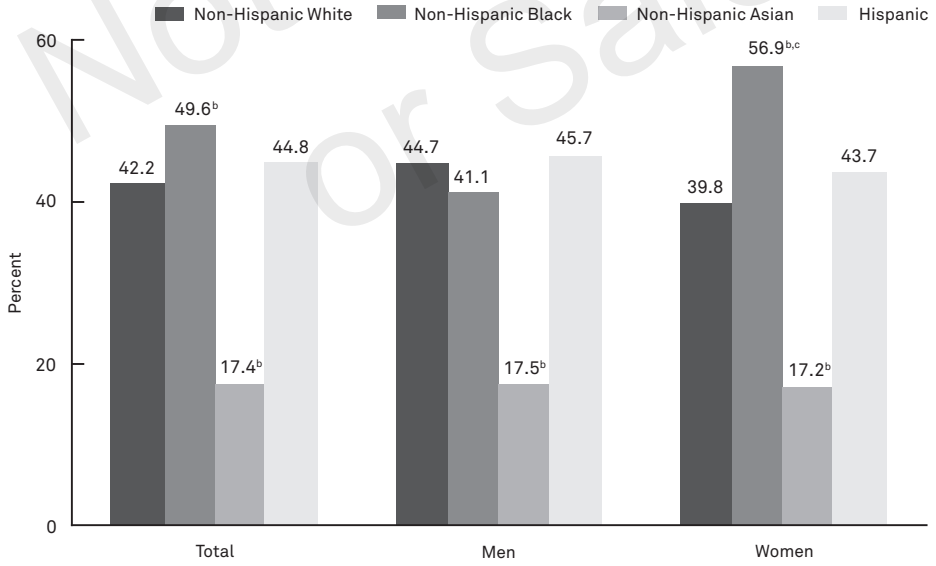


Estimates were age adjusted by the direct method to the 2000 US Census population using the age groups 20 to 39, 40 to 59, and 60 and over.

[a] Significant linear trend.

Adapted from Hales CM, Carroll MD, Fryar CD, Ogden CL. *Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017-2018*. NCHS Data Brief no. 360. National Center for Health Statistics; 2020. Accessed August 22, 2022. www.cdc.gov/nchs/products/databriefs/db360.htm.[30]

FIGURE 1.12 Age-adjusted prevalence of obesity among adults aged 20 years and older, by sex, race, and Hispanic origin, in 2017–2018 in the United States[a,30]



[a] Report identified participants as men and women. Gender was not further specified.

[b] Significantly different from all other race and Hispanic-origin groups.

[c] Significantly different from men for same race and Hispanic-origin group.

Estimates were age adjusted by the direct method to the 2000 US Census population using the age groups 20–39, 40–59, and 60 and over.

Adapted from Hales CM, Carroll MD, Fryar CD, Ogden CL. *Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017-2018*. NCHS Data Brief no. 360. National Center for Health Statistics; 2020. Accessed August 22, 2022. www.cdc.gov/nchs/products/databriefs/db360.htm.[30]

Changes in Weight Throughout the Life Span

In Childhood

BMI is used to determine weight status among children just as it is in adults. However, in children and adolescents, BMI cutoff points defining obesity are age-specific and sex-specific in a manner that is typically referred to as BMI-for-age.[31] The CDC growth charts are commonly used to categorize children's and adolescents' weight-for-age status into corresponding percentiles. Obesity in children and adolescents is defined as a BMI at the 95th percentile or greater. Weight-for-height tends to increase in late childhood before puberty. It then falls during puberty, as linear growth accelerates. Weight then rises again in late adolescence and the period of emerging adulthood. Using BMI-for-age criteria, obesity prevalence rises with increasing age. Data from 2017–2018 show that the prevalence of obesity was 13.4% among 2- to 5-year-olds, 20.3% among 6- to 11-year-olds, and 21.2% among 12- to 19-year-olds. As is true for adults, the prevalence of obesity is higher among Hispanic children (25.6%) and non-Hispanic Black children (25.2%), as compared to non-Hispanic White children (16.1%) or non-Hispanic Asian children (8.7%).[29]

In Emerging Adulthood

Recent analyses have focused on the period of life from age 18 years to 25 years as a life stage for which obesity prevalence has been growing. This period, referred to as emerging adulthood, is characterized developmentally as a time of life when individuals transition from school to work and develop lifelong lifestyle habits along with an adult identity. An analysis of NHANES data showed that, between 1976 and 2018, the average BMI among emerging adults increased from 23.1 to 27.7. The prevalence of obesity in this group increased from 6.2% in 1976–1982 to 32.7% in 2017–2018. In contrast, the prevalence of normal weight in this group decreased from 68.7% to 37.5% over the same time. A particularly sharp rise in the prevalence of obesity occurred between 2016 and 2018.[32] Future studies should focus on the establishment of lifelong lifestyle habits in this group of young adults.

During Pregnancy

Weight gain during pregnancy is normal and important for the development of the fetus. However, excessive weight gain can lead to adverse consequences for both birth parent and child that may extend beyond pregnancy. Individuals gain an average of 14.1 kg (31 lb) during pregnancy, although those with obesity gain less weight—those with class 1 obesity gain an average of 12.2 kg (27 lb); those with class 2 obesity, 10.3 kg (23 lb); and those with class 3 obesity, 8.2 kg (18 lb).[33] In 2009, the National Academy of Medicine issued guidance on the appropriate degree of gestational weight gain. These recommendations were based on the risk of adverse health consequences to the baby and birth parent associated with excessive gestational weight gain. These guidelines suggested a range of appropriate gestational weight gain of 5 to 9 kg (11 to 20 lb) for individuals with obesity.[34] In 2019, the LifeCycle Project–Maternal Obesity and Childhood Outcomes Study Group conducted a meta-analysis of the relationship between gestational weight gain and infant and birth parent outcomes in people with obesity. They suggested that the appropriate level of gestational weight gain in those with class 1 obesity was 2 to 6 kg (4 to 13 lb); in those with class 2 obesity, it was less than 4 kg (9 lb); and in those with class 3 obesity, less than 6 kg (13 lb).[35] A more recent retrospective

cohort study, using US national birth and infant death data from 2011 to 2015, examined the relationship between gestational weight gain and infant morbidity and mortality, with the goal of identifying optimal weight gain in individuals with obesity.[36] The most important finding of this study was that insufficient weight gain was associated with adverse infant outcomes, even in those with obesity. This study suggests that a goal of weight loss or even weight maintenance might be inappropriate for those with obesity during pregnancy. In addition, excessive gestational weight gain, especially during the first trimester, is strongly associated with postpartum weight gain, and subsequent adverse weight and health status later in life for the birth parent.[37]

During Menopause

During the menopausal transition, most individuals gain weight. Weight gain typically begins a year or two before the last menstrual period. The average gain during menopause is 0.45 to 0.68 kg (1 to 1.5 lb) per year, although the numbers vary a great deal. Twenty percent of people will gain a total of 4.5 kg (10 lb) during this transition. Much of the weight gain is due to increased body fat; there is a redistribution of fat from the lower body to the abdomen and a loss in lean body mass.[38] This increase in central adiposity is associated with an increased risk for metabolic diseases. The weight gain is due to a number of factors, including aging, a fall in estradiol levels, a decrease in energy expenditure, a reduction in spontaneous physical activity, and, possibly, a rise in levels of follicle-stimulating hormone. Compelling data from animal models indicate that falling estradiol levels result in a reduction in spontaneous physical activity, which predisposes one to a positive energy balance. There is growing evidence to support this phenomenon in human beings as well.[39] As a result, encouraging individuals to increase their physical activity during the menopausal transition may be an important strategy for combating weight gain. Novel data from mouse models suggest that the rise in follicle-stimulating hormone levels at menopause may have an independent effect on body weight, although data to support this effect in human beings are currently lacking.[40]

In Older Age

Weight tends to increase until the age of 65 years. After that, weight tends to gradually decline, although there is considerable interindividual variation. This is caused, in part, by a gradual reduction in skeletal muscle mass (sarcopenia), while fat mass continues to increase.[41] Weight loss may occur in older adults, in part, due to changes in taste and smell, a reduction in hunger, difficulties with eating due to dental or neurological conditions, and challenges with acquiring and preparing palatable food. Increased BMI is less associated with adverse health risks in older individuals than it is in younger individuals. The greatest health risks are associated with sarcopenic obesity (increased fat mass with reduced skeletal muscle mass) in older adults.[42] Consequently, weight loss through restriction of energy intake alone, which may promote the loss of lean body mass, may be less valuable in older individuals. The inclusion of regular physical activity in weight loss interventions for older people helps preserve lean body mass and improve functional capacity.

Recent thinking has highlighted the importance of the duration of exposure to obesity in the development of adverse health consequences. Emerging data suggests that the risk of certain complications, such as type 2 diabetes, hypertension,

and lipid abnormalities, increases the longer a person has been obese.[43] These data support the concerns over the high prevalence of obesity in young people, as well as the importance of identifying and addressing obesity as early in life as possible.

The Consequences of Obesity

Obesity is defined as a degree of excess weight that predisposes an individual to adverse health consequences. Excess body fat is associated with a range of adverse health consequences, including type 2 diabetes, hypertension, coronary artery disease, metabolic dysfunction–associated steatotic liver disease, obstructive sleep apnea, reproductive dysfunction (including infertility and hypogonadism in males), degenerative arthritis, depression, and a number of cancers, to name just a few.[44,45] Some of the medical complications of obesity are shown in Figure 1.13.

Perhaps because of these associated complications, obesity is associated with increased rates of mortality. A plot of mortality vs BMI shows a curvilinear relationship (refer to Figure 1.14).[46] Individuals who are underweight have an increased risk of mortality, and those who are obese also have an increased risk of mortality. This relationship between BMI and mortality risk is the basis for the currently used cutoff points for overweight and obesity.

Researchers have raised questions about the accuracy of this relationship, as the original data showing this relationship came from the 1960s and 1970s, when fewer people were obese. In the 1990s and early 2000s, obesity became far more prevalent. This change in prevalence means that individuals with a BMI of 30 in 1970 might not be directly comparable to individuals with a BMI of 30 in 2000. People who had a BMI of 30 in 1970 would have been genetically more predisposed to gain weight in an environment that was not as obesogenic as the environment of 2000, so they may have had a greater risk for metabolic disease. In addition, the treatment of weight-related comorbidities, including hypertension, hyperlipidemia, and diabetes, has improved since these original studies were done, thus reducing the mortality risk associated with obesity in connection with comorbidities. An ideal body weight would be a level of body fat that is associated with the lowest mortality risk. In current guidelines, this ideal weight is established at a BMI of 20 to 25. There is, however, some reason to think that the ideal weight range now might be 25 to 30, especially in older individuals, in whom the relationship between weight and mortality is less than in younger people.[47]

Two of the most important contributors to morbidity in people with obesity are type 2 diabetes and insulin resistance. The risk of developing type 2 diabetes rises dramatically with increased BMI, as illustrated in Figure 1.15 on page 22.[48,49] These complications are associated with central accumulation of adipose tissue. With excess fat accumulation, circulating levels of free fatty acids rise and are thought to impair insulin action. In addition, the expanded fat tissue mass is associated with increased circulating inflammatory markers, which also interferes with normal insulin action. Finally, the inability of adipose tissue to store lipid normally because it has reached or exceeded its storage capacity results in lipid accumulation in other tissues, including skeletal muscle and pancreatic β cells. This "lipotoxicity" is associated with decreased insulin action in skeletal muscle and a reduction in insulin secretory capacity. Weight loss has been shown to reverse a number of these defects and improve insulin action, demonstrating the causal link between obesity and insulin resistance.[50]

Cardiovascular disease is more common in people with obesity.[51] This is, in part, due to changes in circulating lipid levels that favor small, dense, low-density lipoproteins, increased triglycerides, and reductions in high-density lipoprotein cholesterol. Obesity is also associated with increased rates of hypertension, which

FIGURE 1.13 Medical complications of obesity

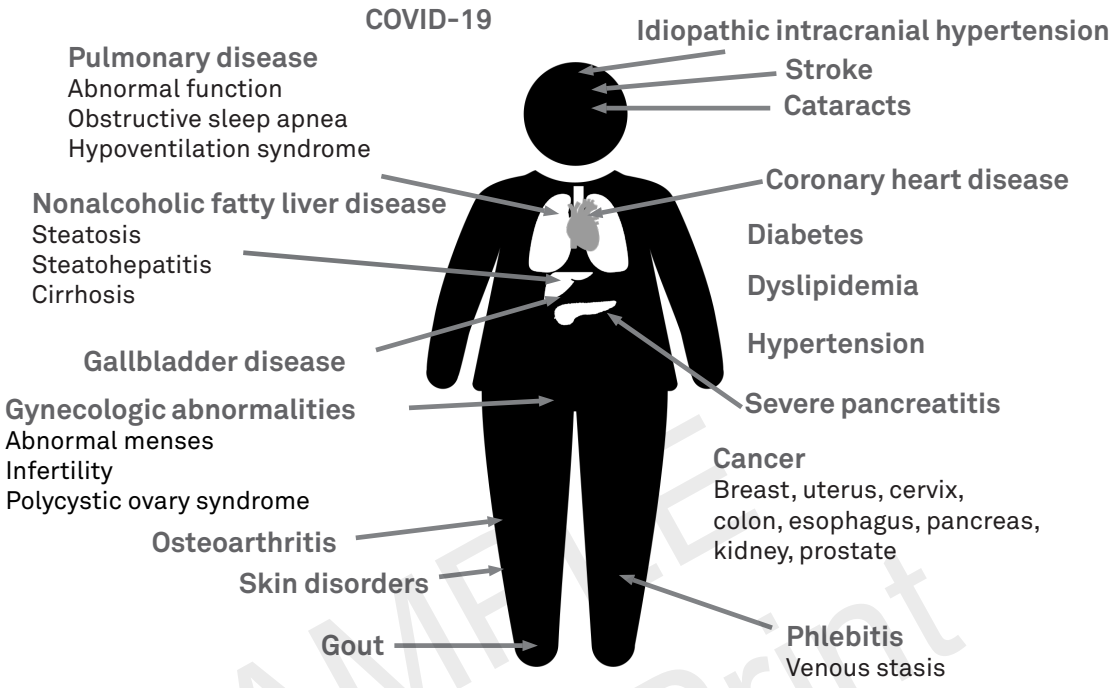
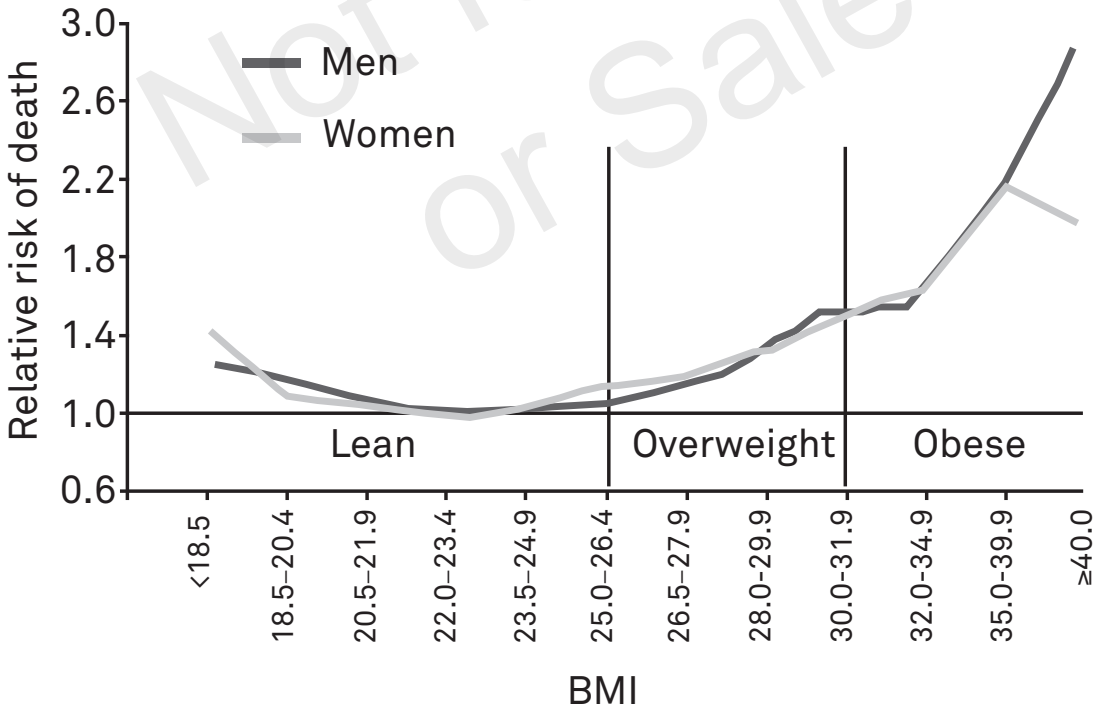


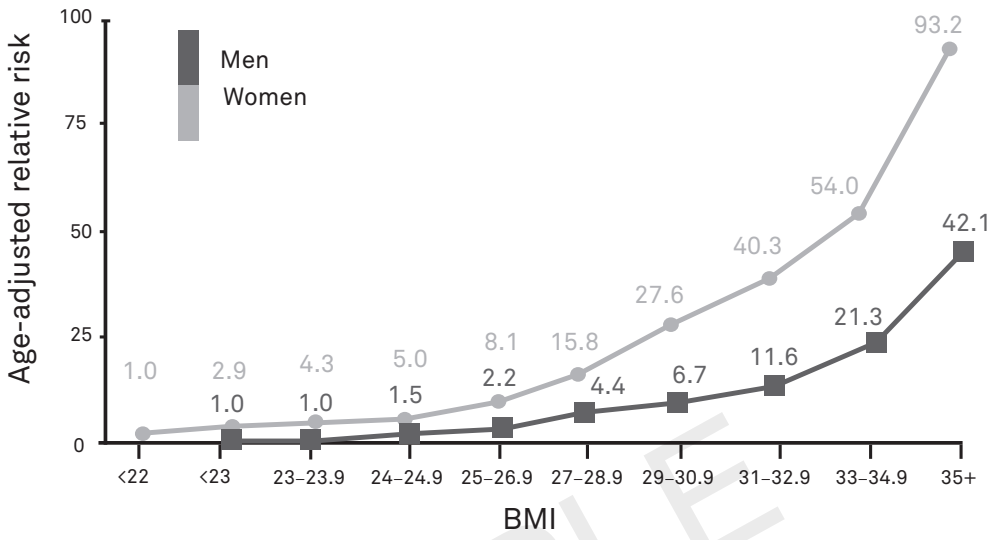
FIGURE 1.14 Relationship between BMI and cardiovascular disease mortality[a,46]



Adapted with permission from Robert Eckel, MD.

[a] Study participants were described as men and women. Gender was not further specified.

FIGURE 1.15 Relationship between BMI and risk of developing type 2 diabetes[a,48,49]



Adapted with permission from Robert Eckel, MD.

[a] Study participants were described as men and women. Gender was not further specified.

also contribute to the risk for cardiovascular disease. Increased sympathetic tone, circulating blood volume, and increased cardiac output all contribute to a risk for hypertension in the setting of obesity. Insulin resistance and type 2 diabetes also contribute to the increased risk for heart disease in people with obesity.

Breast cancer and endometrial cancer are more common in females with obesity. Males with obesity have higher mortality rates from cancers of the prostate and colon. A number of other cancers have also been linked to obesity.[52] The mechanisms of these associations are not entirely clear, but increased inflammatory mediators and insulin resistance may play important roles. Although insulin is typically known for its metabolic effects, it is also a growth factor. With increasing body weight, insulin resistance occurs with compensatory increases in circulating insulin levels. The insulin resistance, however, is only in the metabolic signaling pathway within cells, while the growth-promoting effects of insulin appeared to be maintained. As a result, the increased circulating of levels of insulin may promote cell growth and division, leading to cancer in individuals at risk.

Increased fat mass can directly cause a number of problems as well. Increased body weight can lead to degenerative joint disease, especially in the hips and knees. Surgeons may be reluctant to replace joints in individuals with obesity, out of fear that the prosthetic joints may be subject to excessive stress and fail. The accumulation of adipose tissue in the abdomen can result in increased intra-abdominal pressure, leading to gastroesophageal reflux and urinary incontinence. The accumulation of fat in the retropharynx and neck can lead to obstructive sleep apnea. The ectopic storage of fat in the liver can lead to metabolic dysfunction–associated steatotic liver disease and even cirrhosis. Insulin resistance may trigger increased androgen secretion by the ovaries and the development of polycystic ovary syndrome in susceptible females, resulting in irregular menses and infertility. Males with obesity may develop hypothalamic hypogonadism. Low testosterone levels may increase with weight loss.

Although it is clear that obesity increases a person's risk for a large number of health problems, not all people with obesity have the same level of risk. Individuals with "metabolically healthy" obesity have normal serum levels of lipids and glucose, and normal blood pressure.[53] These individuals are at lower risk of developing adverse health consequences than individuals of normal weight with elevated lipid and glucose levels and hypertension. However, they are at a higher risk than individuals of normal weight with normal metabolic parameters.[54] It may be that high levels of physical activity protect some people with obesity from adverse health consequences.[55]

In addition, a growing body of literature is reporting on what has come to be known as the "obesity paradox."[56] Studies of people with heart failure surprisingly demonstrated that a number of outcomes were better in people with obesity than in people of normal weight. This unexpected observation of a protective effect of obesity has been seen in connection with several other health conditions, including renal failure, and in patients in the intensive care unit. While controversial, it may be that once a person has a serious illness, a modest increase in body fat protects them from the catabolic effects of that condition.

Summary

Although not every person with obesity suffers serious adverse consequences, excess body fat is clearly associated with a wide range of some of the most commonly seen health problems in adults. Weight loss can improve many of these adverse consequences, and greater benefits are seen with greater degrees of weight loss.

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