

ENERGY METABOLISM AND OBESITY

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The average adult human consumes close to 1 million calories per year. Despite this huge energy intake, most healthy individuals are able to strike a remarkable balance between energy intake and energy expenditure, resulting in a state of energy balance. This accurate balance between energy intake and energy expenditure is an example of homeostatic regulation and results in maintenance of body weight and body energy stores. Regulation of energy balance is achieved over the long-term despite large fluctuations in energy intake and energy expenditure within and between days. The accuracy and precision by which the body maintains energy balance is highlighted by the fact that even a small error in the system can have detrimental consequences over time. If energy intake exceeds energy expenditure by as little as 25 kcal/d, over time, a person becomes obese. The achievement of energy balance is driven by the first law of thermodynamics, which states that energy can be neither destroyed nor created. This principle necessitates that when energy intake equals energy expenditure, body energy stores must remain constant. Obesity is the end result of a mismatch between energy intake and energy expenditure, such that intake exceeds expenditure, resulting in net accumulation of energy stores in the body. It remains unclear, however, whether obesity is due to excess energy intake or a reduction in energy expenditure. This article reviews the influence of energy expenditure on the cause of obesity.

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COMPONENTS OF ENERGY BALANCE: ENERGY INTAKE, ENERGY EXPENDITURE, AND BODY ENERGY STORAGE

Energy intake is defined as the caloric or energy content of food as provided by the major sources of dietary energy: carbohydrate (4 kcal/g), protein (4 kcal/g), fat (9 kcal/g), and alcohol (7 kcal/g). The energy that is consumed in the form of food can be stored in the body in the form of fat (the major energy store), glycogen (short-term energy and carbohydrate reserves), or protein (rarely used by the body for energy except in severe cases of starvation and other wasting conditions, as discussed later) or used by the body to fuel energy-requiring events.

The energy that is consumed in the form of food is required by the body for cellular, metabolic, and mechanical work, such as breathing, heart beat, and muscular work, all of which require energy and result in heat production. The largest use of energy is needed to fuel resting or basal metabolic rate, which is the energy expended by the body to maintain basic physiologic functions (e.g., heart beat, muscle contraction and function, respiration). Basal metabolic rate is the minimum level of energy expended by the body to sustain life. It can be measured after a 12-hour fast while the subject is maintained in a warm quiet environment. In most situations, it is difficult to measure the basal metabolic rate except perhaps during sleep because energy expenditure increases above basal levels as a result of the energy cost of arousal. Because of the difficulty in achieving basal metabolic rate under most measurement situations, resting metabolic rate is frequently measured using the same measurement conditions stated for basal metabolic rate. The major difference between basal and resting metabolic rate is the slightly higher energy expended during resting metabolic rate (approximately 3%) as a result of subject arousal. Because of this small difference, the terms *basal* and *resting metabolic rate* are often used interchangeably. Resting metabolic rate occurs in a continual process throughout the 24 hours of a day and remains relatively constant within individuals over time. In the average adult human, resting metabolic rate is approximately 1 kcal/min. Basal or resting metabolic rate is the largest component of energy expenditure.

In addition to resting metabolic rate, there is an increase in energy expenditure in response to food intake. This increase in metabolic rate after food consumption is often referred to as the thermic effect of a meal (or meal-induced thermogenesis) and is the energy that is expended to digest, metabolize, and store ingested macronutrients. The energy cost associated with meal ingestion is primarily influenced by the composition of the food that is consumed and is relatively stable within individuals over time. The thermic effect of a meal usually constitutes approximately 10% of the caloric content of the meal that is consumed. The third source of energy expenditure in the body is the increase in metabolic rate that occurs during physical activity (includes exercise as well as all forms of physical activity). *Physical activity energy expenditure* (or the

thermic effect of exercise) is the term frequently used to describe the increase in metabolic rate that is caused by use of skeletal muscles for any type of physical movement. Physical activity energy expenditure is the most variable component of daily energy expenditure and can vary greatly within and between individuals to the volitional and variable nature of physical activity patterns.¹³

In addition to the three major components of energy expenditure, there also may be a requirement for energy for two other minor needs. The energy cost of growth occurs in growing individuals but is negligible except within the first few months of life. Finally, adaptive thermogenesis is heat production during exposure to reduced temperatures, but this rarely occurs in humans except during the initial months of life.

Energy balance occurs when the energy content of food is matched by the total amount of energy that is expended by the body. When energy intake exceeds energy expenditure, a state of positive energy balance occurs. Positive energy balance occurs when excessive overfeeding relative to energy needs occurs, and the body increases its overall energy stores. When energy intake is lower than energy expenditure, negative energy balance occurs. Energy balance can occur regardless of the levels of energy intake and expenditure; energy balance can occur in inactive individuals as well as in highly active individuals, provided that adequate energy sources are available.

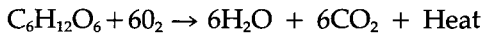
Although the body continuously consumes a mixed diet of carbohydrate, protein, fat, and sometimes alcohol, the preferred store of energy is fat. There is a clearly defined hierarchy of energy stores that outlines a preferential storage of excess calories as fat. For alcohol, there is no storage capacity in the body. Alcohol that is consumed is immediately oxidized for energy. For protein, there is a limited storage capacity, and under most situations, protein metabolism is well regulated. For carbohydrate, there is only a limited storage capacity, in the form of glycogen, which can be found in the liver and in muscle. Glycogen provides a small, short-term energy store, which can easily be depleted after an overnight fast or after a bout of exercise. Ingested carbohydrate is mostly used immediately for energy and there are limited mechanisms in humans for converting excess carbohydrate to fat for energy storage.²⁴ Instead, when excess carbohydrates are consumed, the body adapts by preferentially increasing its use of carbohydrate as a fuel, in effect, burning of any excessive carbohydrate consumption.²⁶ No such adaptive mechanism for fat exists, however. In other words, if excess fat is consumed, there is no mechanism by which the body can increase its use of fat as a fuel. Instead, when excess fat calories are consumed, the only option is to accumulate the excess fat as an energy store in the body, and this process occurs at a low metabolic cost and is an extremely efficient process. To store excess carbohydrate as glycogen is much more metabolically expensive and a less efficient option. Another important reason why fat is the preferred energy store over glycogen is that glycogen can be stored only in a hydrated form that requires 3 g of water for each gram of glycogen, whereas fat does not require any such

process. The energy density of stored glycogen is 1 kcal/g (1 g of glycogen = 4 kcal, plus 3 g of water = 0 kcal), compared with the benefit of fat, which can be stored as 9 kcal/g.

ENERGY EXPENDITURE

Concept of Energy Expenditure

The process of energy expenditure and the oxidation or combustion of food for energy in the body is analogous to a woodburning stove, which burns wood to release heat in a controlled fashion. In the wood stove analogy, large chunks of wood are fed to the stove, and the wood is gradually combusted in the presence of oxygen to release carbon dioxide, water vapor, and heat. This process is similar to what happens in the body when food is consumed: Food is consumed by the body and is oxidized or combusted in the presence of oxygen to release carbon dioxide, water, and heat. When ingested food is used for energy, however, the release and transfer of energy occurs through a series of tightly regulated metabolic pathways, in which the potential energy from food is released slowly and gradually over time. This process ensures that the body is provided with a gradual and constant energy store, rather than relying on a sudden release of energy from an immediate combustion of ingested food. As a simple example of how the body uses food for energy, consider the combustion of a simple glucose molecule as follows:



Similar chemical reactions can be described for the combustion of other sources of energy, such as fat and other types of carbohydrates. These types of reactions are continuously occurring in the body and constitute energy expenditure. As discussed previously, the three major sources of energy expenditure in the body are to fuel resting metabolic rate, the thermic effect of meals, and physical activity. As discussed in more detail subsequently, energy expenditure can be measured by assessment of total heat production in the body (direct calorimetry) or by assessment of oxygen consumption and carbon dioxide production (indirect calorimetry).

Historical Aspects of Energy Expenditure

The burning or combustion of food in the body was originally described in the classic experiments of Lavoissier, who worked in France in the late 1700s. Lavoissier discovered that a candle would burn only in the presence of oxygen. In addition, he was the first to describe how living organisms produced heat in a similar way as they required oxygen for life and combusted food as they released heat. His experiments were

the first to document the heat production of living organisms. Working before the invention of electricity, he built the first calorimeter, in which a small animal was placed in a sealed chamber. Lavoissier packed ice into a sealed pocket around the chamber (he could perform these studies only in the winter when ice was collected from the ground), then placed the chamber and ice layer inside an insulated chamber. Lavoissier then collected and measured the volume of melting water. Because the ice layer was insulated from the outside world, the only way the ice could melt was by the increase in heat produced by the living animal. Lavoissier measured the volume of melted ice water and by so doing was able to calculate accurately the amount of heat that had to be produced by the animal to melt the measured amount of ice.

Measurement of Energy Expenditure

Lavoissier's device was the first calorimeter that was used to measure heat production. This approach is termed *direct calorimetry* because heat production is measured directly. Direct calorimeters have been designed for measuring heat production in humans, but this approach is technically demanding, especially in human studies, and is now infrequently used. Indirect calorimetry measures energy production indirectly via assessment of respiratory gas analysis. This approach is based on oxygen consumption and carbon dioxide production that occurs during the combustion (or oxidation) of protein, carbohydrate, fat, and alcohol, as shown in the example of glucose combustion. Respiratory gas analysis can be achieved in humans over short measurement periods at rest or during exercise using a facemask, mouthpiece, or canopy system for gas collection and over longer periods of 24 hours (and longer) by having subjects live in a metabolic chamber. Resting metabolic rate is typically measured by indirect calorimetry under fasted conditions while subjects lie quietly at rest in the early morning for 30 to 40 minutes. The thermic effect of a meal is typically measured by monitoring the changes in metabolic rate by indirect calorimetry for 3 to 4 hours after consumption of a test meal of known caloric content.

Total energy expenditure can be measured over extended time periods (1 to 2 weeks) using the doubly labeled water method,²⁹ which requires a person to ingest small amounts of *heavy* water that is isotopically labeled with deuterium and oxygen-18 ($^2\text{H}_2\text{O}$ and H_2^{18}O). These forms of water are naturally occurring, stable (nonradioactive) isotopes of water that differ from the most abundant form of water. In deuterium-labeled water, the hydrogen is replaced with deuterium, which is an identical form of water except that deuterium has an extra neutron in its nucleus compared with hydrogen and is a heavier form of water; similarly, oxygen-18-labeled water contains oxygen with an additional two extra neutrons. These stable isotopes act as molecular tags so that water can be tracked in the body. After a loading dose, deuterium-labeled water is washed out of the body as a function of body water

turnover; oxygen-18 is also lost as a function of water turnover but is lost via carbon dioxide production. Using a number of assumptions, the rate of carbon dioxide production and energy expenditure can be assessed based on the different rates of loss of these isotopes from the body.^{41, 47}

The major advantages of the doubly labeled water method are that the methodology is truly noninvasive and nonobtrusive (subjects are unaware that energy expenditure is being measured), and measurement is performed under free-living conditions over extended time periods (7 to 14 days). When used in combination with indirect calorimetry for assessment of resting metabolic rate, physical activity-related energy expenditure can be assessed by the difference (i.e., total energy expenditure - resting metabolic rate - the thermic effect of meals = physical activity energy expenditure). The additional power of assessing total energy expenditure with the doubly labeled water method is that this approach can provide a measure of total energy intake in subjects who are in energy balance.⁴² This is because, by definition, in a state of energy balance, total energy intake must be equivalent to total energy expenditure. This aspect of the technique has been used as a tool to validate energy intakes using other methods, such as food records and dietary recall.⁴² For example, it has been known for some time that obese subjects report a lower than expected value for energy intake. At one time, it was thought that this may be explained by low energy requirements in the obese as a result of low energy expenditure and reduced physical activity. Using doubly labeled water, it has now been established that obese subjects underreport their actual energy intake and actually have a normal energy expenditure, relative to their larger body size.⁴³

The major disadvantages of the technique are the periodic nonavailability and expense of the oxygen-18 isotope (approximately \$500 for a 70-kg adult), the need and reliance on expensive equipment for analysis of samples, and that the technique is really not well suited for large-scale epidemiologic studies. Although the technique can be used to obtain estimates of physical activity energy expenditure, it does not provide any information on physical activity patterns (i.e., type, duration, and intensity of physical activity periods during the day).

The doubly labeled water technique has been validated in humans in several laboratories around the world by comparison with indirect calorimetry in adults and infants.^{44, 47} These studies generally show the technique to be accurate to within 5% to 10%, relative to data derived by indirect calorimetry for subjects living in metabolic chambers. The theoretic precision of the doubly labeled water technique is 3% to 5%.⁴⁵ The experimental variability is $\pm 12\%$ under free-living conditions because of fluctuations in physical activity levels¹⁴ and $\pm 8\%$ under more controlled sedentary living conditions.¹⁹ The good accuracy and reasonable precision of the technique allow the doubly labeled water method to be used as a gold standard measure of free-living energy expenditure in humans against which other methods can be compared.

The energy expended in physical activity can be measured under laboratory conditions using indirect calorimetry during standard activities. In addition, free-living, physical activity-related energy expenditure over extended time periods of 2 weeks can be measured by the combination of doubly labeled water to measure total energy expenditure and indirect calorimetry to measure resting energy expenditure and the thermic effect of a meal. Using this approach, physical activity energy expenditure is estimated as the difference between total energy expenditure (by doubly labeled water) and resting energy expenditure (by indirect calorimetry) plus the thermic effect of feeding (measured or often estimated as 10% of total energy expenditure).

Factors That Influence Energy Expenditure

Each of the components of energy expenditure is determined by various factors. Resting metabolic rate is highly variable between individuals ($\pm 25\%$, even when related to fat-free mass) but is consistent within individuals ($\pm <5\%$).³³ Because resting metabolic rate occurs predominantly in muscle and the major organs of the body, the main source of individual variability in resting metabolic rate is organ and muscle mass. Fat-free mass (total mass of the body that is not fat, i.e., predominantly organs and muscle) explains 60% to 80% of the variation in resting metabolic rate between individuals.³⁷ Because fat-free mass is a heterogeneous mixture of all nonfat body components, the metabolic rate associated with each kilogram of fat-free mass depends on the quality of the fat-free mass, in terms of hydration and relative contribution of the different organs that make up the fat-free mass. For example, skeletal muscle constitutes approximately 43% of total mass in an adult but contributes only 22% to 36% of resting metabolic rate, whereas the brain constitutes only approximately 2% of mass but contributes 20% to 24% of the resting metabolic rate. In addition, the metabolic cost of each kilogram of fat-free mass decreases with developmental progression, probably because of developmental increases in the muscle mass-to-organ mass ratio within fat-free mass. The relationship between resting metabolic rate and fat-free mass is not linear across all ages and is estimated to be 79.2 kcal/kg between age 0 and 2.5 years, 36 kcal/kg in 4- to 7-year-old children, 28.3 kcal/kg during adolescence, and 21.0 kcal/kg in adulthood.⁵³

Resting metabolic rate is also influenced by fat mass even though fat mass is generally thought to be metabolically inert. Fat mass contributes approximately 10 to 13 kcal/kg to resting metabolic rate.¹⁷ In healthy adults, resting metabolic rate declines with age, over and above that expected given the age-related decline in fat-free mass.³⁵ Resting metabolic rate is also influenced by sex in that males have a higher value than females by approximately 50 kcal/d.² This difference is independent of the gender difference in fat-free mass and is consistent across the life span; the source of the difference is not well understood. More active

people tend to have a higher resting metabolic rate than inactive individuals.³⁴ This difference may be explained, in part, by the residual effects of chronic exercise on metabolic rate. In other words, resting metabolic rate appears to be elevated because of the long-lasting effects of the thermic effect of exercise. Other factors are also involved, however, because the higher resting metabolic rate in more active individuals persists long after the last bout of exercise has been completed. Collectively, fat-free mass, fat mass, age, sex, and physical activity explain 80% to 90% of the variance in resting metabolic rate. In addition, a portion of the unique variance in resting metabolic rate across individuals has been ascribed to genetic factors, although the specific source of this genetic variation is not yet identified.⁵

The thermic effect of meal ingestion is primarily influenced by the quantity and macronutrient quality of the ingested calories. The thermic effect of food has also been termed *meal-induced thermogenesis*, or the specific dynamic action of food. The increase in metabolic rate that occurs after meal ingestion occurs over an extended period of at least 5 hours; the cumulative energy cost is equivalent to approximately 10% of the energy ingested. In other words, if one consumed a mixed meal of 500 kcal, the body would require 50 kcal to digest, process, and metabolize the contents of the meal. The thermic effect of feeding is higher for protein and carbohydrate than for fat. This higher thermic effect is because for fat, the process of energy storage is efficient, whereas for carbohydrate and protein, additional energy is required for metabolic conversion to the appropriate storage form (i.e., excess glucose converted to glycogen for storage and excess amino acids from protein converted to fat for storage).

Physical activity energy expenditure encompasses all types of activity, including sports and leisure, occupational activities, and general activities of daily living as well as fidgeting. The metabolic rate of physical activity is determined by the amount or duration of activity (i.e., time), the type of physical activity (e.g., walking, running, typing), and the intensity at which the particular activity is performed. The metabolic cost of physical activities is frequently expressed as metabolic equivalent, or METs, which represents multiples of resting metabolic rate. By definition, sitting quietly after a 12-hour fast is equivalent to 1 MET. The cumulative total daily energy cost of physical activity is highly variable within and between individuals. Physical activity provides the greatest source of *plasticity* or flexibility in the energy expenditure system and is the component through which large changes in energy expenditure can be achieved.

The major factors accounting for interindividual variation in total energy expenditure include factors such as body weight, fat-free mass, and resting metabolic rate, which account for 40% to 60% of the variation.⁸ Total energy expenditure is similar between lean and obese individuals after taking differences in fat-free mass into account.^{3, 36, 51} Fatness has negligible effects on total energy expenditure, other than the small effect on resting metabolic rate, as discussed previously. The lack of

effect of increased body fat on total energy expenditure is probably due to the opposing effects of the additional energy cost of weight-bearing activities in subjects with greater body fat and the greater resting metabolic rate associated with the increased fat mass versus the decreased likelihood of physical activity that is associated with carrying additional fat mass. With regards to age, some studies suggest only a limited change in total energy expenditure (relative to resting metabolic rate) from childhood through adulthood, although a decline occurs in the elderly.¹³ Data also suggest a gender-related difference in total energy expenditure, in addition to that previously described for resting metabolic rate. In a meta-analysis that examined data from a variety of published studies,⁸ absolute total energy expenditure was significantly higher in males compared with females by 741 kcal/d (2440 ± 502 kcal/d in females; 3158 ± 742 kcal/d in males), and nonresting energy expenditure remained higher in men by 263 kcal/d.

ROLE OF ENERGY EXPENDITURE IN THE CAUSE OF OBESITY

Stated simply, obesity is the end result of positive energy balance or an increased energy intake relative to expenditure. It is often stated, or assumed, that obesity is simply the result of overeating, lack of physical activity, or a reduced metabolic rate. The cause of obesity, however, is not so simple, and many complex and interrelated factors are likely to contribute to the development of obesity; it is extremely unlikely that any single factor causes obesity. Many cultural, behavioral, and biologic factors drive energy intake and energy expenditure and contribute to the homeostatic regulation of body energy stores. In addition, many of these factors are influenced by individual susceptibility, which may be driven by genetic, cultural, and hormonal factors. Obesity may develop gradually over time, such that the actual energy imbalance is negligible and undetectable.

Although it is a popular belief that a reduced level of energy expenditure and physical activity leads to the development of obesity, this hypothesis remains controversial and has been difficult to prove. There are good examples of an inverse relationship between physical activity and obesity (e.g., athletes are lean, nonobese individuals)^{21, 48} as well as good examples of the positive relationship between obesity and physical inactivity (obese individuals tend to be less physically active). Not all studies, however, provide supporting evidence. For example, several studies suggest that increased television viewing (as a marker for inactivity) increases risk of obesity,^{1, 21} whereas others do not.⁴⁰ Similar to the results for physical activity, some studies suggest that a low level of energy expenditure predicts the development of obesity, and others do not support this hypothesis.

Some evidence suggests that a reduced energy expenditure may be involved in the cause of childhood obesity.^{22, 39} Roberts et al³⁹ examined

the relationship between total energy expenditure and weight gain in 18 infants of both underweight (prepregnancy weight <5th percentile) and overweight (prepregnancy weight >5th percentile) mothers, from birth to 1 year of age. Total energy expenditure at 3 months of age was 20.7% lower in infants who later became overweight. This result suggested that lowered total energy expenditure contributed to later weight gain in infants who became overweight. This finding was not reproduced in two later studies in infants of lean and obese mothers, as reported by Davies et al¹⁰ and Stunkard et al.⁴⁹

Other cross-sectional studies in prepubertal children do not support the concept that reduced energy expenditure may be related to obesity. Delany et al¹¹ divided a group of 46 children into tertiles according to their body weight. Fat mass was significantly different across tertiles, whereas fat-free mass was not. There were no significant differences in total, resting, or physical activity-related energy expenditure across groups. Similarly, Treuth et al⁵¹ examined total energy expenditure by the doubly labeled water method, 24-hour sedentary metabolic rate in a chamber, and resting metabolic rate in obese and nonobese girls. All components of energy expenditure were similar after adjusting for body composition.⁵¹ Differences in fat mass were not related to variation in energy expenditure components in these cross-sectional studies. Similarly, cross-sectional studies in adolescents³ and adults³⁶ have also shown that energy expenditure components are higher in obese individuals and similar to lean individuals after adjusting for body composition. A meta-analysis of total energy expenditure studies in adults has shown that total energy expenditure is not influenced by fat mass.⁸ Another meta-analysis of total energy expenditure data has shown that percent body fat is inversely related to physical activity energy expenditure in men but not women.⁵⁴

Children of obese parents have been examined as preobese models of obesity. Degree of parental obesity was examined as a potential determinant for energy expenditure in 74 prepubertal children (5.0 ± 0.9 years of age) of both lean and obese parents.¹⁵ Children were divided into four groups according to the obese status of the parents: both parents nonobese, obese father and nonobese mother, obese mother and nonobese father, or both parents obese. Total energy expenditure and physical activity-related energy expenditure were not significantly different among the four groups after adjusting for fat-free mass.¹⁵ Relative to children with two nonobese parents, resting energy expenditure adjusted for fat-free mass was 50 kcal/d lower in children when only the mother was obese or only the father was obese but not when both parents were obese. There were no significant correlations between components of energy expenditure in children and body fat in mothers or fathers.

Other studies of the role of energy expenditure in the cause of obesity have included studies in subjects with genetic conditions associated with obesity. For example, the doubly labeled water method has been used to examine energy expenditure and requirements in children

with Down's syndrome, who have a high prevalence of obesity.³⁰ In this study, 13 prepubescent children with Down's syndrome had decreased resting metabolic rate compared with control subjects ($n = 10$) of similar body sizes, but there were no significant differences for total and non-resting energy expenditure.

Other *preobese* models that have been used to study the potential role of energy expenditure on the cause of obesity include examination of ethnic groups at higher risk of obesity (e.g., Mohawk Indians and African-Americans). In Mohawk children in upstate New York, the prevalence of obesity has been estimated as 44%.²⁷ Total energy expenditure, however, was 8.5% higher in Mohawk compared with white children living in Vermont because of a 37% higher physical activity-related energy expenditure in the Mohawk children.¹⁸ In African-American children, a 14% lower resting energy expenditure was found compared with white children, adjusting for age, gender, weight, fat-free mass, and fat mass.²⁸ Among girls aged 6 to 16 years, lower resting energy expenditure was also found in African-Americans than in whites, adjusting for body weight and lean body mass.³² Several other studies have shown a significantly lower energy expenditure in African-American compared with white subjects independent of ethnic differences in body composition.^{12, 32, 55} This finding has been shown across the life span but has not been observed in all studies.⁵⁰ It remains to be seen whether this ethnic difference is a contributing factor to the increased prevalence of obesity among African-Americans.

A major limitation for most studies that have examined the role of energy expenditure in the cause of obesity is their cross-sectional design. Because growth of individual components of body composition is likely to be a continuous process, longitudinal studies are needed to evaluate the rate of body fat change during the growing process. The influence of energy expenditure components on the rate of change in body fat relative to fat-free mass over a 4-year period has been examined in prepubertal children of lean and obese parents.²⁰ The average rate of change in absolute fat mass was 0.89 ± 1.08 kg/y (range, -0.44 to 5.6 kg/y). The rate of change in fat mass adjusted for fat-free mass was 0.08 ± 0.64 kg/y (range, -1.45 to 2.22 kg/y) and was similar among children of two nonobese parents and children with one nonobese and one obese parent but significantly higher in children with two obese parents (0.61 ± 0.87 kg/y). The major determinants of change in fat adjusted for fat-free mass were gender (greater relative fat gain in girls), initial fatness, and parental fatness; none of the components of energy expenditure were inversely related to change in fat adjusted for fat-free mass.²⁰

Several other longitudinal studies have examined the influence of resting metabolic rate on weight gain in adults. Seidell et al⁴⁶ did not detect a relationship between resting metabolic rate at baseline and subsequent weight change over 10 years in a sample of 775 men. Weinsier et al⁵² used a *postobese* model in which obese women were reduced to normal body weight, then examined 4 years later after weight regain, and resting metabolic rate after weight loss did not predict subsequent

4-year weight gain. The only positive finding in adults was the study by Ravussin et al³⁸ in 126 Pima Indians in whom resting metabolic rate was lower in those who gained greater than 10 kg; however, resting metabolic rate was not related to the rate of weight gain in the subsequent 2- to 4-year period. In the same study, low daily energy expenditure in a metabolic chamber did predict the rate of subsequent weight change.³⁸

Collectively the findings presented here demonstrate that there are discrepant findings regarding the role of energy expenditure in the cause of obesity. This discrepancy could potentially be explained by a number of additional factors. For example, differences or changes in energy expenditure and energy intake could occur at distinct critical periods of development (such as in early infancy or adolescence), and may result in energy imbalance. In addition, there could be individual differences and susceptibility to the impact of altered energy expenditure on the regulation of energy balance, as demonstrated in studies such as those of Bouchard et al,^{4,7} in which twins were challenged with underfeeding or overfeeding. The impact of energy expenditure on the cause of obesity could vary among different subgroups of the population (e.g., male versus female, active versus inactive, different ethnic groups) and could also have differential effects within individuals at different stages of development. It is conceivable that susceptible individuals fail to compensate for periodic fluctuations in energy expenditure. Although a 14-day measure of energy expenditure by doubly labeled water is considered a long-term measure, this time period is actually short when compared with the time scale for the development of obesity, which can be a slow and gradual process. For example, in a previously cited longitudinal study²⁰ comparing children of two obese parents versus children of two nonobese parents, the difference in the rate of change in fat mass relative to fat-free mass was less than 1 kg of fat per year, or less than 3 g of excess fat gain per day. This rate is equivalent to a continual daily energy imbalance of 25 kcal/d (approximately 2% of total daily energy flux). From a methodologic standpoint, even the most sophisticated of current techniques would be unable to identify this energy imbalance as a *defect* in energy expenditure components (or as an excess in energy intake, relative to needs).

Aside from the role of physical activity-related energy expenditure, several studies^{16, 31} suggest that the time devoted to physical activity may have a more important influence on energy regulation and obesity than the daily energy cost of physical activity. After adjusting for fat-free mass, gender, and age, body fat mass was significantly and inversely related to physical activity in hours per week derived by questionnaire ($r = -0.3$) but not physical activity-related energy expenditure over 14 days by the doubly labeled water method.¹⁶ Similarly, in 49 8- to 11-year-old girls, self-reported hours of physical activity at high intensity were significantly related to blood lipid levels, whereas activity energy expenditure by doubly labeled water was not.⁹ Maffeis et al³¹ examined the relationship between physical activity energy expenditure (estimated

from heart rate monitoring) and other physical activity variables by questionnaire, and fatness in 28 9-year-old boys over a wide range of fatness (8% to 42% body fat). The only physical activity variable that was significantly related to level of body fatness was time spent in sedentary activities, rather than energy expenditure. Collectively, these findings support the notion that qualitative aspects of physical activity not measured by doubly labeled water (i.e., duration and frequency of physical activity) may be more important than physical activity-related energy expenditure in the regulation of energy balance and health in children.

Although there are physiologic and genetic influences on the various components of energy metabolism and body weight regulation, and a major portion of individual differences in body weight can be explained by genetic differences,⁵ it seems unlikely that the increased global prevalence of obesity has been driven by a dramatic change in the gene pool. It is more likely and more reasonable that acute changes in behavior and environment have contributed to the rapid increase in obesity, and genetic factors may be important in the deferring individual susceptibilities to these changes.²⁵ The most striking behavioral changes that have occurred have been an increased reliance on high-fat and energy-dense fast foods, with larger portion sizes, coupled with an ever-increasing sedentary lifestyle. The more sedentary lifestyle is due to an increased reliance on technology and labor-saving devices, which has reduced the need for physical activity for everyday activities.²³ Examples of energy-saving devices that have resulted in a decline in physical activity include (1) increased use of automated transport rather than walking or biking; (2) central heating and use of automated equipment in the household, such as washing machines; (3) reduction in physical activity in the workplace as a result of computers, automated equipment, and electronic mail, which all reduce the requirement for physical activity at work; (4) increased use of television and computers for entertainment and leisure activities; (5) use of elevators and escalators rather than stairs; (6) increased concern for crime, which has reduced the likelihood of outdoor playing; and (7) poor urban planning, which does not provide adequate biking paths or sidewalks in some communities. The increasing prevalence, numerous health risks, and astounding economic costs of obesity clearly justify widespread efforts toward prevention efforts.^{26, 42}

SUMMARY

Over the long-term, most adult humans are able to maintain body energy stores through the process of energy balance, which regulates how much energy is consumed to match how much energy is expended. Energy expenditure is required for resting metabolic rate to maintain basic physiologic functions (e.g., heart beat, muscle function, respiration) and metabolize, digest, and store food that is consumed as well as for physical activity. Resting metabolic rate is the largest component of daily

energy expenditure, and physical activity-related energy expenditure is the most variable. Cross-sectional studies in children and adults have shown that energy expenditure, including physical activity-related energy expenditure, are similar in lean versus obese subjects, especially after controlling for differences in body composition. A major limitation for most studies that have examined the role of energy expenditure in the cause of obesity is their cross-sectional design.

Some longitudinal studies support the idea that reduced energy expenditure is a risk factor for the development of obesity, but most do not. There are several possibilities that could account for such discrepant findings. First, the ambiguous findings in the literature might be explained by the possibility that differences in energy expenditure and physical activity and their impact on the development of obesity are different at the various stages of maturation. Second, there could be individual differences in the impact of altered energy expenditure on the regulation of energy balance. The impact of energy expenditure on the cause of obesity could vary among different subgroups of the population (e.g., boys versus girls and different ethnic groups) and could have a differential effect within individuals at different stages of development. A specific example is the lower energy expenditure in Pima Indians, which predisposes to increased risk of obesity. It remains to be seen whether the lower metabolic rates that have been observed in African-Americans will relate to subsequent weight gain. It is conceivable that susceptible individuals fail to compensate for periodic fluctuations in energy expenditure. Third, given that obesity can arise as a result of a small energy balance over time, it is unlikely that existing techniques are capable of measuring such small differences. Finally, it can be argued that a focus on energy metabolism as a possible explanation of obesity is unlikely to yield interesting information because of the wide range in energy expenditure in the population even after adjusting for body composition. The major dependent variable that needs to be examined in relation to the cause of obesity is not energy expenditure but change in energy balance over time and the ability to regulate body energy stores. Given that the sudden change in obesity prevalence has occurred during a time of rapid environmental and cultural changes, additional focus on the behavioral and environmental effects on regulation of energy balance is warranted.

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