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Unanswered questions about the causes of obesity

Obesity is now a global pandemic, but there is little consensus about the causes

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Featured

Obesity is a major health issue that has reached pandemic status with no clear solutions. Much has been learned over the past 50 years about the regulation of body fat. Examples include the discovery of the hormone leptin, finding thermogenic brown adipose tissue in adult humans, elucidating pathways in the brain that affect hunger and feeding behavior, quantifying adipocyte turnover and the lipids therein, identifying single genes that produce rare but severe obesity, and finding thousands of genetic variants associated with individual differences in body mass index (BMI). Despite this progress, there remain several key questions to be answered to aid the prevention and treatment of obesity.

Confusion about the causes of obesity has arisen based on the false dichotomy of genes versus environment (rather than the combined effects of genes and environment). At any point in time, most of the variance in levels of obesity among individuals may be genetic. But, changes across time are predominantly driven by the environment. Which individuals deposit the most fat in response to environmental change is influenced by both.

Adult human body weight is often stable over long periods within a given environment. Moreover, individuals often respond to imposed perturbations of

environment. Moreover, individuals often respond to imposed perturbations of energy balance by altering components of energy expenditure and intake to resist weight change. Frequently, body weight (and fatness) returns to a similar level to what it was before the perturbation after it ends. This might suggest that body weight is regulated around an individual set point ([1]). But if that is the case, why is there an obesity pandemic? Two alternatives to a strict set point model include that the so-called regulation is an illusion because when individuals gain weight, they also increase expenditure ([2]), which brings them to a new equilibrium (the "dynamic equilibrium point"). Or, there are two "control points" that stop humans from getting too fat or too thin, but between those limits there is very little control (the "dual intervention point model") ([1]). However, these alternative models are inadequate descriptors of the whole obesity phenomenon.

To develop more-comprehensive models, it is necessary to understand the molecular mechanisms of intake and expenditure control. For example, during periods of energy deficit, hunger is increased, and energy expenditure is suppressed. Leptin appears to play a major role in these responses but does not fully explain them. Little is known about the mechanisms behind responses to overfeeding. Rodent studies suggest that activation of thermogenic brown adipose tissue or futile energy cycling elsewhere are potentially involved, but their contributions in humans remain unclear. A system that directly senses overall weight (a gravitostat) might be involved ([3]), but the molecular basis is ill-defined.

The sizes of individual organs and tissues also seem to be regulated. People with obesity, almost without exception, also have increased lean body mass (all nonadipose parts of the body, including skeletal muscles, bones, and viscera) ([4]). The mechanisms involved in partitioning energy imbalances between lean versus adipose tissues have not yet been elucidated. The mass of adipose tissue depends on the balance between adipogenesis and apoptosis and between lipogenesis and lipolysis in adipocytes, but the mechanisms controlling this are incompletely understood. Moreover, the factors that influence the relative deposition of lipids into adipose versus nonadipose tissues are particularly important to understand because ectopic lipid deposition seems to be implicated in metabolic disease. Elucidating these control mechanisms has the potential to reveal therapeutic targets.

body and food intake. However, little is known about how these needs are sensed and how the corresponding signals influence appetite and behavior. For example, although short-term bouts of exercise may not reliably influence food intake ([5]), prolonged exercise interventions and high activity stimulate food consumption ([6]). Although leptin acts as a long-term circulating signal of overall body energy stores and stimulates hunger when they are shrinking, other currently unknown mechanisms appear to link expenditure to intake through resting metabolic rate and fat-free mass ([7]). Discovery of these signals will likely be important targets for modulating fat storage. However, it is important to recognize that the different routes of energy expenditure (physical activity, rest, and thermoregulation) may not be related to each other in an independent additive fashion. Elevations of one aspect of expenditure may cause compensatory decreases in other components and/or changes in intake. The long- and short-term consequences of manipulating different components of energy balance remain unclear.

Food intake and energy expenditure are controlled by the brain. Yet, it is unclear how the brain orchestrates eating behavior in response to signals from the periphery and the environment. The brain integrates signals from the body regarding nutrient and energy needs to modulate food choice and the amount consumed. The hindbrain and hypothalamus regulate food intake in response to signals from the gut and circulating hormones. The recent success of glucagon-like peptide 1 receptor agonists for the treatment of obesity is because they engage these brain regions at pharmacological doses. There are probably many other brain regions involved. For example, there is less knowledge about the roles of brain regions that support motivation, reward, habit formation, cognitive abilities, and emotional control and how these integrate mutually and with environmental cues to generate the total feeding response.

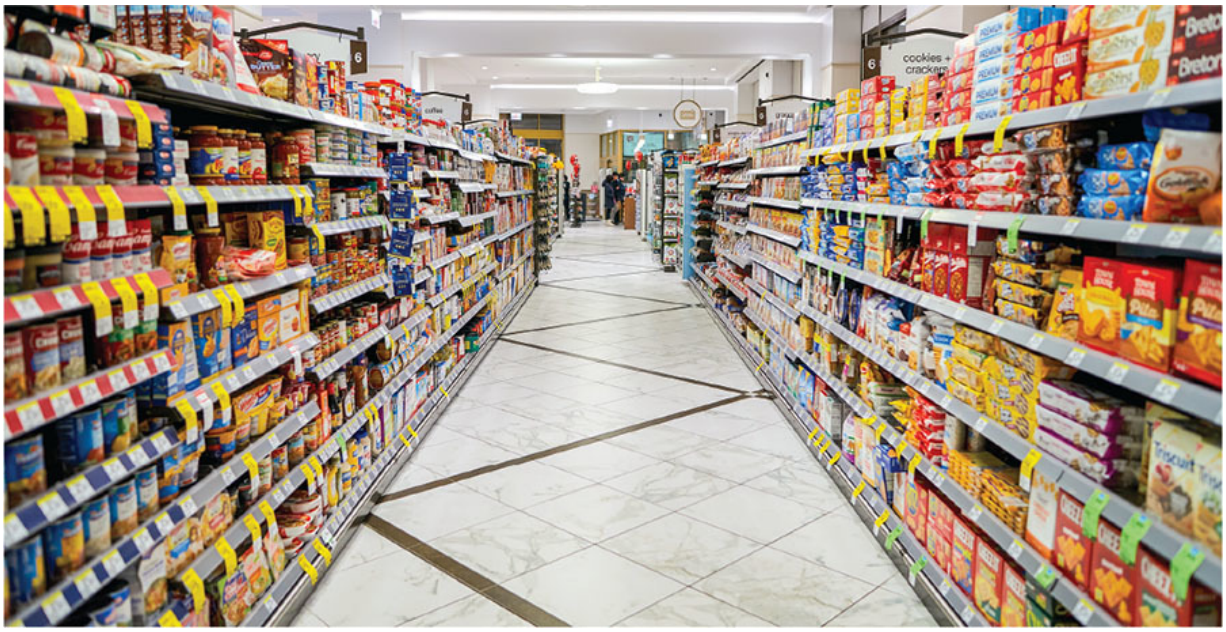
It is presently unclear what social and physical factors in the environment are driving increased obesity prevalence. Physical changes in the food environment have likely been important contributors to increasing obesity prevalence, but the most important factors in food that induce obesity remain unknown. Intake is not only for energy but for specific nutrients as well. How nutrients are sensed and the signals that control nutrient-specific appetites are poorly understood. The protein leverage model ([8]) suggests that protein content has been diluted by

excess carbohydrate and fat, thereby promoting excess energy intake to meet the body's protein needs. However, the determinants of protein requirements, the signals of protein deficiency and surplus, and the resultant mechanisms controlling total protein intake are unclear. Alternatively, the carbohydrate-insulin model ([9]) suggests that the increase in high glycemic carbohydrates in food results in increased insulin levels and thereby drives adipose tissue lipid accumulation and consequently increased appetite and decreased energy expenditure. But, the mechanisms remain to be elucidated. Fructose does not stimulate insulin but may elicit different mechanisms that lead to fat storage.

Energy density of food, determined partly by water and fat content, has a profound effect on energy intake, at least over the short term ([10]). Laboratory rodents and humans consuming high-fat diets eat less weight of food but overconsume energy. This leads to some intriguing questions about why the intake of high–energy density foods is so difficult to regulate and to what extent increased availability of high–energy density foods has contributed to the pandemic. Conversely, a reduction in low–energy density alternatives may be a driver. For instance, dietary fiber has low energy density, and its intake has declined over the past 30 years in the USA. Are there mechanisms by which fiber exerts effects on satiety and thereby limits energy intake other than by lowering food energy density? The availability and marketing of ultraprocessed foods have substantially increased over several decades, and diets high in such foods promote greater energy consumption ([11]). It is not yet known what attributes of ultraprocessed food result in excess energy intake. Certain nutrient combinations may be hyperpalatable and influence the activity of brain regions involved in reward and motivation, thereby promoting their overconsumption, but the specific mechanisms remain unclear. Whether noncaloric sweeteners and the thousands of food additives common in modern foods affect satiety and energy intake is also unclear.

Social factors may be a feature of the obesogenic environment that differs among and within societies, and the distribution and impact of these factors may have changed over time. A strong environmental correlate of obesity is social adversity, including poverty, particularly in high-income countries ([12]). However, in low- and middle-income countries, poverty tends to be associated with lower BMI. Perhaps, a combination of food availability and food insecurity explains this

availability become obese. But what triggers the perception of food insecurity, and what the physiological reaction to it is, including increased fat storage, remain unknown. Chronic stress may be an important factor. Moreover, these relationships appear more prominent among women than men and may contribute to obesity occurring more frequently in women than in men. Such processes may be reinforced owing to the stigmatization and discrimination that people with obesity suffer, creating a vicious cycle.



Some aspects of the changing food environment, combined with other environmental factors and genetic predisposition, have created the current obesity pandemic. However, the details of this interaction remain elusive, leading to many unanswered questions about what might appear to be a simple problem of positive energy balance. PHOTO: SORBIS/SHUTTERSTOCK

The environment and societal changes may also have affected physical activity. Occupational physical activity in the USA has declined since the 1950s ([13]), but leisuretime activity has increased. Energy expenditure resulting from physical activity has not declined since the late 1980s in the USA and Europe ([14]). Moreover, low energy expenditure from physical activity does not predispose individuals to obesity. Although people with obesity are less active, they do not spend less total energy on activity. Although it is often asserted that increasing sedentary behavior is a major cause of the obesity pandemic, this is far from clear, and present evidence does not support this conclusion.

Environmental drivers of the obesity pandemic have not resulted in uniform increases in adiposity within and between populations, potentially also because of genetic differences between individuals. Individual variation in responses to many of the physiological and environmental factors contributes to variation in obesity susceptibility. Much is known about the rare, extreme monogenic forms of obesity, but there are thousands of single-nucleotide variants (SNVs) associated with BMI ([15]). However, knowledge about the mechanisms by which these SNVs become associated with BMI is limited, both because of the inadequacy of BMI as a measure of obesity and because of uncertainty about the causal mechanisms linking genetic variants to phenotypes. Moreover, at the fetal stage and early in life, individuals are wholly dependent on their mothers for nourishment. Studies of rats and mice show that maternal obesity and diet influence offspring susceptibility to obesity, possibly by epigenetic mechanisms ([15]), but whether this also applies to humans is uncertain.

Given the diversity of environmental and genetic causes of obesity, there are many routes to excess adiposity. There may be subtypes of obesity, which could guide specific prevention and treatment. At present, however, there are many uncertainties, such as how the different subtypes might be defined. Individual variation in food preference is enormous, but the basis of this variation and its consequences for obesity development remain unknown. Whether different food choices lead to adaptations of the gut and the resident microbiota to alter energy absorption efficiency is also unclear. In some laboratory rodent models, differences in absorption efficiency can be sufficient to drive large differences in fat storage, but whether the same applies to humans has not been sufficiently studied. Gut microbiota differences may be associated with absorption efficiency and may have effects on other aspects of energy balance. It remains unclear whether differences in the microbiota between people with and without obesity are consistent and reproducible and whether these differences are consequences or causes of obesity.

By building on the considerable advances made in the past 50 years, the study of the causes of obesity promises to be a rich area for discovery that may be transformative for the lives of millions of people. Improving our understanding of environmental drivers and how these interact with genetic composition is vital to making future inroads to this serious medical condition.

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