

On the pathogenesis of obesity: causal models and missing pieces of the puzzle

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Application of the physical laws of energy and mass conservation at the whole-body level is not necessarily informative about causal mechanisms of weight gain and the development of obesity. The energy balance model (EBM) and the carbohydrate–insulin model (CIM) are two plausible theories, among several others, attempting to explain why obesity develops within an overall common physiological framework of regulation of human energy metabolism. These models have been used to explain the pathogenesis of obesity in individuals as well as the dramatic increases in the prevalence of obesity worldwide over the past half century. Here, we summarize outcomes of a recent workshop in Copenhagen that brought together obesity experts from around the world to discuss causal models of obesity pathogenesis. These discussions helped to operationally define commonly used terms; delineate the structure of each model, particularly focussing on areas of overlap and divergence; challenge ideas about the importance of purported causal factors for weight gain; and brainstorm on the key scientific questions that need to be answered. We hope that more experimental research in nutrition and other related fields, and more testing of the models and their predictions will pave the way and provide more answers about the pathogenesis of obesity than those currently available.

At a fundamental level, life itself is made possible by a complex network of biochemical reactions that occur inside cells. Many of these reactions require chemical energy, in the form of adenosine triphosphate, which is generated by other reactions that provide energy. Cells can use a variety of metabolic substrates, located locally or remotely, for energy provision or storage. Matching energy supply with energy needs and the ability to store excess energy so that it can be mobilized upon demand are, therefore, central to cellular function.

These processes conform to the physical laws of conservation of energy and mass and have been extrapolated from the cellular to the whole-body level. Accordingly, changes in food intake and, to a lesser extent, energy expenditure are believed to be responsible for variations in body fat stores. This direction of causality dominates texts

of human bioenergetics and metabolism and those on the role of diet (and exercise) in the pathogenesis and treatment of obesity¹. Nevertheless, although the relationship between chronic positive energy balance and weight gain remains unassailable, it does not prove cause and effect^{2–4}. It is possible that intrinsic or extrinsic factors (for example, endocrine and neuronal factors, characteristics of the food itself or other environmental influences) stimulate body fat storage and then increase food intake or decrease energy expenditure as a downstream effect, rather than the latter being the causal driver^{5,6}.

What causes obesity?

Our understanding of the pathophysiology of obesity has evolved substantially in past decades. Two apparently competing models on

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the pathogenesis of obesity have evolved in an attempt to explain how dietary changes and possibly other environmental influences on human physiology resulted in the observed increase in the prevalence of obesity: the EBM and the CIM⁷. This debate has implications for obesity science and public health and has often resulted in controversial discussions and remarks in scientific publications, popular books and social media^{3,8}. With this in mind and while acknowledging that other models of obesity exist (for example, focusing on appetite for protein⁹, the psychosocial domain¹⁰, climate change and environmental pollutants¹¹ or viruses¹², to name a few), the Novo Nordisk Foundation invited scientists with contrasting opinions on the pathogenesis of obesity to a 2-d workshop (11–12 September 2023) in Copenhagen, Denmark.

The workshop did not aspire to reach consensus on what causes obesity, but rather the intent was to (1) operationally define commonly used terms (Table 1), (2) delineate the structure of each model and overlay suggested routes and causal pathways on top of a common physiological background of energy metabolism and body weight regulation, (3) discuss the importance of purported causal factors for weight gain, (4) brainstorm on the key scientific questions that need to be answered and (5) outline the general principles of appropriate experiments to test between the relevant hypotheses. Ultimately, the goal of the workshop was to help resolve controversies and drive the field forward and thereby serve the scientific community and the public.

Physiological regulation of energy metabolism

Before considering potential causes of obesity, it is important to understand that any model put forth to explain the obesity phenotype and its increasing prevalence in the population must take into account normal physiology. Specifically, the physiological system that normally enables an individual to obtain sufficient energy and nutrients to meet the needs of the body for normal growth, development and physical function while maintaining sufficient triglyceride (fat) stores in adipose tissue to survive periods of insufficient exogenous energy availability (Fig. 1).

Processes and mechanisms of intermediary metabolism determine the disposition of metabolic fuels within cells and among tissues to maintain energy homeostasis. The brain continuously receives and integrates multiple signals, directly via the blood or from peripheral autonomic afferent neural input, which convey information about the metabolic status of individual organs and tissues and the availability of circulating fuels and hormones in the bloodstream and the gastrointestinal tract. These signals include hormones secreted from the gastrointestinal tract (for example, glucagon-like peptide 1 (GLP1), glucose-dependent insulinotropic polypeptide (GIP), peptide YY, cholecystokinin, ghrelin), the pancreas (for example, insulin, glucagon), adipose tissue (for example, leptin, adiponectin), muscle (for example, interleukin 6) and liver (for example, fibroblast growth factor 21)^{13,14}; energy-yielding substrates in the intestine and the circulation (for example, glucose)^{15,16}; and numerous afferent neural inputs (for example, via the vagus nerve and the enteric nervous system). The brain integrates these internal signals with external signals from the food and non-food environment, including psychosocial cues and competing demands or incentives, thereby inhibiting or promoting food-intake behaviour. The brain can also affect energy expenditure and peripheral metabolism by modifying the activity of the autonomic nervous system, altering the secretion of neurohormones and influencing levels of physical activity.

Ingestion of food, which is preceded by food-anticipatory hormonal changes collectively referred to as the cephalic response¹⁷, triggers a coordinated neurohormonal response as food components pass through the gut, are digested and are absorbed by the gut and released into the hepatic portal vein or, in the case of fat, into the lymphatic system and eventually appear in the systemic circulation. Some energy from food (for example, from dietary fibre) cannot be absorbed in the upper gastrointestinal tract and is eventually lost in faeces, although

part of it is made available in the lower gastrointestinal tract (mostly the colon) in the form of short-chain fatty acids produced by the action of gut microbes on undigested food material¹⁸. Accordingly, diets with the same gross energy content but varying composition can provide different amounts of metabolisable energy (84–97% of gross energy), partly because of their differing content in indigestible food components and partly because they modulate the composition and metabolic activity of the gut microbiome¹⁹.

Following the consumption of a typical, mixed macronutrient-containing meal, the ensuing fed state is characterized by an increase in energy expenditure (that is, thermic effect of food) and a shift in the mixture of substrates being oxidized from fat to carbohydrate (that is, metabolic flexibility)^{20,21} to an extent determined, in part, by the composition of the ingested food. For any given mixture of fuels consumed, there is a prioritisation of substrate oxidation, which is inversely related to the substrate's storage capacity in the body: alcohol (which cannot be stored) is at the top of this metabolic hierarchy, followed by carbohydrate and protein (which can be stored to a limited extent) and then by fat (which has the largest storage capacity)²².

These changes in energy metabolism and substrate oxidation are accompanied by robust alterations in the flux of substrates into and out of organs and tissues. Glucose production and release from the liver decrease, hepatic de novo lipogenesis is stimulated, and uptake of glucose by muscle increases (which is channelled toward glycogen synthesis for storage, conversion to lactate for release or complete oxidation). There is also an increase in glucose uptake by the liver (used toward glycogen synthesis for storage or interconversion to amino acids) and by adipose tissue, where it is converted into lactate for release or fatty acid synthesis for storage as triglycerides. At the same time, fatty acid release from adipose tissue decreases, whereas fatty acid uptake by adipose tissue (toward storage as triglycerides) and also by lean tissues such as the liver and muscle (toward complete oxidation or storage as 'ectopic' triglycerides) increases^{20,21}. These dynamic changes in substrate flux rates into and out of organs and tissues and in intracellular channelling toward oxidative and storage pathways (that is, fuel partitioning), the net result of which determines (but is also affected by) the availability of energy-yielding substrates in the circulation, are under genetic, hormonal and neural control and may also be affected by energy intake, diet composition, physical activity and environmental factors.

One important signal triggered by meal ingestion is the postprandial increase in levels of insulin circulating in plasma and the concomitant increase in the insulin-to-glucagon ratio. Food-derived nutrients differentially affect pancreatic insulin and glucagon secretion. Carbohydrates increase insulin and decrease glucagon levels; fat increases glucagon levels and does not affect or mildly increases insulin levels; protein increases both insulin and glucagon levels^{23–26}. Accordingly, the integrated pancreatic hormonal response after mixed meal ingestion depends on the size of the meal (that is, its calorie content) and macronutrient composition (that is, the relative amounts of carbohydrate, fat and protein) but also on the specific type of these macronutrients (for example, the glycaemic index of carbohydrates, fructose content, the degree of fat saturation, the source of protein and its amino acid composition). In the several hours following meal ingestion, the metabolic, hormonal and neural responses eventually subside, and the body progressively shifts back to fat oxidation as the predominant source of energy in the postabsorptive or fasted state. Modern humans in Westernized societies spend most of the day in the postprandial state (more than 15 h), consume multiple distinct meals (three to six eating occasions, with a median between-meal interval of about 3 h) and tend to abstain from eating only while sleeping^{27,28}.

EBM

According to the EBM (Fig. 2), the changing food environment caused increased obesity prevalence primarily by increasing food intake above

Table 1 | Operational definitions of terms

Adipose tissue expansion	The process of net deposition of fat in adipose tissue. Excessive fat mass occurs via increased adipocyte size (hypertrophy) and increased number of adipocytes (hyperplasia).
Energy (im)balance	The difference between net energy intake and whole-body energy expenditure over a specified period of time.
Energy density (of food)	The amount of metabolisable or bioavailable energy per unit of total (wet) weight for a food or a beverage (and sometimes for the whole diet), expressed in joules or kilocalories per gram.
Energy expenditure	The energy derived from oxidation of fat, carbohydrate, protein and occasionally alcohol, spent for basic physiological functions (basal metabolism), for processing and storing ingested nutrients (thermic effect of food), for supporting all body movements and physical activities (voluntary and involuntary) and, in some cases, for thermoregulation. Measured at the whole-body level.
Energy intake, gross	The amount of chemical energy released during complete combustion (in a bomb calorimeter) of ingested foods and drinks.
Energy intake, net (metabolisable energy intake)	The difference between ingested gross energy and energy lost in faeces and urine (or vomiting in some circumstances), also accounting for the energy made available to the host via the action of the gut microbiome on undigested food material.
Food palatability	The pleasantness of a specific food, determined by its sensory properties (for example, smell, taste, texture, visual appearance). It is measured by the relative preference to other foods and/or subjective hedonic ratings and may be innate or modified by prior experience or physiological state (for example, fasted or fed).
Food reward	The multifactorial process integrating sensory information with interoception resulting in reinforcement of food seeking and consummatory behaviour, often below conscious awareness.
Fuel partitioning	The processes of routing energy-yielding substrates toward deposition into or mobilisation from body stores, partitioning metabolic fuels among different tissues of the body (for example, adipose versus lean tissues) and channelling them between storage or oxidation within cells.
Glycaemic index	The ability of a carbohydrate-containing food to raise blood glucose concentrations relative to a reference food (usually, glucose or white bread). Typically, it is calculated as the incremental area under the curve for glucose over 2 h after consuming a standard amount of bioavailable carbohydrate (usually, 50 g) from the test food relative to the area after the reference food.
Glycaemic load	The product of the glycaemic index of a carbohydrate-containing food and the amount of that food carbohydrate that is consumed.
Hunger	A motivational 'need state' related to physiological cues of lack of energy or lack of a specific nutrient.
Hyperphagia (overeating)	A substantial increase in food intake relative to a 'normal' baseline or control condition or group. Over a sustained period of time, overeating is substantiated by net fat accumulation in the body. Accordingly, the term is equivalent to weight gain and cannot inform on the causal direction.
Metabolic flexibility	The ability of cells, tissues or the whole body to align the mixture of substrates being oxidized for energy with the substrates that are available, particularly in response to dynamic changes in nutrient availability (induced by meal ingestion, dietary changes, physical activity, hormonal and neural inputs). It has both magnitude (that is, 'how much') and temporal (that is, 'how fast') dimensions.
Obesity (phenotype)	A state of the body characterized by increased or excessive fat mass in a way that adversely affects health and is often resistant to reduction and prone to relapse if such a reduction occurs by eating less and exercising more.
Obesogenic environment	An environment that hypothetically promotes weight gain and obesity because of a variety of food-related factors (for example, composition, price, convenience) and non-food-related factors (for example, built environment, sociocultural context) that favour increased food intake and decreased energy expenditure.
Postabsorptive (fasted) state	The metabolic state that occurs typically from ~8 to ~14 h after eating (that is, after an overnight fast). It is characterized by accelerated catabolic pathways, a greater contribution of fat oxidation to meet energy demands and a relative steady state in the concentrations of hormones and metabolic fuels in the bloodstream.
Postprandial (fed) state	The metabolic state that occurs immediately after consuming a meal and typically lasts for ~3 up to ~8 h depending on the caloric content and macronutrient composition of the meal. It is characterized by accelerated anabolic pathways, a greater contribution of carbohydrate oxidation to meet energy demands and dynamic changes in the concentrations of hormones and metabolic fuels in the bloodstream.
Predisposition (to obesity)	A set of genetic and/or behavioural traits of some individuals in a population associated with increased ease of gaining weight and developing obesity.
Susceptibility (to obesity)	The tendency of some individuals to gain weight and develop obesity under the influence of specific environmental exposures.
Ultraprocessed food	Food resulting from extensive industrial processing, using relatively inexpensive ingredients, additives and preservatives rarely found in home kitchens, formulated to enhance palatability and appearance and prolong shelf life and maximize convenience.
Weight gain, dynamic phase	A period of typically slow, progressive weight gain that characterizes obesity development for most people.
Weight gain, stable/static phase	The period after obesity has been developed, during which weight gain slows or plateaus.

requirements (positive energy balance), resulting in excess accumulation of body fat. The energy imbalance associated with obesity could be also driven by reductions in the level of physical activity^{29–31}, although recent evidence suggests the total energy expended for physical activity has not declined in recent decades^{32,33}, indicating that the increased energy cost of moving the greater body mass offset any decline in the level of activity. Basal metabolic rate (BMR), however, adjusted for changes in body composition, decreased over many decades and, therefore, may have contributed to the energy imbalance³². Also, the reduction in the level of physical activity may have contributed to obesity

indirectly, by stimulating appetite and energy intake when decreased below some threshold^{34–37}. Be that as it may, elevated food intake is considered the primary driver of obesity in the EBM³⁸. Specifically, the widespread availability and marketing of a wide variety of inexpensive, convenient, calorie-dense, ultraprocessed and highly palatable foods, often in large portion sizes, that are low in fibre and protein leads to eating beyond the body's energy and nutrient demands.

The EBM posits that external, food-related cues along with properties of the foods themselves (step 1 in Fig. 2) either disrupt the signals of energy and nutrient availability and demand or alter the brain's

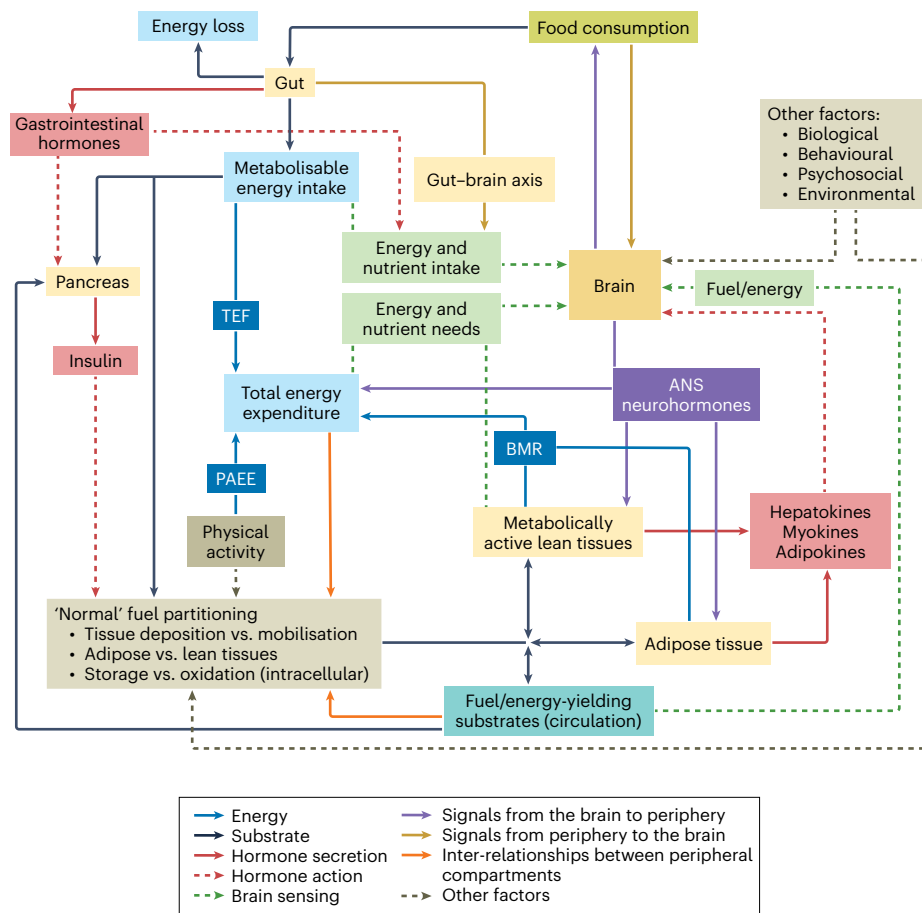


Fig. 1 | Physiological regulation of energy metabolism. Humans eat food primarily to meet the body's energy and nutrient needs for life-sustaining functions (basal metabolic rate, BMR) and all body movements (physical activity energy expenditure, PAEE) and, in some cases, thermoregulation. Food passes through the gut, and nutrients are absorbed into the systemic circulation, affecting secretion of gastrointestinal and pancreatic hormones (for example, insulin). Energy expenditure increases because of the thermic effect of food (TEF), and energy-yielding substrates are partitioned among tissues and intracellularly between oxidation and storage pathways, depending on their

availability and demand, under the influence of many hormonal and neural signals. Energy can be stored in and mobilized from various organs and tissues. The brain can sense signals relaying information about energy and nutrient needs, body energy stores and circulating fuels and adjust food intake and peripheral metabolism accordingly by various efferent neural signals (for example, via the autonomic nervous system (ANS)) and by modulating the secretion of neurohormones. Physical activity and many other factors (genetic, behavioural, psychosocial and environmental) can modulate these pathways.

sensing and integration of these signals or both (step 2). As a result, caloric overconsumption relative to energy requirements ensues (step 3), and the normal physiology of fuel partitioning results in most of the excess energy, regardless of the macronutrient source, being stored as body fat (step 4) and, to a lesser extent, as lean mass (step 5). Therefore, whole-body BMR and total energy expenditure increase (step 6) as obesity develops, because more energy is required to support and move the greater body weight. Body composition-adjusted expenditure, however, remains unaltered (that is, the metabolic activity of different tissues per unit mass does not change as obesity develops in an individual), although there is an additional small amount of energy expended that is associated with the cost of tissue deposition³⁹.

Attributes of the modern food environment that, according to the EBM, are believed to be most responsible for driving food choices and cause excess energy intake, and the biological mechanisms by which these factors alter the brain circuits controlling food intake are beginning to be elucidated^{40–42}. The tight regulation of protein intake interacting with dietary protein dilution ('protein leverage')⁹ and interactions between gut signals and brain regions supporting food reward (broadly defined and not limited to hedonics⁴³) and hypothalamic regions supporting homeostatic control of food intake are particularly intriguing^{44–46}.

The EBM allows for calorie-independent, macronutrient-specific effects on peripheral hormones, metabolism and substrate oxidation but posits that excess energy intake results in similar net fat deposition in adipose tissue regardless of the macronutrient composition of the diet³⁸. Adipose tissue expansion in an individual according to the EBM is, therefore, a downstream consequence of increased dietary energy intake. The historical increase in obesity prevalence in the population is potentially exacerbated by declining tissue metabolic activity (that is, body composition-adjusted BMR) over time, due to some as yet unidentified factor(s)³², which augments positive energy balance.

CIM

According to the CIM (Fig. 3), the primary cause of increased obesity prevalence is an alteration in fuel partitioning that favours channeling of ingested energy-yielding substrates away from pathways of oxidation toward storage in adipose and perhaps other tissues. This metabolic shift is perceived by the brain as a state of lack of energy, leading to decreased energy expenditure or increased food intake to compensate, eventually resulting in obesity^{47–49}.

Increased deposition of energy in the body is facilitated by qualitative (and at least partially calorie-independent) aspects of the modern diet, particularly, a high intake of refined, rapidly digestible

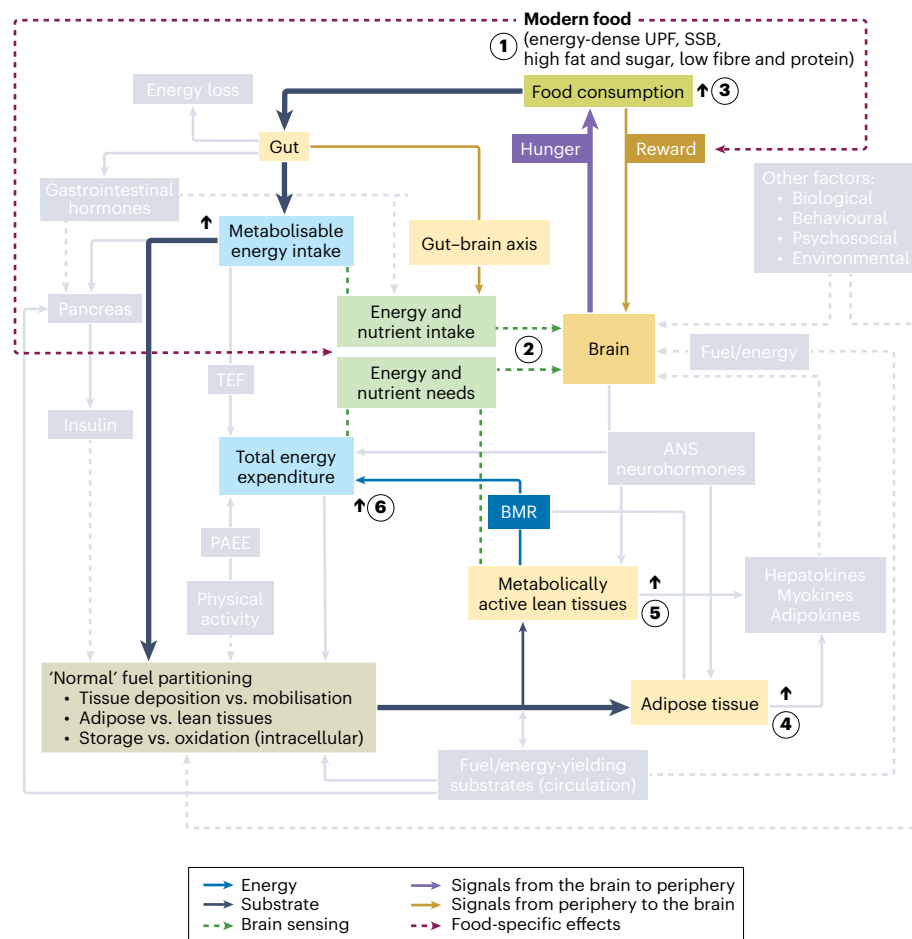


Fig. 2 | The EBM of obesity. The energy and nutrient needs of the body are transmitted to the brain where these signals are integrated with signals from the environment to control food intake. Modern food (1) (particularly energy-dense ultraprocessed foods (UPF), sugar-sweetened beverages (SSB) and foods rich in fat and sugar and low in protein and fibre) disrupts the signals and/or sensing of

the supply and demand of energy and nutrients (2), resulting in increased food intake (3) and subsequently increased metabolisable energy, exceeding energy requirements. The excess energy is mainly stored in adipose tissue (4) but also in lean tissues of the body (5). Concomitant to weight gain, energy expenditure increases (6). Refer to the legend in Fig. 1 for other abbreviations.

carbohydrate-containing foods (with high glycaemic index and load), exacerbated by increased consumption of foods and beverages that are rich in fructose (step 1 in Fig. 3). Meals with a high glycaemic index cause greater-than-normal increases in the ratio of insulin to glucagon and elicit other hormonal responses (for example, a decreased GLP1-to-GIP ratio) that accentuate the stimulation of anabolic pathways and the suppression of catabolic pathways that normally occur early in the postprandial state (for example, upregulation of lipogenesis and downregulation of lipolysis and fatty acid oxidation). Altered routing and partitioning of energy-yielding substrates (step 2), initially postprandially but eventually manifesting at all times of the day, leads to increased energy storage in tissues (step 3). Consequent to this sequestration of energy, the concentration of circulating metabolic fuels, such as glucose, free fatty acids and ketone bodies, is reduced several hours after eating (step 4) during the dynamic phase of weight gain, signalling low energy availability to the brain (step 5). This results in decreased energy expenditure as a result of suppressed tissue metabolic activity (step 6) and/or in increased hunger and food intake (step 7).

The most likely response under free-living, ad libitum eating conditions is an increase in food consumption, which tends to prevent a decrease in energy expenditure from manifesting^{47,48}. According to the CIM, therefore, the shift away from oxidation toward storage and energy sequestration is upstream of the positive energy balance that accompanies chronic weight gain. During the static phase of

weight gain, insulin resistance in adipose and other tissues results in elevations in metabolic fuels throughout the postprandial and postabsorptive periods.

Comparing the EBM and the CIM

There is a considerable amount of evidence from animal studies, genetic studies, observational studies and experimental studies in humans with various diet interventions but also medications that can be used to support or refute both the EBM and the CIM^{38,48}. Evaluating the robustness of all these studies fell outside the scope and the time frame of the workshop. Instead, the focus was on identifying commonalities and differences.

Agreement between models

Humans consume food for many reasons, but fundamentally they do so to meet the needs of the body for energy and nutrients, which, in some circumstances, serves to replenish body fat stores or to functionally anticipate future needs. The two models do not disagree on this physiological background. Furthermore, both models agree that transient imbalances in energy or macronutrient availability in the body, regardless of how they are initiated, occur on a daily basis but cause only miniscule effects on net fat storage, which can be offset over subsequent days. In the context of obesity development, cumulative net imbalances in energy or macronutrients are required over

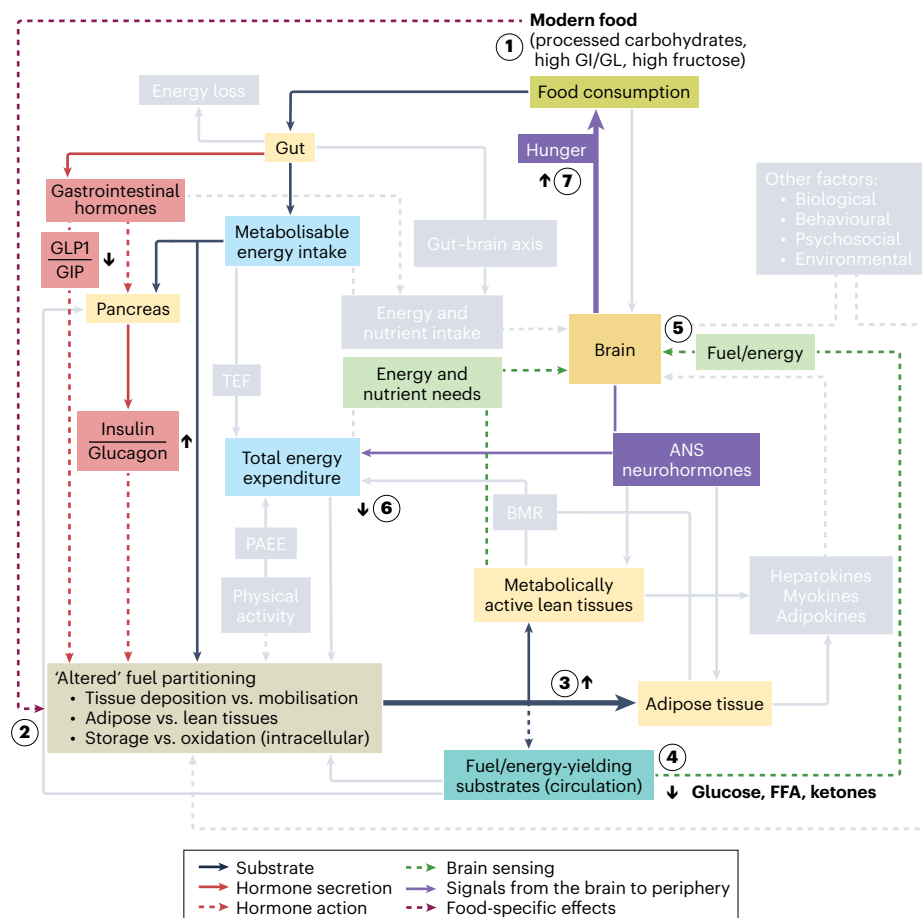


Fig. 3 | The CIM of obesity. The availability of fuels in some key locations around the body, particularly the bloodstream, is monitored by the brain, and energy expenditure and/or food intake are adjusted accordingly. Modern food (1) (particularly refined carbohydrates with high glycaemic index and glycaemic load (GI/GL)) alters fuel partitioning (2) under the influence of increased insulin-to-glucagon ratio and decreased GLP1-to-GIP ratio. This results in sequestration

of fuels in adipose tissue, liver and muscle (3) and, subsequently, reduced availability of energy-yielding substrates such as glucose, free fatty acids (FFA) and ketone bodies in the bloodstream (4). This is perceived by the brain as a state of internal starvation (5), eliciting compensatory responses, including decreased energy expenditure (6) and/or increased hunger and food consumption (7). Refer to the legend in Fig. 1 for other abbreviations.

prolonged periods of time. Both models recognize that longer time scales are most relevant for understanding obesity and try to explain why obesity develops in individuals and why its prevalence increased in recent decades in the population, within this overall physiological framework. The focus of the two models is on different components of the food environment that eventually lead to excess adiposity, that is, either on the ubiquitous, calorie-dense, ultraprocessed foods that are high in rewarding nutrient combinations rarely appearing in nature, such as certain mixtures of fat and sugar, fat and salt, and carbohydrates and salt (EBM), or on high-glycaemic index carbohydrate-containing foods and fructose-rich beverages (CIM).

The models recognize the potential role of many biological factors (for example, genetic predisposition, foetal programming, gut microbiome), behavioural factors (for example, physical activity, sleep patterns, weight cycling, medication use), psychosocial factors (for example, income, education, occupation) and environmental factors (for example, endocrine-disrupting chemicals, viruses, built environment) that may contribute to obesity in some individuals. Any such factor, however, dietary or other, must manifest itself through a biological mechanism that eventually alters energy intake, energy expenditure or substrate partitioning and thereby leads to net fat accumulation, adipose tissue expansion, weight gain and obesity. Both the EBM and the CIM provide plausible frameworks for this to happen, although there are some important differences between the two.

Points of divergence

One key difference between the two models rests on the point of entry of the modern food ‘insult’ (or any other causal factor) into the physiological system regulating energy metabolism and ultimately controlling fat storage (Figs. 2 and 3). The EBM posits that this happens in the brain (that is, an overwhelming food environment alters the sensing of energy supply and demand), whereas the CIM posits that this happens in the periphery (that is, the modern food environment alters fuel partitioning).

A second, fundamental difference that follows is that, according to the EBM, the ability of the brain to control food intake is overwhelmed or disrupted by the food environment, resulting in increased energy intake despite internal signals of energy sufficiency. By contrast, according to the CIM, the ability of the brain to control food intake remains intact, which is why food consumption increases and/or energy expenditure decreases in response to internal cues signalling less available energy resulting from altered fuel partitioning in the periphery.

A third important difference is that the CIM predicts a reduction in energy expenditure and/or a loss of lean mass if the individual resists the drive to eat more or if not enough food is available, but no change or even an increase in energy expenditure and lean mass if food intake increases, which is the most likely response⁴⁷. Thus, the CIM allows for increased adiposity to be initiated without an increase in energy intake over a baseline during which fat stores are stable. On the other hand,

the EBM predicts an increase in lean mass and whole-body energy expenditure concomitant to greater food intake and weight gain but no change in weight or energy expenditure (at the whole-body level or when adjusted for body composition) with unchanged energy intake. Thus, an increase in food intake is the initiating factor of increased adiposity in the EBM.

Differences between the EBM and the CIM (Table 2) and their predictions provide opportunities for model testing and should inform the design of appropriate experiments. However, direct testing of each model is not always possible. For example, while the EBM regards changes in energy expenditure as a consequence of increased food intake and obesity, the CIM places alterations in energy expenditure in the causal pathway for obesity. Still, this fundamental conceptual difference is not easy to test, as alterations in energy expenditure at the cellular or tissue levels are temporal in nature and will depend on the stage of obesity development and the concomitant changes in food intake and will likely be undetectable at the whole-body level by current methodologies and instrumentation.

Nevertheless, differences between the two models are not simply semantic in nature (offering divergent views about the direction of causality) but may have important implications for the management of obesity⁵⁰. Reducing the prevalence of obesity from the EBM perspective might prioritize addressing factors that promote increased energy intake and facilitate induction of positive energy balance. Interventions might need to focus primarily on re-engineering the local or broader food environment to promote the availability of affordable, convenient, high-quality foods and to reduce the availability and marketing of foods high in energy density, with particularly rewarding nutrient mixtures, large portion sizes and low protein and fibre contents. By contrast, reducing obesity prevalence from the CIM perspective might prioritize addressing factors that affect substrate partitioning by modifying dietary composition, for example, by limiting the consumption of high-glycaemic index carbohydrate foods and fructose-rich beverages, without the need for a primary focus on decreasing total energy intake. The implications reach beyond research to individual obesity management in clinical practice, food marketing, policymaking and dietary guidelines to the public.

From physiological models of energy metabolism regulation to the epidemic of obesity

Physiological models of any disorder, such as obesity, are conceptual representations of the system (here, the human body and its environment) that trace the chain of events leading to the disorder and attempt to disentangle the initiating and driving forces, to outline interdependencies between intrinsic and extrinsic factors (for example, genetic predisposition, susceptibility, environmental influences) and to describe cause-and-effect relationships. A model should be consistent with a set of observations and allow for the construction of testable hypotheses, thereby informing the design of appropriate experiments that are capable of confirming or refuting explicit and, ideally, precise predictions. Importantly, when applied to disease trends, prevention and treatment, a model should be able to explain changes in prevalence and perhaps even be able to predict the outcome upon altering the values of one or more parameters in the system⁷.

Admittedly, conceptual representations of the physiology of energy metabolism regulation in humans are not likely adequate to explain phenomena occurring at a global level that have important psychosocial and sociocultural dimensions^{51,52}. Accordingly, such factors may well be responsible for the epidemic of obesity; however, testing this hypothesis in a definitive manner will be a very difficult, if not an impossible task. Nevertheless, even psychosocial and sociocultural factors must eventually act on individual biology to drive increased deposition of fat in the body, and the issue remains whether these factors promote obesity via purely behavioural effects (that is, increased food intake), via changes in hormonal milieu and fuel partitioning, or both.

Table 2 | Key differences between the EBM and the CIM of obesity

	EBM	CIM
Causal direction	Positive energy balance results in net fat deposition	Altered fuel partitioning results in net fat deposition and, subsequently, positive energy balance
Primary dietary driver	Increased availability and marketing of a wide variety of inexpensive, convenient, energy-dense ultraprocessed foods that are high in portion size, fat, salt and sugar and low in protein and fibre	Carbohydrate-rich foods with high glycaemic index and fructose-rich beverages
Point of entry into the regulatory system	Brain	Periphery
Brain's response to signals of energy and nutrient availability or needs	Overwhelmed or impaired	Intact
Predicted change in energy expenditure	Increased at the whole-body level; unaltered if adjusted for changes in body composition	Decreased if food intake does not increase; unchanged or even increased if food intake increases

The above lines notwithstanding, knowing the cause of a disease does not necessarily mean that removing that cause will treat the disease; although, it should certainly help prevent it. As an analogy, smoking may cause lung cancer, but stopping smoking does not treat lung cancer, although it likely decreases the risk of developing it. The implication of this relationship for obesity is that elucidating which component (if any) of the modern food environment is responsible for weight gain does not mean that removing that component from the diet will help treat obesity. However, it will likely help prevent the epidemic in parts of the world where obesity is still a comparatively smaller public health issue, such as Africa, Southeast Asia (for example, India) and the Western Pacific (for example, China)⁵³, and it may also help prevent the development of obesity early in life, for example, among children and adolescents. Conversely, delineating the characteristics of the optimal diet for weight loss does not de facto mean that a diet with the opposite characteristics causes weight gain and obesity.

Open questions and directions for future research

While testing the components and proposed pathways of the EBM and the CIM is necessary, it might not be sufficient to understand the obesity epidemic, which could also be rooted in sociocultural factors. Different mechanisms could lead to obesity in different individuals, operate at different stages of the natural course of the disorder and contribute to the slow progression and persistence of this phenotype. Eventually, a plausible theory, based on available data and confirmed by appropriate experiments, will be needed that can explain the historical development of obesity at the global level within the framework of each model. Such a theory will help understand the causes of obesity and inform effective approaches for its prevention and treatment.

Epidemiological, ecological and cross-sectional observational analyses might point to potential factors that differentiate between the two models^{38,48}, but results from such studies are too confounded to be used for comparative model testing and mutually exclusive argumentation. We argue that more experimental research in humans is needed that, together with longitudinal cohorts and studies in animal models, can offer valuable insights, provide answers to key overarching questions and test specific assumptions and predictions of the EBM and the CIM (Table 3).

Table 3 | Model-independent questions to identify causes of obesity and model-specific questions to test components of the EBM and the CIM

Model independent
• Which components of the modern food environment are more conducive to weight gain? How do they affect the mechanisms regulating energy metabolism and fat storage?
• Which components outside the food environment contribute to weight gain? How do they affect energy intake, energy expenditure, substrate metabolism, fat storage and body composition?
• Do these food-related and non-food-related factors affect all individuals equally and, if not, why?
• Does less exposure to those food-related and non-food-related factors help prevent weight gain?
• What are the mechanisms responsible for the relatively effortless weight loss after experimental overfeeding, and how do they contrast with the mechanisms underlying the inability of most individuals with obesity to achieve and maintain substantial weight loss?
• What are the temporal changes in energy intake, energy expenditure, substrate oxidation, availability of circulating fuels and changes in body composition during the initial stages of obesity development?
Model specific
• Does net fat storage in the body respond to the ‘quality’ of the diet (macronutrient composition) in the long term? Does the food source of these nutrients matter?
• Do long-term isocaloric diets of different macronutrient composition have different effects on net fat storage and body composition-adjusted energy expenditure?
• Can experimental manipulation (decrease or increase) of the level of circulating fuels lead to corresponding changes (that is, decrease or increase, respectively) in whole-body and body composition-adjusted energy expenditure when food intake is not allowed to increase?
• How does the brain sense the energy and nutrient needs of the body, and to what extent and how are these detection mechanisms altered in the development of obesity?
• What is the impact of physical activity on non-homeostatic appetite control? Can low physical activity exacerbate hedonic behaviours and promote overconsumption?

Although questions ideally should be relatively easy to formulate, designing the appropriate experiments to test the relevant hypotheses is challenging and not always possible. This is particularly true for human experimental nutrition research⁵⁴, for reasons related to cost, sample size, duration of the intervention, metabolic adaptations, level of control over dietary intake and other behaviours (for example, physical activity), dietary compliance, issues of efficacy versus effectiveness, imprecision of the tools used for the measurement of outcomes and small effect sizes, to name a few. Experiments in animals are devoid of many of these limitations, however, oftentimes at the expense of poor translatability when it comes to interventions aimed at both preventing and treating obesity⁵⁵.

We suggest that, to move the field forward, it will be important to conduct (1) highly controlled feeding trials in domiciled volunteers (ideally, with diet arms lasting several weeks) with deep metabolic phenotyping to discover the mechanisms and reliably dissect transient from adaptive responses, (2) dietary interventions in free-living individuals (for 12–24 months) with adequate intensity and support to facilitate long-term behaviour change and diet adherence and evaluate ‘real-world’ effects (even though we recognize that the value of such studies in the context of determining which paradigm is correct is limited), (3) longitudinal cohort studies (lasting 5–20 years) with genotyping and frequent assessments of energy intake, energy expenditure, body composition and a variety of metabolic measures to gain insight into the temporal relationship between metabolic alterations and body fat accumulation and to assess genetic and phenotypic predictors of

future weight gain and (4) studies in animal models to test putative mechanisms informed by observations from human studies (that is, from humans to mice).

Currently, a major obstacle to conducting definitive dietary trials to test the components and validate the EBM and the CIM is lack of funding. For instance, a phase 3 trial for a single pharmacological agent (including drugs for obesity) costs a median of ~20 million USD or >40,000 USD per participant⁵⁶, whereas the vast majority of dietary trials funded by the NIH must make do with budgets <10% of that amount (for example, 1,000–3,000 USD per participant in the Look AHEAD trial depending on the intensity of the intervention)⁵⁷. Consequently, these trials typically lack adequate control of the experimental conditions or high intensity of the interventions (for example, full diet provision, frequent behavioural support) or do not last sufficiently long (that is, years)⁵⁴. Better funding for novel, innovative, highly rigorous dietary intervention trials is, therefore, necessary. Importantly, scientists with contrasting opinions should strive to jointly design, carry out and interpret such studies to increase their credibility. Such ‘adversarial collaborations’ would be facilitated by maintenance of a respectful and collegial tone among all parties to this debate.

Conclusions

Since the early 1970s, when scientists met in London⁵⁸ and Bethesda⁵⁹ to discuss the ‘causes of obesity’, we have discovered many potential pieces of the puzzle of obesity pathogenesis in humans. Half a century later, in October 2022, when scientists gathered again in a Royal Society Meeting to discuss the same topic (<https://royalsociety.org/science-events-and-lectures/2022/10/causes-obesity/>)^{60,61}, we had realized that the causes of obesity are exceedingly complex and still remain largely unknown, despite half a century of expanding knowledge.

What became clear during the Copenhagen workshop in 2023 is that getting scientists with opposing views together, stepping out of one’s comfort zone, keeping an open mind and accepting that any hypothesis may be right or wrong until rigorously, repeatedly and independently tested, is critically important for advancing science. A need for mutually agreed testing of the models emerged, which requires model assumptions and predictions to be made explicit and precise. Looking beyond the food environment is also necessary to discover external factors that may have been undervalued or even overlooked. Designing appropriate experiments and funding ambitious interventions are needed to understand the mechanisms leading to obesity and the intrinsic and extrinsic factors that are involved in the pathogenesis of this disorder.

It is our hope that research and discovery will pave the way, and appropriate strategies and policies for prevention and treatment will follow, so that the next generation of scientists need not gather after another 50 years to discuss, yet again, the ‘causes of obesity’! Or at least, if they do so, they will have more answers than those currently available.

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Competing interests

F.M., T.I.A.S., N.V.D., A.B.-W., M.F.H., E.R., M.I.F., K.D.H., J.R.S. and A.A. have nothing to declare. M.F.H. and A.A. are full-time employees of the Novo Nordisk Foundation. R.J.F.L. has been an advisory board member and speaker for Ely Lilly and the Novo Nordisk Foundation, for which she has received payments. C.C. is a cofounder of Ousia Pharma, a biotechnology company developing therapeutics for the treatment of obesity. D.R., G.T. and D.S.L. have authored books for the public about food intake, diets and their relationship with health and disease. D.B.A. has received personal payments or promises for the same from Amin, Talati, Wasserman for KSF Acquisition (Glanbia); General Mills; Kaleido Biosciences; the Law Offices of Ronald Marron; the Novo Nordisk Foundation; and Zero Longevity Science (as stock options). Donations to a foundation have been made on his behalf by the Northarvest Bean Growers Association, Communiqué. D.B.A.'s institution, Indiana University, and the Indiana University Foundation have received funds or donations to support his research or educational activities from the Alliance for Potato Research and Education, the American Egg Board, Arnold Ventures, Eli Lilly and Company, Mars, the National Cattlemen's Beef Association, the National Pork Board, Pfizer, the USDA, WW (formerly Weight Watchers) and numerous other for-profit and non-profit organisations.

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Author contributions

F.M. drafted the manuscript and created the visual elements; M.I.F., K.D.H., D.S.L. and J.R.S. critically revised the manuscript for important intellectual content; T.I.A.S., D.R., N.V.D., R.J.F.L., A.B.-W., C.C., M.F.H.,

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