PHILOSOPHICAL TRANSACTIONS B

royalsocietypublishing.org/journal/rstb

Opinion piece

Cite this article: Sørensen TIA. 2023 An adiposity force induces obesity in humans independently of a normal energy balance system—a thought experiment. *Phil. Trans. R. Soc. B* **378**: 20220203. https://doi.org/10.1098/rstb.2022.0203

Received: 3 February 2023
Accepted: 16 June 2023

One contribution of 16 to a discussion meeting issue 'Causes of obesity: theories, conjectures and evidence (Part I)'.

Subject Areas:
environmental science, evolution, genetics, health and disease and epidemiology, physiology, theoretical biology

Keywords:
obesity, energy, evolution, genetics, social challenges

Author for correspondence:
Thorkild I. A. Sørensen
e-mail: tias@sund.ku.dk

THE ROYAL SOCIETY PUBLISHING

An adiposity force induces obesity in humans independently of a normal energy balance system—a thought experiment

Thorkild I. A. Sørensen

University of Copenhagen, Novo Nordisk Foundation Centre for Basic Metabolic Research and Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, DK-2200 Copenhagen, Denmark

TIAS, 0000-0003-4821-430X

Obesity in humans represents a cumulative retention of a tiny fraction of total energy intake as fat, which is accompanied by growth of the metabolically active, energy-demanding, lean body mass. Since the energy balance regulation operates irrespective of the excess fat storage, availability of the required energy supplies is a permissive condition for obesity development. It occurs predominantly among people genetically predisposed and/or living with social or mental challenges. I propose a theory in which the body responds to social disruptions as threats of a future lack of food by an adiposity force building a reserve of energy independent of the regulation of the energy balance. It is based on the assumption that our evolutionary development required collaboration in gathering and sharing of food, combined with precautionary measures against anticipated failing food supplies. Social challenges are perceived as such threats, which activate the adiposity force through the brain to instigate the growth of fat and lean mass by neuro-hormonal signalling. If both perceived social threats and food abundance continue, the adiposity force pushes the fat accretion process to continue without inhibition by feedback signals from the fat mass, eventually leading to more obesity, and more so among the genetically predisposed.

This article is part of a discussion meeting issue 'Causes of obesity: theories, conjectures and evidence (Part I)'.

1. Introduction

Fat has double the energy value per weight of carbohydrates and protein, it is water-insoluble, and it appears biologically inert when assembled in intracellular triglyceride droplets. It can be carried around in substantial amounts, securing internal, directly accessible, energy supplies. Thus, fat is an optimal energy reserve under circumstances of reduced or uncertain food supplies. Fat depots are highly prevalent in nature and are likely to be essential for the lives of multiple species. The fat depots range from miniscule depots in microorganisms up to tons of fat in blue whales, and the depots exhibit massive seasonal variation in hibernating animals and migrating birds.

Humans have a similar ability to build fat storage in adipose compartments. A limited amount of body fat may play an essential role in some developmental phases, such as during infancy and during pubertal development, especially for females, and the subsequent reproductive life phase, including pregnancy, breast-feeding and child-caring periods [1]. Otherwise, fat depots may be of little importance for the survival and reproduction of the human species. However, an increase in adipose mass under the condition of potential future food scarcity or limited internal fuel supplies, e.g. during diseases, may have been advantageous in humans.

In spite of there being no indications of such risk of food scarcity in increasing parts of the world population, they have, during the last half century, experienced

an ever-increasing adipose body mass [2]. It exceeds the threshold for health-threatening obesity in a rapidly increasing number of individuals. Although this prevalence shows great variations within and between populations, it has now reached a pandemic level, which is a massive burden on global public health.

Numerous attempts to reduce the growth of adiposity may have slowed it down in some human populations, but, in general, they have so far clearly failed to mitigate it. The fundamental principle in all these attempts has been to reduce the energy available to the body and thereby inhibit fat deposition, or, if fat is already deposited in excess, enforce withdrawal of fat from the adipose compartment [3]. Although this principle appears straightforward and inevitable, and may help for a while in some patients with obesity [3–5], the general failure of this approach calls for much better and more broadly applicable solutions than those currently available. This will undoubtedly require a better understanding of the causes and mechanisms of obesity development than we currently have.

2. Incomplete understanding of the causes of obesity

Some individuals may develop obesity despite persistent and rigorous attempts to control it by dietary restrictions, e.g. various types of monogenic and syndromic obesity. However, the persistent availability of food is an obvious permissive condition for common obesity development. Thus, without the improved global food supply during recent decades there would probably not have been an obesity pandemic [6]. However, while obesity does not develop during famines, major segments of most populations that are privileged with food abundance do not develop obesity [2]. Given that a societally implemented active reduction in food availability is politically and culturally impossible, it is important from both an individual and a public health perspective to know the causal factors that operate in addition to food abundance.

Clearly, obesity development involves a complex set of genetic and environmental causal factors and processes, probably producing obesity through different pathways [7–10]. Whereas we have extensive and rapidly growing knowledge about many details of these factors and the implied mechanisms in obesity development, the coordination and interplay of the processes eventually leading to the increase of the adipose mass both individually and across populations remain unclear.

I suggest that we need a quantitatively based, unifying, evolutionarily justified theory of causes and mechanisms of obesity. This theory should integrate the available knowledge and should offer predictions about gaps in our knowledge to guide us into future research aimed at filling these gaps.

The theory must fit the fact that development of obesity is accompanied by an increase in energy turnover [11], and that the gain in adipose mass accounts for cumulatively less than 1% of total energy intake (easily assessed as the total energy value of the total body fat mass as a percentage of the total energy intake over the time period of obesity development) [12,13]. Although this small fraction likely represents just an average of fluctuations over the years of development of obesity, the theory should accommodate the fact that the development of obesity is usually so slow that the cumulative effects can only be observed over long time intervals, e.g. months and years.

The theory should explain the obesity phenotype, characterized by resistance to weight loss and strong tendency to re-establish the lost fat mass on the background of an energy balance regulation that apparently reacts normally to alterations in energy supplies and expenditures, irrespective of the size of the stored fat mass.

A comprehensive theory should provide an explanation of the evidence that obesity preferentially affects people who are genetically predisposed [7,9,10], or socially or mentally challenged [8,14–16]. The theory should incorporate the facts that obesity affects all age groups, but increases with advancing age, affects both sexes, but usually women more than men, and has great diversity of onset, speed and current levels across the planet [2]. The theory should also point at the causal factors that have changed and thereby induced the obesity pandemic, and at the possible reasons why these changes have happened.

Finally, to be useful, the validity of theory and its conjectural components should be empirically testable vis-à-vis alternative theories.

3. Alternative theories

Most of the currently debated theories and causes of obesity in humans are essentially based on the assumption that obesity is a manifestation of processes producing a surplus of energy in the body that is assumed to be deposited as fat within the adipose compartment by a passive overflow of energy [17–19]. While there may be several reasons for the energy surplus, these theories are hereafter collectively named ‘overflow theories’.

I propose an alternative theory—the ‘adiposity-force theory’—based on a postulated adiposity force that enhances the processes of fat storage in the adipose compartment independently of the normal regulation of the energy balance of the lean body mass. I assume that the adiposity force has been advantageous in the past, but induces obesity when triggered under the circumstances that characterize the current obesity pandemic.

This theory emerges from a recognition of the development of the obesity phenotype as being based on processes independent of but superimposed upon an otherwise normally functioning whole-body energy balance regulation. However, it must be kept in mind that the adiposity-force theory is just a thought experiment at this stage, put as an alternative to the overflow theories.

The adiposity-force theory separates the processes of continued fat accretion in the adipose compartment from the disturbances of the energy balance in the body outside that compartment. The theory aims at integrating the fat accretion processes—initiated by the adiposity force—by conjectures about how these processes operate and are controlled.

4. Dynamics of the energy balance system and the overflow theories

The whole-body energy balance is dynamically changing over time, being the net result of many varying influences altering energy input and output [19,20]. There are regular

high-frequency fluctuations across the daily routine intake of meals, fasting, daytime physical activity, sleep inactivity, and almost constant basal metabolism. There are also less regular fluctuations of varying amplitudes, where the daily routines are broken by modifications such as excessive food intake during holidays, dieting aimed at slimming, or excessive physical training. The energy balance system appears quite well regulated, being able to cope with these superimposed, multi-frequency upward and downward perturbations of varying magnitudes, as demonstrated by the common stability of body weight and body composition within rather narrow intervals over longer time periods, e.g. months or even, in some cases, years. This has led to the development of several control theories explaining how the interaction between the energy balance system and the body weight takes place [21,22].

It is an integral part of this system that deviations in the energy balance activate mechanisms that tend to re-establish the preceding balance and body weight. Thus, a profound negative energy balance, such as during prolonged fasting or severe food restriction, is strongly opposed by the eliciting of enhanced appetite and reduced energy expenditure, thereby defending the function and integrity of the lean body mass. On the other hand, when excessive food intake produces an energy surplus, part of the surplus may be deposited as fat, although it might also be accompanied by an increase in energy expenditure or energy loss, limiting the fat accretion.

The overflow theories assume that the process of fat accretion during obesity development is in some way based on a perturbation or dysfunction of this whole-body energy balance system. Typically, elevated appetite is assumed to result in increased food intake providing energy in excess of the needs of the lean body mass. Low energy needs due to low basal metabolism or reduced physical activity are often assumed to contribute to the surplus. This is assumed to produce a persisting overflow of surplus energy to the adipose compartment despite the accompanying counteracting mechanisms. In the long run, these mechanisms also include growth of the metabolically active, hence energy-demanding, lean body mass [20,23]. Why the eventual accumulated amount of fat after obesity development under these conditions usually remains limited to less than 1% of the total turnover during the years of the fat accretion is difficult to explain with these theories.

A major empirical element that needs to be explained by any theory of obesity development is the very strong tendency to regain body weight, including restoration of the fat mass, after a substantial body weight loss [4,17,19]. In the overflow theories, the regulatory system is assumed to accommodate the growing fat mass in such a way that the defence against a negative energy balance is activated by dietary restrictions even though there is an accessible enlarged fat mass, but how this comes about remains elusive.

5. The adiposity-force theory

In the adiposity-force theory the causal processes of obesity development are disconnected from the regulated energy balance system. The adiposity force may be in action irrespective of the state and dynamics of the system, but co-acting with it in determining the current size of the adipose mass. Thus, irrespective of the level of the progressive fat accretion, the size of the fat mass at any given point in time may be subject to manipulations making the energy balance positive or negative.

The adiposity-force theory therefore implies that there are two distinct, but mutually independent processes that may lead to growth of the fat content of the adipose compartment: changes in fat content that reflect the overflow as a function of the energy balance system, and changes that reflect the process of fat accretion resulting in obesity over time.

This proposal clearly bypasses the commonly perceived crucial element in most overflow theories. The enlargement of the adipose mass ending in obesity is not the result of food intake providing an amount of energy that for a variety of reasons exceeds the need of energy in the whole-body metabolism. It is rather a force that pushes the process of fat deposition in the adipose mass independently of the concurrent energy balance.

Thus, the adiposity-force theory allows co-action with the normally functioning energy balance system. When the adiposity force has activated the process of fat accretion, it goes on despite possible dynamic fluctuations of the whole-body energy balance and corresponding fluctuations in the amount of fat in the adipose compartment. It may eventually lead to obesity, usually after several years, and worsen obesity if the process continues.

6. Experimentally induced energy overflow does not produce obesity

Voluntary overfeeding studies [24,25] may be considered as an experimentally induced overflow of energy. As expected, prolonged overfeeding increases the adipose mass, but this condition does not have the typical characteristics of obesity. Thus, the increased fat mass easily shrinks after overfeeding has ceased. A similar increase in adipose mass as part of obesity development will require deliberate dieting to be made to disappear, and the body weight will very likely return to the previous elevated level if dieting ceases.

In the human overfeeding experiments, the fat accretion is variable and much lower than expected given the excess energy intake, implying variation in the compensatory activation of energy expenditure and energy loss. In view of the responses to massive overfeeding, increasing food intake by an amount corresponding to the eventual tiny fraction of the energy intake that ends in the fat depots during obesity development would not lead to observable fat accretion.

It may be speculated, however, that the overfeeding experiments have all been far too short (running for up to 6 months) to mimic the effects of continued excess food intake leading to a slow development of obesity, where the defence by the body of the enlarged adipose mass is becoming manifest. On the other hand, continuous massive overfeeding among people who have not yet developed obesity will be likely to induce lipotoxicity and possibly health-threatening metabolic disturbances [24,25].

7. Adiposity force versus the energy balance regulation

The action of the energy balance regulation with or without activation of the adiposity force raises questions about the long-term outcome of the size of the fat stores under various conditions and about what proportion of the fat mass present at any one point in time is due to either of the processes.

Irrespective of the adiposity force, the changes in energy content of the body, induced by short-term enforced external manipulation of energy input relative to energy output, may alter the amount of energy stored as fat in the adipose compartment, as demonstrated in the overfeeding experiments [24,25]. The response to such manipulations may well be described in accordance with the models of the regulated energy balance system [21,22]. The experiments suggest that when the adiposity force is inactive, enforced increases in adipose mass are fully and rapidly reversible. On the other hand, if the adiposity force is concomitantly activated, then such gains would be less likely to be reversible. However, the fat accretion induced by the adiposity force will also be reversed when the adiposity force is deactivated and/or if there is a need of the stored fat as energy source.

An active adiposity force requires a derived secondary adjustment of the energy-balance system to the eventual tiny fat accretion in the adipose compartment. Considering the much greater perturbations of the whole-body energy balance system that the regulatory processes normally can cope with, the fraction withdrawn by the adiposity force for obesity development in the long run is easily accommodated.

The growth of the metabolically active and hence energy-demanding lean body mass may account for the generally observable and measurable increase in food intake when obesity has developed [20]. This increased need for energy is regulated as an element in the energy balance system, independent of the activity of the adiposity force. The same applies to the energy expenditure allocated to physical activity. People with obesity usually move less than people without obesity, but on average they spend as much energy on moving the heavier body [26].

When obesity has developed and reached a stable level, the changes in food intake and physical activity are thus concomitant companions of the enlarged lean body mass and the heavier body. If obesity development continues, kept going by an activated adiposity force, it will still be a tiny fraction of that excessive food intake that may be deposited as additional fat in the adipose compartment. The co-action of the adiposity force and the overflow of surplus energy in enlarging the fat mass raises the question of what proportion of the fat mass is attributable to the processes due to activated adiposity force or any overflow of energy. The theory postulates that at any given point in time, the size of the fat mass is a result of the preceding combinations of the adiposity force and the homeostatic regulatory processes with possible departures from whole-body energy balance, upwards by overflow of energy to the adipose tissue or downwards during energy deficits. During the early phases of obesity development, the fraction attributable to the adiposity force is relatively small, whereas it is far bigger than the daily energy balance fluctuations when obesity has developed. At whole-body energy balance with stable levels of body fat among people with obesity, all accumulated fat derives from the action of the adiposity force. Substantial weight loss in people with obesity may overrule the adiposity force, which, however, takes over later during re-establishment of the fat mass.

8. Evolutionary origin of the adiposity force

But why is there an activation of the adiposity force in some individuals, and not in others? That the process can go on—permitted by the abundance of food—does not imply that it will go on. This is clearly demonstrated by the absence of obesity in large population segments that do have the privilege of lasting food abundance [2]. What triggers the adiposity force is therefore an essential question. The answer may be found in the proposed evolution of the adiposity force.

It is a fundamental and necessary feature of the human species (as it likely was for our hominid ancestors) to be able to collaborate in getting and sharing food, as well as conducting other essential collaborative behaviours [27–29], such as defending the group against enemies and predators. It requires a drive to supportive social behaviour to secure adequate coping with the mutual social dependency, and also when the group of people are challenged by environmental changes affecting all members of the group. The evolutionary development of this capability is assumed to have enhanced the likelihood of survival through reproduction of the individuals.

This ability is particularly important and hence more strongly developed in young women than in men, because of their need for extra energy reserves due to the greater risk of not being able to secure food supplies during pregnancy, breast-feeding and childcare [1]. The common tendency for women to further increase their fat mass during successive pregnancies may reflect their increasing need for safeguarding energy supplies with multiple children.

The adiposity-force theory proposes, as an integral part of the evolution of our species, that we have developed a specific ability to perceive and react unconsciously to social challenges or disruptions as anticipations of food insecurity, i.e. future risk of eventual failing supplies. In response to these imminent threats the adiposity force is activated to build up energy reserve by fat accretion in the adipose compartment. Building and running the accompanying enlargement of the lean body mass may be seen as a necessary bodily adaptation, despite the increased energy costs.

In the adiposity-force theory, sensing and reacting to the perception of the social challenges imply a mental, possibly unconscious, integration that subsequently activates neural and neuro-hormonal brain signals carried forward to the adipose compartment, initiating or strengthening the fat accretion.

There are other evolutionary theories based on the assumption that the development of obesity may be a response to food scarcity, food insecurity and social challenges perceived as food insecurity [30–32]. These theories thus embrace the same ideas as the adiposity force, but they all differ from the adiposity force by proposing mechanisms that primarily act by stimulating the appetite, resulting in increased food intake as a safeguard against the threat of a future lack of food. In the same vein, comfort or emotional, stress-induced eating in response to mental challenges may be considered a similar process [33]. The appetite dependency puts these theories into the category of the overflow theories, discussed and contrasted with the adiposity-force theory above.

9. Variation in the adiposity force within and between individuals

The strength of the adiposity force and hence the rate of the process of fat accretion may vary over time within each

individual and may differ between individuals, wherefore the eventual size of the fat mass will depend on the energy supplies relative to the strength of the adiposity force.

Obesity development may be accelerated compared with settings with limited supplies if the activated adiposity force is unopposed by the competing requirement of energy for the increased lean body mass. The duration and strength of the unopposed activated adiposity force will be a major determinant of the eventual size of the fat mass. It is an implicit and important feature of the adiposity force that it is not responsive to negative feedback signals indicating size of the fat mass, which allows it to grow far beyond the likely need of a reserve of energy. An example is the rapid and excessive increase in fat mass during pregnancy in many women, which may be due to an unopposed strong activation of the adiposity force. Another example is the increasing prevalence and degree of obesity with advancing age in many populations. Obviously, the older the individual, the more opportunities they have had for continuing the fat accretion, the greater the fat mass may become, until various ageing processes induce declines in body components, possibly by disintegration of steps in the adiposity-force pathway [34,35].

On the other hand, if a caloric restriction is approaching the level of famine, the adiposity force may be so strongly opposed that obesity will not develop, irrespective of continued activity of the adiposity force. However, in extremely rare cases, the adiposity force may be strong enough to induce fat accretion even when energy supplies are less than are needed to keep the energy balance outside the adipose compartment. While this has been observed experimentally in one female rodent study [36], it will be very difficult to reveal a similar phenomenon in human studies. Observations in humans of associations between food insecurity and obesity, most pronounced in women, may be considered as proxy evidence [30–32].

While the adiposity force is not downregulated by feedbacks from the size of the fat mass, it may be deactivated by removal of the stimulus that activated it after the development of obesity, in which case the fat mass may shrink, in analogy with the regulation of the energy balance seen after cessation of voluntary overfeeding enforcing enlargement of the fat mass. This may explain the occurrence of apparently spontaneous, but slow regression of obesity seen in some people [37,38].

The strong tendency to regain body weight, including restoring the fat mass, following weight loss induced by caloric restriction by whatever method is likely due to a combination of several mechanisms [39–41]. It may be the result of combined forces of the homeostatic counter-regulations aiming at re-establishing the energy balance and the effects of a very active adiposity force. The adiposity force will try to re-establish the fat mass, but the course depends on how strongly it is opposed by continued caloric restriction. The increased hunger and lowered energy expenditure, induced by the caloric restriction, will facilitate the restoration of the adipose mass by the adiposity force.

If the adiposity force is incidentally deactivated after such reduction, there may be no restoration of the fat mass, possibly explaining the rare cases of successful long-term maintenance of a diet-induced weight loss, which usually is assumed to require effective control of the energy balance opposing a presumed tendency to regain body weight [42].

10. Redundant activation of the adiposity force

If the activation of the adiposity force is triggered by social challenges, the absence of negative feedback signals from the enlarged fat mass allows it to go on even though a lack of food never emerges. Therefore, as long as the permissive condition of food abundance prevails, the process of fat accretion may continue to develop and worsen obesity.

In population segments with a persistent abundance of food supplies, obesity development is strongest and obesity prevalence therefore highest among people exposed to social challenges, such as lower social hierarchical position, poverty, insecurity, deprivation and adversities [14–16]. These effects of the social environment are manifest at multiple levels, from the individual, to generations, families, social groups, neighbourhoods, municipalities, regions and countries [16,43–46].

Because the social environment is subjectively perceived and processed, purely mental challenges unrelated to the objective social environment may also activate the adiposity force. These challenges may be various cognitive–emotional states, e.g. disappointments, frustrations, stress and low self-esteem due to mismatch of expectations to oneself or other people in the social environment (parents, siblings, friends, peers colleagues, etc.) and the perceived relations and achievements. Thus, among individuals who are socially privileged, but subjectively experience such mental challenges, the adiposity force may be activated and produce obesity [47].

The mentally activated adiposity force becomes particularly striking in societies where population segments with greater social challenges do not develop obesity because they suffer from inadequate food supplies inhibiting the effects of the adiposity force, typically in low-income and parts of middle-income countries [48,49]. Furthermore, in high-income countries, the political–cultural conditions may also be perceived as social challenges irrespective of food abundance, leading to activation of the adiposity force [43–47].

Triggering of the adiposity force by social challenges creates an unfortunate possibility of a vicious cycle, further promoting obesity development through weight stigmatization. The increased food intake and decreased physical activity accompanying the development of obesity may be perceived as anti-social behaviour, breaking the evolutionary-based social interdependency in obtaining and sharing food. The consumption of food by an individual that would otherwise be shared may be condemned as gluttony, and a smaller contribution to getting food to the group by being physically inactive as sloth. Seeing the obese body may be immediately interpreted as a sign of such behaviour. This may elicit stigmatization of, and negative attitudes towards people with obesity, and eventually lead to discrimination and exclusion, which may strengthen the activity of the adiposity force [47].

Frustration, shame and a feeling of weakness and insufficiency when not being able to get rid of obesity may be perceived as a challenge that further strengthens the adiposity force and contributes to the vicious cycle [50].

11. Mechanisms of the adiposity force

The adiposity force is not postulated to be yet another signalling molecule or singular biological pathway, but rather an integrated, coordinated process, which, when activated,

comprises a series of processes that enhance fat accretion in the adipose compartment and the accompanying growth of the lean body mass.

Adipose tissue exhibits a potentially modifiable dynamic turnover of both adipocytes and the triglyceride content of each adipocyte [51,52]. This calls for the development of obesity to be seen as a series of tiny adjustments of the slow, lasting turnover of adipogenesis versus apoptosis of adipocytes in the adipose tissue [51], and of the more rapid and versatile turnover of lipogenesis versus lipolysis within the adipocytes [52]. The adiposity-force theory postulates that signalling from the brain may operate by influencing these adjustments, thereby resulting in net fat accretion in the adipose compartment.

Tight direct neuronal and indirect neuro-hormonal connectivity (by the autonomic sympathetic system, the leptin system, the hypothalamic–pituitary–adrenal axis, the autonomic parasympathetic system influencing hormone secretion, e.g. of insulin and cortisol) between the brain, the adipose tissue and the individual adipocytes may provide the channels for these signals [53,54]. We know many details of the various implicated mechanisms, especially regarding their influence on lipogenesis and lipolysis [53–56]. Yet, we do not know how they are integrated and coordinated in producing the adiposity force.

A particular mechanism of fat accretion with similarities to the adiposity-force mechanism has been proposed as the basis of the so-called carbohydrate–insulin model of obesity [57]. In this model the fat accretion process is driven by eating food providing a high glycaemic load. This elicits elevated postprandial insulin levels, which stimulate uptake of fatty acids and glucose and inhibit lipolysis and thereby contribute to increased fat accretion in the adipocytes. This theory implies exacerbated diurnal fluctuations in the fat content of the adipose compartment, but it does not *per se* explain the progressive fat accretion ending in the development of obesity. To do so, this theory must assume a mechanism carrying a tiny surplus of fat accretion from one day to the next. Combining this model with an activated adiposity force could possibly explain individual differences in the association of diet composition with differences in adipose mass.

The mechanism of the enlargement of the lean body mass associated with the growth of the adipose mass [20,23] remains unknown, but it is considered a process supporting the functions of the body carrying the increased adipose mass. Although, across individuals, there is on average an enlargement of the lean body mass, the relation between the two compartments shows considerable individual variation. This indicates that the growth of lean body mass is not entirely determined by the processes of growing adipose mass.

The increased energy needs following the growth of lean body mass increase the food intake. In socially challenged people, especially the poor, this may lead to a preference for high-caloric density, and cheap and palatable foods and drinks, e.g. food high in carbohydrate and fat content and sugar-sweetened beverages [6,58]. Some overflow theories and the above-mentioned carbohydrate–insulin model consider food composition as a driver of the development of obesity, but change in food composition may instead be seen primarily as a consequence of the accompanying growth of the lean body mass and ensuing elevated hunger in combination with limited financial resources of those affected.

12. Maximum effects of the adiposity force and metabolic complications

The adjustments of the turnover of adipocytes in the adipose tissue and turnover of fat content in the adipocytes may not always be mutually balanced, producing adipose tissue either with many smaller adipocytes (hyperplastic) or fewer larger adipocytes (hypertrophic) [55,56]. This may define individual differences in the maximum effect of the adiposity force. The maximum increase in the number of adipocytes may be determined by the capacity of continued adipogenesis from the pool of stem cells relative to the rate of apoptosis. The maximum of increase in fat storage in each adipocyte is determined by the upper limits of enlargement of the fat droplet.

When the storage of fat in the adipocytes has reached its maximum, but the adiposity force continues without further increase in the number of fat cells to accommodate the fat, then the cells become dysfunctional and less insulin-sensitive [55,56], as also observed in the overfeeding studies [24,25]. This process elicits local tissue hypoxia and inflammation, increased apoptosis, and fibrosis, which inhibit further growth of the adipose compartment [59,60]. The systemic effects lead to a variety of metabolic abnormalities, ending in the metabolic syndrome in accordance with the so-called adipose expandability theory [59]. The increasing likelihood of development of a metabolic syndrome and its associated clinical manifestations of higher body fat mass may reflect the increasing likelihood of both the adipogenesis and the adipocyte fat storage having reached their maximum.

13. Genetic and epigenetic variations in the adiposity force

The evolutionary development of the energy balance system and the adiposity-force mechanisms operating through the mind–brain–body reactions, both those securing food supplies and those safeguarding against insufficiency of supplies, necessarily involves an extremely complex adaptation of the genome and its regulation and function. This explains the implicated activities of thousands of genes and their regulatory elements, predominantly active in the brain [7].

However, accompanying this evolutionary genomic adaptation, multiple, presumably random, mutations across the genome have occurred in each generation, altering the specific elements of the functions of the system [7,22]. Cumulatively across the genome, these genetic variants may be associated with either a weaker or stronger influence of both the regulation of the energy balance and the elements in the adiposity-force pathway. The mutations that have escaped extinction by not limiting reproduction of the individuals are those that constitute the current panel of genetic variants. In this way they have produced the present very wide genomic variation, including thousands of single nucleotide variants across the genome, presumably associated with most if not all the elements in these processes. This genomic variation continues to be expanded in each generation, and has led to the great diversity in the adiposity phenotype and in the occurrence of obesity within otherwise apparently homogeneous populations living under similar environmental conditions.

Dependent on the gene functions that have been altered by the mutations, their expressions in the adiposity phenotype

may differ among individuals and be modified by individuals' environments [7]. The mutations may have created differences in the profile of the genetic variants between different populations around the planet, which may contribute to different genetic associations with obesity and different obesity levels. Most mutations have induced minor alterations in gene function, but a few have produced the more severe monogenic and syndromic forms that may have been carried forward by being only recessively expressed.

Epigenetic alterations induced by environmental influences, possibly including social challenges, transmitted from parents to offspring through mechanisms operating either in the gametes before conception, in the foetus during pregnancy, or during infancy, may also be implicated [61]. This may contribute to further facilitating and perhaps boosting transgenerational functioning of the systems [16].

14. Causes of the obesity pandemic

The question of what has caused the current pandemic of obesity must be distinguished from the more general question about what causes obesity. The pandemic of obesity is due to changes over time in the exposure distribution of some of the causes of obesity in the global populations, and the questions are which of the causes have changed and why have they changed.

The steady increase, particularly during the past half century, in access to excessive food supplies for various population segments [6] may have been the crucial determinant of the obesity pandemic by supporting the increasing energy demands of the concomitantly growing lean body mass. This may have allowed the adiposity force to play out in more and more people, to an ever increasing extent and for longer periods of time.

Compared with the conditions before the onset of the obesity pandemic, improved food supplies are an essential component of the improvement of the general living conditions that has occurred together with the obesity pandemic. These improvements should therefore reduce the likelihood of populations being exposed to the social challenges that could activate the adiposity force. However, considerable and frequently profound social inequalities, co-existing with the improved food supplies in many societies, may still be perceived as social challenges strong enough to lead to activation of the adiposity force, irrespective of food abundance.

The finding in high-income countries of an increasing prevalence of obesity in population segments that have not lived under conditions of limited food supplies [2] suggests that the political–cultural conditions may have changed in a manner leading to increased frequency and persistence of activation of the adiposity force [8]. Obesity-related changes in assortative mating, fertility and family structures may also have influenced the occurrence of obesity.

Considering the extreme complexity of the function of the adiposity force, it is also possible that it has been modified by novel or increased physico-chemical or biological exposures (e.g. pollution, atmospheric CO_2, noise, ambient temperature, diurnal and sleep disruptions, microbial environment, viral infections or drugs) [8]. The interference with the system may have happened in early formative stages of the individuals or acted continuously, and may have strengthened the sensitivity or the effects of the adiposity force.

15. Assessment of the adiposity-force theory

The adiposity-force theory and all the alternative theories are based on pieces of solid empirical evidence about elements of the causal chain that is integrated into the theories by still-unproven conjectures. The assessment of these theories may compare the value of alternative theories in explaining the same phenomena, development of obesity, its pandemic spread, and its characteristics as outlined earlier. The arguments presented in this paper favouring the adiposity-force theory over the overflow theories in this regard are first steps in this approach.

The next step is to identify options for testing the specific conjectures by alterations of upstream elements in the causal chain of the theory, either by existing real-world differences allowing quasi-experimental inference, or by manipulations in experimental settings. The theory implies the possibility of making predictions of effects of alterations in the social environment at different well controlled levels of food supplies on the ensuing observable downstream elements of the causal chain, ultimately in the fat accretion process and possible obesity development, which would be the overarching test of the theory.

However, the fact that obesity development usually takes many years and ends up in only a tiny average fat accretion has the unfortunate consequence that it is very difficult, if at all possible, with currently available tools and techniques to measure the fat accretion and its determinants as an instantaneous process, or even over short time frames, in what might otherwise be feasible studies [13]. So, any predictions about downstream effects of the alteration of upstream elements in the causal chains need to be constrained by the range of this quantity. Net differences in the energy balance components corresponding to the change in size of the adipose compartment and its regulatory processes between people eventually developing obesity and those who do not will only be discernible during phases of fast fat accretion, e.g. in the rebuilding of the fat mass following dietary-induced weight loss or during pregnancy.

The sequence of the development of the observable excess food intake and the obesity development may provide a possibly testable difference in prediction, distinguishing between the overflow theories and the adiposity-force theory. In accordance with the results from the overfeeding experiments, the overflow theories require increases in energy intake that are large enough to exceed the subsequently increasing energy expenditure in the growing lean body mass, and thereby eventually create the small passive overflow of energy to the adipose compartment. In the adiposity-force theory, the fat accretion may go on in the adipose compartment, requiring only an almost unmeasurable adjustment of the energy balance outside the adipose compartment, until later when the subsequently enlarged, metabolically active and energy-demanding lean body mass does require an excess food intake. Observation of the sequence of the altered energy intake and expenditure versus fat accretion may therefore contribute to support for of one of the theories versus the others.

An apparently counterintuitive consequence for the overflow theories of the separate phases of increase in energy turnover and fat accretion is that elevated energy turnover induced by excessive food intake would be predictive of later fat accretion, which, however, is not the case [62]. In fact, a low energy turnover may predict later fat accretion by

facilitating the increasing energy supply to the growing lean body mass in weaker opposition to an activated adiposity force.

The argument may be taken one step further to an experimental setting, where observation of a continued fat accretion when energy intake is limited would be incompatible with the overflow theories, but supports the adiposity-force theory. This is in fact seen in some analogous rodent studies [35], but the feasibility of such studies in humans is questionable.

What is ultimately needed is the experimental or quasi-experimental demonstration, including quantification, of the assumed coordinated causal links of the activation, operation and effects of the adiposity force: from the triggering occurrences in the social environment via altered mental state, altered brain function, neuro-hormonal signalling to the adipose tissue, modulation of the adipocyte and lipid turnover, and net fat accretion, to the eventual cumulative effects that constitute obesity development. A further qualification of the theory would require a dose–response quantification of the action of the adiposity force under different conditions influencing energy balance, ranging from food abundance to food scarcity.

Data accessibility. This article has no additional data.

Conflict of interest declaration. I declare I have no competing interests.

Funding. I received no funding for this study.

Acknowledgements. I would like to acknowledge here that in this endeavour I am indebted to many colleagues, including the peer reviewers of this paper, but first and foremost to my former American mentor and collaborator, the late Professor Albert J. Stunkard, who made seminal contributions to the elucidation of the importance of genetic and social factors in obesity [9,10,14,15]. I am very grateful for constructive comments on the draft from colleagues (Morten K. Grønbæk, Gorm B. Jensen, Jens Henrik Henriksen, Jens Lund, Erik Lykke Mortensen, Jens Aage Stauning), and for English proofreading by Birgitte Kanstrup, Esther Mortensen and Edward Taylor.

References

1. Power ML, Schulkin J. 2008 Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. *Br. J. Nutr.* **99**, 931–940. (doi:10.1017/S0007114507853347)
2. NCD Risk Factor Collaboration (NCD-RisC). 2017 Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet* **390**, 2627–2642. (doi:10.1016/S0140-6736(17)32129-3)
3. Hill JO, Wyatt HR, Peters JC. 2012 Energy balance and obesity. *Circulation* **126**, 126–132. (doi:10.1161/CIRCULATIONAHA.111.087213)
4. Heymsfield SB, Wadden TA. 2017 Mechanisms, pathophysiology, and management of obesity. *N. Engl. J. Med.* **376**, 254–266. (doi:10.1056/NEJMra1514009)
5. Alkhezi OS, Alahmed AA, Alfayez OM, Alzuman OA, Almutairi AR, Almohammed OA. 2022 Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: a network meta-analysis of randomized clinical trials. *Obes. Rev.* **24**, e13543. (doi:10.1111/obr.13543)
6. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, Gortmaker SL. 2011 The global obesity pandemic: shaped by global drivers and local environments. *Lancet* **378**, 804–814. (doi:10.1016/S0140-6736(11)60813-1)
7. Loos RJF, Yeo GSH. 2021 The genetics of obesity: from discovery to biology. *Nat. Rev. Genet.* **23**, 120–133. (doi:10.1038/s41576-021-00414-z)
8. Davis RAH, Plaisance EP, Allison DB. 2018 Complementary hypotheses on contributors to the obesity epidemic. *Obesity* **26**, 17–21. (doi:10.1002/oby.22071)
9. Stunkard AJ, Sørensen TI, Hanis C, Teasdale TW, Chakraborty R, Schull WJ, Schulsinger F. 1986 An adoption study of human obesity. *N. Engl. J. Med.* **314**, 193–198. (doi:10.1056/NEJM198601233140401)
10. Stunkard AJ, Harris JR, Pedersen NL, McClearn GE. 1990 The body-mass index of twins who have been reared apart. *N. Engl. J. Med.* **322**, 1483–1487. (doi:10.1056/NEJM199005243222102)
11. Prentice AM, Black AE, Coward WA, Cole TJ. 1996 Energy expenditure in overweight and obese adults in affluent societies: an analysis of 319 doubly-labelled water measurements. *Eur. J. Clin. Nutr.* **50**, 93–97.
12. Hall KD, Sacks G, Chandramohan D, Chow CC, Wang YC, Gortmaker SL, Swinburn BA. 2011 Quantification of the effect of energy imbalance on bodyweight. *Lancet* **378**, 826–837. (doi:10.1016/S0140-6736(11)60812-X)
13. Sørensen TI. 2009 Challenges in the study of causation of obesity. *Proc. Nutr. Soc.* **68**, 43–54. (doi:10.1017/S0029665108008847)
14. Moore ME, Stunkard AJ, Srole L. 1962 Obesity, social class, and mental illness. *JAMA* **181**, 962–966. (doi:10.1001/jama.1962.03050370030007)
15. Goldblatt PB, Moore ME, Stunkard AJ. 1965 Social factors in obesity. *JAMA* **192**, 1039–1044. (doi:10.1001/jama.1965.03080250017004)
16. Hemmingsson E, Nowicka P, Ulijaszek S, Sørensen TIA. 2023 The social origins of obesity within and across generations. *Obes. Rev.* **24**, e13514. (doi:10.1111/obr.13514)
17. Schwartz MW, Seeley RJ, Zeltser LM, Drewnowski A, Ravussin E, Redman LM, Leibel RL. 2017 Obesity pathogenesis: an Endocrine Society scientific statement. *Endocr. Rev.* **38**, 267–296. (doi:10.1210/er.2017-00111)
18. Ludwig DS, Sørensen TIA. 2022 An integrated model of obesity pathogenesis that revisits causal direction. *Nat. Rev. Endocrinol.* **18**, 261–262. (doi:10.1038/s41574-022-00635-0)
19. Hall KD, Heymsfield SB, Kemnitz JW, Klein S, Schoeller DA, Speakman JR. 2012 Energy balance and its components: implications for body weight regulation. *Am. J. Clin. Nutr.* **95**, 989–994. (doi:10.3945/ajcn.112.036350)
20. Hopkins M, Finlayson G, Duarte C, Gibbons C, Johnstone AM, Whybrow S, Horgan GW, Blundell JE, Stubbs RJ. 2019 Biological and psychological mediators of the relationships between fat mass, fat-free mass and energy intake. *Int. J. Obes.* **43**, 233–242. (doi:10.1038/s41366-018-0059-4)
21. Speakman JR *et al.* 2011 Set points, settling points and some alternative models: theoretical options to understand how genes and environments combine to regulate body adiposity. *Dis. Model. Mech.* **4**, 733–745. (doi:10.1242/dmm.008698)
22. Speakman JR, Elmquist JK. 2022 Obesity: an evolutionary context. *Life Metab.* **29**, 10–24. (doi:10.1093/lifemeta/loac002)
23. Hwaung P, Bosy-Westphal A, Muller MJ, Geisler C, Heo M, Thomas DM, Kennedy S, Heymsfield SB. 2019 Obesity tissue: composition, energy expenditure, and energy content in adult humans. *Obesity* **27**, 1472–1481. (doi:10.1002/oby.22557)
24. Cuthbertson DJ, Steele T, Wilding JP, Halford JC, Harrold JA, Hamer M, Karpe F. 2017 What have human experimental overfeeding studies taught us about adipose tissue expansion and susceptibility to obesity and metabolic complications? *Int. J. Obes.* **41**, 853–865. (doi:10.1038/ijo.2017.4)
25. Bray GA, Bouchard C. 2020 The biology of human overfeeding: a systematic review. *Obes. Rev.* **21**, e13040. (doi:10.1111/obr.13040)
26. Carneiro IP, Elliott SA, Siervo M, Padwal R, Bertoli S, Battezzati A, Prado CM. 2016 Is obesity associated with altered energy expenditure? *Adv. Nutr.* **7**, 476–487. (doi:10.3945/an.115.008755)
27. Melis AP. 2013 The evolutionary roots of human collaboration: coordination and sharing of resources. *Ann. N. Y. Acad. Sci.* **1299**, 68–76. (doi:10.1111/nyas.12263)
28. Melis AP, Grocke P, Kalbitz J, Tomasello M. 2016 One for you, one for me: humans' unique turn-

taking skills. *Psychol. Sci.* **27**, 987–996. (doi:10.1177/0956797616644070)
29. Tomasello M. 2022 The coordination of attention and action in great apes and humans. *Phil. Trans. R. Soc. B* **377**, 20210093. (doi:10.1098/rstb.2021.0093)
30. Dhurandhar EJ. 2016 The food-insecurity obesity paradox: a resource scarcity hypothesis. *Physiol. Behav.* **162**, 88–92. (doi:10.1016/j.physbeh.2016.04.025)
31. Nettle D, Andrews C, Bateson M. 2017 Food insecurity as a driver of obesity in humans: the insurance hypothesis. *Behav. Brain Sci.* **40**, e105. (doi:10.1017/S0140525X16000947)
32. Caldwell AE, Sayer RD. 2019 Evolutionary considerations on social status, eating behavior, and obesity. *Appetite* **132**, 238–248. (doi:10.1016/j.appet.2018.07.028)
33. Jacques A, Chaaya N, Beecher K, Ali SA, Belmer A, Bartlett S. 2019 The impact of sugar consumption on stress driven, emotional and addictive behaviors. *Neurosci. Biobehav. Rev.* **103**, 178–199. (doi:10.1016/j.neubiorev.2019.05.021)
34. An R, Xiang X. 2016 Age–period–cohort analyses of obesity prevalence in US adults. *Public Health* **141**, 163–169. (doi:10.1016/j.puhe.2016.09.021)
35. Speakman JR, Westerterp KR. 2010 Associations between energy demands, physical activity, and body composition in adult humans between 18 and 96 y of age. *Am. J. Clin. Nutr.* **92**, 826–834. (doi:10.3945/ajcn.2009.28540)
36. Li X, Cope MB, Johnson MS, Smith Jr DL, Nagy TR. 2010 Mild calorie restriction induces fat accumulation in female C57BL/6J mice. *Obesity* **18**, 456–462. (doi:10.1038/oby.2009.312)
37. Sonne-Holm S, Sørensen TI, Jensen G, Schnohr P. 1990 Long-term changes of body weight in adult obese and non-obese men. *Int. J. Obes.* **14**, 319–326.
38. Andersen LG, Baker JL, Sørensen TI. 2012 Contributions of incidence and persistence to the prevalence of childhood obesity during the emerging epidemic in Denmark. *PLoS ONE* **7**, e42521. (doi:10.1371/journal.pone.0042521)
39. Ochner CN, Barrios DM, Lee CD, Pi-Sunyer FX. 2013 Biological mechanisms that promote weight regain following weight loss in obese humans. *Physiol. Behav.* **120**, 106–113. (doi:10.1016/j.physbeh.2013.07.009)
40. van Baak MA, Mariman ECM. 2019 Mechanisms of weight regain after weight loss — the role of adipose tissue. *Nat. Rev. Endocrinol.* **15**, 274–287. (doi:10.1038/s41574-018-0148-4)
41. Aronne LJ, Hall KD, Jakicic JM, Leibel RL, Lowe MR, Rosenbaum M, Klein S. 2021 Describing the weight-reduced state: physiology, behavior, and interventions. *Obesity* **29**(Suppl. 1), S9–S24. (doi:10.1002/oby.23086)
42. Flore G, Preti A, Carta MG, Deledda A, Fosci M, Nardi AE, Loviselli A, Velluzzi F. 2022 Weight maintenance after dietary weight loss: systematic review and meta-analysis on the effectiveness of behavioural intensive intervention. *Nutrients* **14**, 1259. (doi:10.3390/nu14061259)
43. Ulijaszek SJ. 2014 Do adult obesity rates in England vary by insecurity as well as by inequality? An ecological cross-sectional study. *BMJ Open* **4**, e004430. (doi:10.1136/bmjopen-2013-004430)
44. Devaux M, Sassi F. 2013 Social inequalities in obesity and overweight in 11 OECD countries. *Eur. J. Public Health* **23**, 464–469. (doi:10.1093/eurpub/ckr058)
45. Anekwe CV, Jarrell AR, Townsend MJ, Gaudier GI, Hiserodt JM, Stanford FC. 2020 Socioeconomics of obesity. *Curr. Obes. Rep.* **9**, 272–279. (doi:10.1007/s13679-020-00398-7)
46. Offer A, Pechey R, Ulijaszek S. 2010 Obesity under affluence varies by welfare regimes: the effect of fast food, insecurity, and inequality. *Econ. Hum. Biol.* **8**, 297–308. (doi:10.1016/j.ehb.2010.07.002)
47. Tomiyama AJ. 2019 Stress and obesity. *Annu. Rev. Psychol.* **70**, 703–718. (doi:10.1146/annurev-psych-010418-102936)
48. Sobal J, Stunkard AJ. 1989 Socioeconomic status and obesity: a review of the literature. *Psychol. Bull.* **105**, 260–275. (doi:10.1037/0033-2909.105.2.260)
49. Dinsa GD, Goryakin Y, Fumagalli E, Suhrcke M. 2012 Obesity and socioeconomic status in developing countries: a systematic review. *Obes. Rev.* **13**, 1067–1079. (doi:10.1111/j.1467-789X.2012.01017.x)
50. Sainsbury K, Evans EH, Pedersen S, Marques MM, Teixeira PJ, Lähteenmäki L, Stubbs RJ, Heitmann BL, Sniehotta FF. 2019 Attribution of weight regain to emotional reasons amongst European adults with overweight and obesity who regained weight following a weight loss attempt. *Eat. Weight Disord.* **24**, 351–361. (doi:10.1007/s40519-018-0487-0)
51. Spalding KL *et al.* 2008 Dynamics of fat cell turnover in humans. *Nature* **453**, 783–787. (doi:10.1038/nature06902)
52. Arner P *et al.* 2011 Dynamics of human adipose lipid turnover in health and metabolic disease. *Nature* **478**, 110–113. (doi:10.1038/nature10426)
53. Zeng W *et al.* 2015 Sympathetic neuro-adipose connections mediate leptin-driven lipolysis. *Cell* **163**, 84–94. (doi:10.1016/j.cell.2015.08.055)
54. Caron A, Lee S, Elmquist JK, Gautron L. 2018 Leptin and brain–adipose crosstalks. *Nat. Rev. Neurosci.* **19**, 153–165. (doi:10.1038/nrn.2018.7)
55. White U, Ravussin E. 2019 Dynamics of adipose tissue turnover in human metabolic health and disease. *Diabetologia* **62**, 17–23. (doi:10.1007/s00125-018-4732-x)
56. Cypess AM. 2022 Reassessing human adipose tissue. *N. Engl. J. Med.* **386**, 768–779. (doi:10.1056/NEJMra2032804)
57. Ludwig DS *et al.* 2022 Competing paradigms of obesity pathogenesis: energy balance versus carbohydrate-insulin models. *Eur. J. Clin. Nutr.* **76**, 1209–1221. (doi:10.1038/s41430-022-01179-2)
58. Darmon N, Drewnowski A. 2015 Contribution of food prices and diet cost to socioeconomic disparities in diet quality and health: a systematic review and analysis. *Nutr. Rev.* **73**, 643–660. (doi:10.1093/nutrit/nuv027)
59. Carobbio S, Pellegrinelli V, Vidal-Puig A. 2017 Adipose tissue function and expandability as determinants of lipotoxicity and the metabolic syndrome. *Adv. Exp. Med. Biol.* **960**, 161–196. (doi:10.1007/978-3-319-48382-5_7)
60. Vishvanath L, Gupta RK. 2019 Contribution of adipogenesis to healthy adipose tissue expansion in obesity. *J. Clin. Invest.* **129**, 4022–4031. (doi:10.1172/JCI129191)
61. Wu FY, Yin RX. 2022 Recent progress in epigenetics of obesity. *Diabetol. Metab. Syndr.* **14**, 171. (doi:10.1186/s13098-022-00947-1)
62. Ravussin E, Lillioja S, Knowler WC, Christin L, Freymond D, Abbott WG, Boyce V, Howard BV, Bogardus C. 1988 Reduced rate of energy expenditure as a risk factor for body-weight gain. *N. Engl. J. Med.* **318**, 467–472. (doi:10.1056/NEJM198802253180802)