Obesity: global epidemiology and pathogenesis

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Abstract | The prevalence of obesity has increased worldwide in the past ~50 years, reaching pandemic levels. Obesity represents a major health challenge because it substantially increases the risk of diseases such as type 2 diabetes mellitus, fatty liver disease, hypertension, myocardial infarction, stroke, dementia, osteoarthritis, obstructive sleep apnoea and several cancers, thereby contributing to a decline in both quality of life and life expectancy. Obesity is also associated with unemployment, social disadvantages and reduced socio-economic productivity, thus increasingly creating an economic burden. Thus far, obesity prevention and treatment strategies — both at the individual and population level — have not been successful in the long term. Lifestyle and behavioural interventions aimed at reducing calorie intake and increasing energy expenditure have limited effectiveness because complex and persistent hormonal, metabolic and neurochemical adaptations defend against weight loss and promote weight regain. Reducing the obesity burden requires approaches that combine individual interventions with changes in the environment and society. Therefore, a better understanding of the remarkable regional differences in obesity prevalence and trends might help to identify societal causes of obesity and provide guidance on which are the most promising intervention strategies.

Noncommunicable diseases (NCDs), including cardiovascular diseases, cancer and diabetes mellitus, account for >70% of early deaths worldwide, thus representing the leading cause of mortality and premature disability[1]. Obesity — a major risk factor for NCDs — is associated with decreased life expectancy of an estimated 5–20 years lost depending on the severity of the condition and comorbid disorders[2–4]. The WHO defines obesity as excessive fat accumulation that might impair health and is diagnosed at a BMI ≥30 kg/m^2 (REF.[4]).

Obesity substantially increases the risk of metabolic diseases (for example type 2 diabetes mellitus and fatty liver disease), cardiovascular diseases (hypertension, myocardial infarction and stroke), musculoskeletal disease (osteoarthritis), Alzheimer disease, depression and some types of cancer (for example, breast, ovarian, prostate, liver, kidney and colon). In addition, obesity might lead to reduced quality of life, unemployment, lower productivity and social disadvantages. For example, osteoarthritis — a common consequence of obesity — is one of the leading causes of disability and early retirement[5]. Importantly, the World Obesity Federation and other organizations, including the American and Canadian Medical Associations, have declared obesity a chronic progressive disease clearly distinct from being just a risk factor for other diseases[6].

Reducing the obesity-related burden to health and societies as well as reversing the increase in obesity prevalence is a high priority for the WHO, which included the target to halt obesity prevalence at the level it was in 2010 as one of the main targets of the 'Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020'[7]. In the political declaration of the high-level meeting of the UN General Assembly on the prevention and control of NCDs of September 2011, the importance of reducing unhealthy diet and physical inactivity was recognized[8].

Current health recommendations rely on the fact that the fundamental cause of obesity is an energy imbalance between calories consumed and calories expended. However, at the individual level, weight-loss interventions aimed at reducing calorie intake and increasing energy expenditure are frequently not successful in the long term. Although at first glance the responsibility of an individual, behavioural changes (including changes in diet and activity patterns) are more likely to occur as a result of environmental and societal changes[9]. Such behavioural changes might be ineffective in the context of a lack of supportive policies in sectors such as health, agriculture, transport, urban planning, environment, food processing and marketing, education and others[10]. The WHO therefore acknowledges that healthy eating and increasing physical activity in the entire population should be promoted by policies and actions implemented in societies[7].

To this end, differences in obesity prevalence dynamics between countries might provide important insights into

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Key points

- Obesity prevalence has increased in pandemic dimensions over the past 50 years.
- Obesity is a disease that can cause premature disability and death by increasing the risk of cardiometabolic diseases, osteoarthritis, dementia, depression and some types of cancers.
- Obesity prevention and treatments frequently fail in the long term (for example, behavioural interventions aiming at reducing energy intake and increasing energy expenditure) or are not available or suitable (bariatric surgery) for the majority of people affected.
- Although obesity prevalence increased in every single country in the world, regional differences exist in both obesity prevalence and trends; understanding the drivers of these regional differences might help to provide guidance for the most promising intervention strategies.
- Changes in the global food system together with increased sedentary behaviour seem to be the main drivers of the obesity pandemic.
- The major challenge is to translate our knowledge of the main causes of increased obesity prevalence into effective actions; such actions might include policy changes that facilitate individual choices for foods that have reduced fat, sugar and salt content.

which biosocial causes of obesity are the most promising targets for future interventions to reduce the burden of obesity. Therefore, in this Review, I discuss changes in the incidence of obesity and differences between countries in the context of the pathogenesis of obesity.

Pathogenesis of obesity

The fundamental cause of obesity is a long-term energy imbalance between too many calories consumed and too few calories expended (FIG. 1). Evolutionarily, humans and their predecessors had to survive periods of undernutrition; therefore, selection pressure most likely contributed to a genotype that favours overeating, low energy expenditure and physical inactivity. Humans who could stand longer periods of famine and who could store and mobilize energy more efficiently might have reproduced more than those without these adaptations, subsequently leading to the overrepresentation of genetic variants that promote the ability to eat more rapidly, to resorb calories to a higher degree and to expand energy stores in adipose tissue more efficiently[11]. Only in the past few years has overnutrition emerged as a bigger health threat than the consequences of undernutrition (that is, more people are now dying from overweight and obesity than underweight)[7].

Biomedical researchers are exploring the biological mechanisms that cause obesity with the aim of designing interventions to achieve and maintain a healthy body weight. These research efforts have increasingly improved our understanding of how craving for food is disturbed in the brains of individuals with obesity; how adipose tissue, gut or liver hormones regulate appetite and satiety in the hypothalamus; and how dysfunction of adipose tissue causes secondary health problems[12,13]. The key role of certain brain regions in the regulation of body weight became evident from observations that animals with lesions and humans with tumours affecting the hypothalamus develop abnormal food-seeking behaviour and obesity[14,15]. With the finding that a mutation in the *ob* gene (which encodes the adipose tissue hormone leptin[16]) causes severe obesity in *ob/ob* mice[17], it became apparent that central neural circuits that control energy homeostasis integrate signals from peripheral tissues such as adipose tissue[18].

Moreover, observations from twin and adoption studies[19,20] suggested that obesity might be an inherited disorder of energy homeostasis. The heritability of BMI has been estimated as 40–70%[19,20]. Indeed, discoveries that mutations in genes coding for leptin[21,22], leptin receptor[23], melanocortin 4 receptor[24], pro-opiomelanocortin[25] and others might cause severe obesity in humans underlined the importance of biological factors in the pathogenesis of obesity. On the other hand, monogenetic causes of obesity are rare and cannot explain the extent of the obesity pandemic. In addition, genome-wide association studies (GWAS) found that only ~2% of the BMI variability can be explained by common single-nucleotide polymorphisms[26,27]. Clearly, changes in population genetics cannot explain the rise of obesity prevalence in just 40 years.

Is obesity a disease?

The key rationale for defining obesity as a chronic disease (in addition to the health risks directly attributable to excess body weight) is the distinct pathophysiology in people with obesity resulting in powerful homeostatic mechanisms that hinder weight loss and promote further weight gain. These altered biological mechanisms in people with obesity explain why short-term behavioural or medical interventions are frequently not sufficient to result in long-term weight loss. Although attempts to promote healthy eating and more physical activity might be important for obesity prevention at the society level, these recommendations are not sufficient to reduce BMI in individuals already living with a high body weight.

Complexity of obesity. For clinicians who treat patients with obesity, effective obesity management requires a systematic assessment of factors that potentially affect energy intake, metabolism and expenditure. Given the high variability of BMI among individuals sharing the same environment, it is tempting to assume that individual body weight regulation has the most important effects on weight gain and should therefore be targeted in weight-loss interventions. However, treatment of obesity through behaviour changes aiming at reducing energy intake and increasing exercise is frequently not successful, suggesting that the aetiological factors and the interaction between these factors are only incompletely understood.

Current weight-loss strategies targeting the individual might not address the most important underlying causes of energy imbalance[28,29]. Are the factors that determine overeating, low energy expenditure and physical inactivity too complex to be targeted by current weight-loss interventions? The enormous complexity of the causal factors and their interrelationships for the development of obesity has been visualized in the Obesity System Map compiled by the UK Foresight Programme[30]. With such a complex framework, it becomes clear that individual physiology and behaviour are shaped by strong social and local environment factors (FIG. 2). Obesity is not caused by personal choice or by society but rather by the relationship between an individual and their environment.

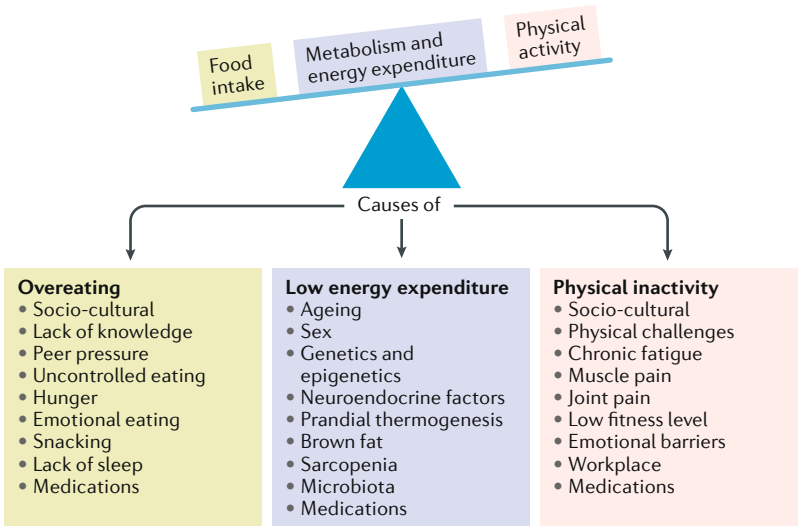

Fig. 1 | **Factors that can influence the chronic positive energy balance, thus subsequently causing obesity.** Weight gain can result from a combination of increased energy intake, low physical activity and reduced energy expenditure. Adapted with permission from REF.[28], Wiley-VCH.

The uncertainties about the complex causes of obesity are even reflected in the tenth revision of the International Code of Diseases (ICD-10), in which obesity is classified within the category 'Endocrine, nutritional and metabolic diseases'[31]. Although hormonal, nutritional and metabolic factors clearly have a role in the pathophysiology of obesity, this categorization ignores other contributors, including energy expenditure, psychological factors and sedentary behaviour[32]. The ICD-10 code 'E 66.0: Obesity due to excess calories' might even be considered a stigmatization of the disease and overemphasizes the nutritional aspects of obesity mechanisms[32]. Therefore, for the ICD-11, the European Association for the Study of Obesity (EASO) has proposed to list obesity as an overarching parent category and to improve the diagnostic criteria for obesity based on aetiology, degree of adiposity and health risk[32]. An international classification of obesity that is more consistent with current terminology and definitions is a prerequisite for improved diagnosis and treatment.

Attitudes of health-care systems. The marked increase in severe obesity might also reflect a failure of health-care systems to treat obesity in its early stages. Many medical systems do not consider obesity to be a progressive chronic disease[6]. This mindset frequently leads to a protraction of effective obesity treatments, eventually leading to the point that bariatric surgery is warranted. Clearly, bariatric surgery cannot be the solution for the worldwide rise in obesity prevalence. Neglecting the progressive and chronic nature of obesity as a disease by health-care providers and health insurance companies also contributes to self-perpetuation of disease progress. With weight gain, the capacity for physical activity is reduced, the psychological effect of body weight stigma and discrimination increases and high-caloric palatable foods are more frequently used as a coping strategy, thus leading to a vicious cycle of further weight gain[33,34]. In some affected individuals, psychological factors, including stress and body weight stigma, contribute to addictive behaviour that might also lead to the same vicious weight gain cycle[35,36]. As a psychological cofactor in obesity development, a behavioural addiction to eating is more typical than a 'food addiction', which implies a substance-related phenomenon[35].

In addition, health-care providers can have strong negative attitudes and stereotypes about people with obesity, which translates into reduced quality of care and thus low adherence of patients to treatment programmes[36]. The failure of the medical system starts as early as with the education of undergraduate medical students. For example, in the United States Medical Licensing Examination (USMLE), the most important concepts of obesity prevention and treatment were not tested in the exams[37].

The major challenge of combating the obesity pandemic is to translate knowledge of the complexity of obesity into solutions both at the individual and societal level[10]. The complexity of obesity needs to be reduced to a few modifiable causes that can be easily understood by policy-makers and the public without becoming overly simplistic. We can certainly learn from trends in obesity incidence from the past 50 years and by identifying global and local drivers of the pandemic.

Global epidemiology of obesity

Over the past ~50 years, the prevalence of obesity has increased worldwide to pandemic proportions[7,11,38,39] (FIGS 3,4). Investigators from the NCD Risk Factor Collaboration have provided the most extensive data on how obesity prevalence has changed worldwide in the past 40 years[38].

According to the most recent study providing trends in BMI for all countries in the world based on measured body weight and height data from 128.9 million children, adolescents and adults, obesity prevalence increased in every country between 1975 and 2016 (REF.[38]). The NCD Risk Factor Collaboration investigators identified remarkable regional differences in BMI changes over time. An accelerated increase in BMI was particularly noted in south Asia (including Bangladesh, Bhutan, India, Nepal and Pakistan), southeast Asia (for example, Indonesia, Malaysia, Philippines, Sri Lanka, Thailand and Vietnam), the Caribbean (for example, Belize, Cuba, Dominican Republic, Jamaica and Puerto Rico) and southern Latin America (Argentina, Brazil, Chile, Paraguay and Uruguay)[38]. Age-standardized mean BMI changes over the ~40 years varied from almost no BMI increase in the region of eastern Europe (Belarus, Latvia, Lithuania, Russian Federation and Ukraine) to significant increases (1 kg/m² per decade) in central Latin America (including Colombia, El Salvador, Guatemala, Mexico, Panama and Venezuela)[38]. The prevalence of a BMI ≥30 kg/m² varies by country[38,39] and ranges from 3.7% in Japan to 38.2% in the United States[40] (FIG. 3). Except for parts of sub-Saharan Africa and Asia, there are more people with obesity than with underweight throughout the world[38–40].

Obesity prevalence among children is >30% in the Cook Islands, Nauru and Palau, with a notable increase

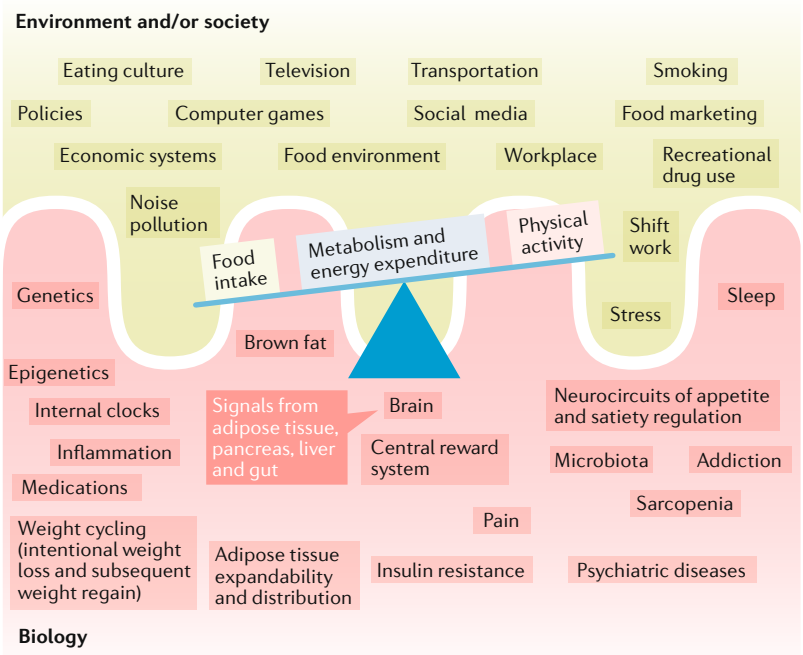

Fig. 2 | **Complex biological, environmental and societal factors contributing to obesity.** Individual factors (such as genetic background or the gut–brain–hormone axis) influence susceptibility to obesity, which may develop in an obesogenic environment (for example, influenced by eating culture, transportation and computerization).

over the past few decades. Worldwide prevalence of obesity increased at an alarming rate in children and adolescents from 0.7% to 5.6% in boys and 0.9% to 7.8% in girls between 1975 and 2016 (REF.[38]). BMI trends in children and adolescents are of particular concern for the prediction of how the burden of obesity might affect the population in the near future. In an intra-individual analysis of continuous BMI courses on a population-based sample of 51,505 children who had consecutive anthropometric data available during childhood and adolescence, the most rapid weight gain was found between age 2 and 6 years, and 90% of children who were obese at an age of 3 years also had overweight or obesity in adolescence[41].

Between 1975 and 2014, the prevalence of obesity (BMI ≥30 kg/m²) increased from 3.2% to 10.8% in adult men and from 6.4% to 14.9% in adult women[39]. In 2014, 0.64% of men and 1.6% of women had morbid obesity (BMI ≥40 kg/m²). In adults, 1975–2014 trends in BMI ranged from virtually no change in North Korea, some countries in sub-Saharan Africa and Nauru (which already had an obesity prevalence >30% in 1975) to increases of >6% during the same time in many other parts of the world[39]. BMI and obesity prevalence dynamics are heterogeneous across countries with regard to the steepness of increases, slowing-down and acceleration periods[39]. Interestingly, the rate of BMI increase has been slower since 2000 in high-income and some middle-income countries than the rates of the past century both in children and in adults[38,39]. Whether this effect reflects changes in the affected societies or even an active response to this growing health concern remains an open question. Present interventions and policy changes have not (yet?) led to a reversal of the rise in mean BMI affecting most countries[42–44].

What causes the obesity pandemic?

Body size preferences. Until the early decades of the past century, obesity was regarded as a symbol of beauty, health and wealth. During periods of famine, when many people died from starvation, being overweight was even a protective factor. In some cultures, increasing body weight was, and still is, intentionally used to make a person attractive for marriage[45]. At the individual level, body 'norms' or body size preferences might shape individual choices. In societies where a large body size is considered beautiful (such as in some Pacific islands[46]), obesity might develop faster than in countries such as Japan, where the social norm favours a small body[47]. On the other hand, ethnographic fieldwork in two countries with a high prevalence of obesity, Nauru and Samoa, suggests that obesity interventions were not necessarily ineffective because they collided with local body norms — on the contrary, they seemed to fail because they re-defined body norms in ways that counteracted and confused their intended purpose[48].

Role of socio-economic status. The rise in obesity prevalence started in high-income countries in the 1970s and was followed by most middle-income countries and more recently by some low-income countries[10,40]. This pattern suggests that increasing obesity levels coincide with improved economy and wealth. As examples from Brazil and other developing countries show, obesity prevalence typically increases first in people with higher socio-economic status in urban areas and then shifts towards groups of lower socio-economic status predominantly in rural areas in parallel with a country's improving economy[10,49–51].

By contrast, since the early 2000s, childhood overweight and obesity seemed to decrease or at least plateau in some high-income countries, including France, Norway, Denmark, Sweden, the United States, Japan and Australia[39,52]. The stable childhood obesity prevalence in these countries could indicate that the incidence of new obesity cases continues to be at the same high level or — less likely — that the duration of obesity has been shortened (for example, by improved treatment)[52].

However, the large heterogeneity in obesity prevalence between and within countries reflects not only economic but also ethnic and other differences. Obesity prevalence ranges from <5% in countries such as Vietnam, Bangladesh, Laos and Japan to >50% in Polynesian and Micronesian islands (such as Nauru, Tonga and Samoa)[39], suggesting strong interactions between individual (including genetic) and environmental factors. Disparities in obesity prevalence between neighbouring countries might be explained by socio-economic differences and exposure to obesogenic foods (for example, in Yemen (low income) the prevalence of obesity is 17.1% versus 35.4% in Saudi Arabia (high income))[39].

Regional disparities in prevalence of obesity. Despite such differences between countries, the question remains as to why susceptibility to obesity varies even under similar economic conditions and how certain factors might affect specific groups of society differently. For example, large regional differences in obesity prevalence exist in Germany,

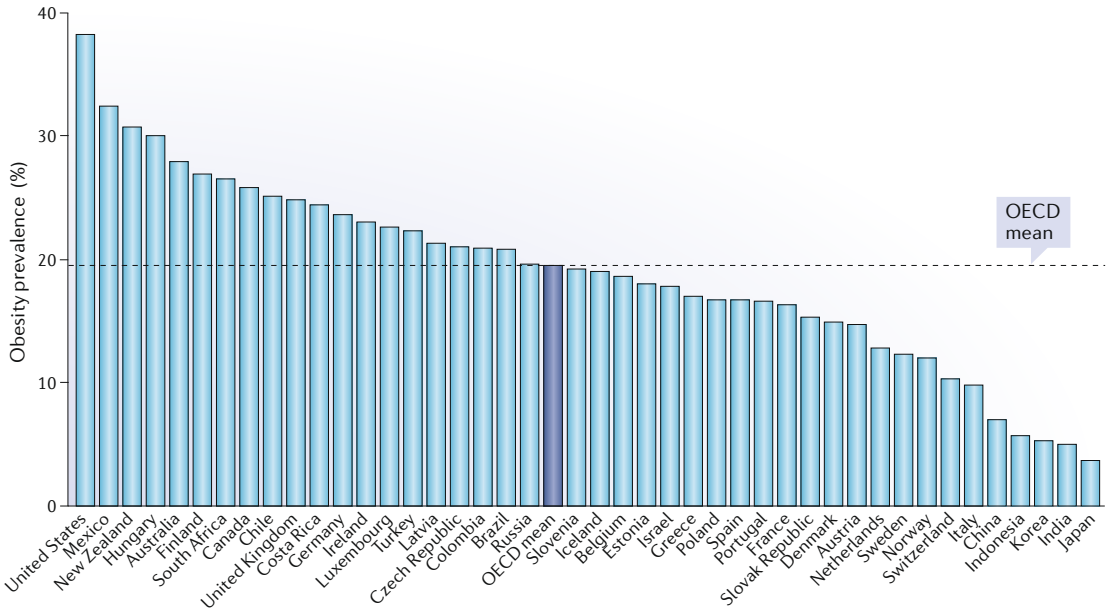

Fig. 3 | **Worldwide prevalence of obesity.** Prevalence of obesity (BMI ≥30 kg/m²) varies between selected countries (Organisation for Economic Cooperation and Development (OECD), 2017; percentage of adults with obesity from measured data). In 2015, across OECD countries, the mean prevalence of obesity in adults was 19.5% (dotted line) and ranged from <6% in Japan to >30% in the United States. Adapted with permission from REF.[40], the OECD.

ranging from ~20% in cities in northwestern Germany to >28% in Saxony-Anhalt[53]. These regional differences are at least in part related to or caused by differences in socio-economic status, high economic disparity between cities and rural areas and differences in some measures of sedentary and eating behaviour[53]. Regional disparities in obesity prevalence have also been reported for the United States, with the lowest rates in counties of the west and northeast and highest rates in the south[54]. In this study[54], the underlying factors driving regional disparities in adult obesity prevalence were systematically evaluated. In addition to regional differences in the distribution of different ethnicities, physician density, poverty, unemployment, indicators related to the food environment (such as number of fast food restaurants per 1,000 people and access to supermarkets), living in small-town settings, community characteristics (such as cultural norms and values related to diet), physical activity and ideal weight and body image unique to particular regions or demographic groups were associated with obesity outcomes[54].

Economic disparity within a society might also contribute to the heterogeneity in obesity prevalence and its associated burden[55,56]. Obesity has been considered one of the major costs of inequality[56]. In their book *The Spirit Level*, Wilkinson and Pickett postulate that wider income gaps cause wider waists[55]. Societies with a lower degree of inequality (such as Japan or Scandinavian countries with narrow income differences) seem to have a lower obesity burden than more unequal societies (for example, the United Kingdom and Portugal)[56].

Local environment. Even within a city, substantial regional differences in obesity rates can exist, as shown, for instance, between neighbourhoods of the city Kiel located in northern Germany[57]. Within the Kiel Obesity Prevention Study (KOPS), obesity was more prevalent in neighbourhoods with an increased frequency of overweight and obese parents, overweight siblings, parental smoking, single parenthood, low socio-economic status, low physical activity in boys and high media consumption in girls[57].

The local environment might substantially modulate an individual's risk of developing obesity[10]. Among important obesogenic moderators, built environment, density of fast food chains, food culture, transport systems, walkability of the neighbourhood, active recreation opportunities and others can have a great influence on obesity in the local and country context[10]. In China, the rapid changes from rural to urban forms of preferred living and the increasing number of people using motorized forms of transportation might be considered some of the main causes of the obesity epidemic[58].

The role of the neighbourhood environment contribution to the development of obesity has been investigated in a social experiment[59]. The prevalence of extreme obesity could be reduced by families moving from a neighbourhood with a high obesity rate and high level of poverty to a wealthier area, suggesting that thus far only incompletely understood local environment factors modulate the individual obesity risk[59].

Clusters of risk factors. Obesity is the result of the interplay between heterogenic factors, deriving from a person's eating behaviour, physical activity and individual energy expenditure determinants[30]. Under this main assumption, the UK Foresight Programme 'Tackling Obesities' project identified seven main clusters (composed of relevant individual, social and environmental context factors and their interdependencies) that determine obesity for an individual or a group[30].

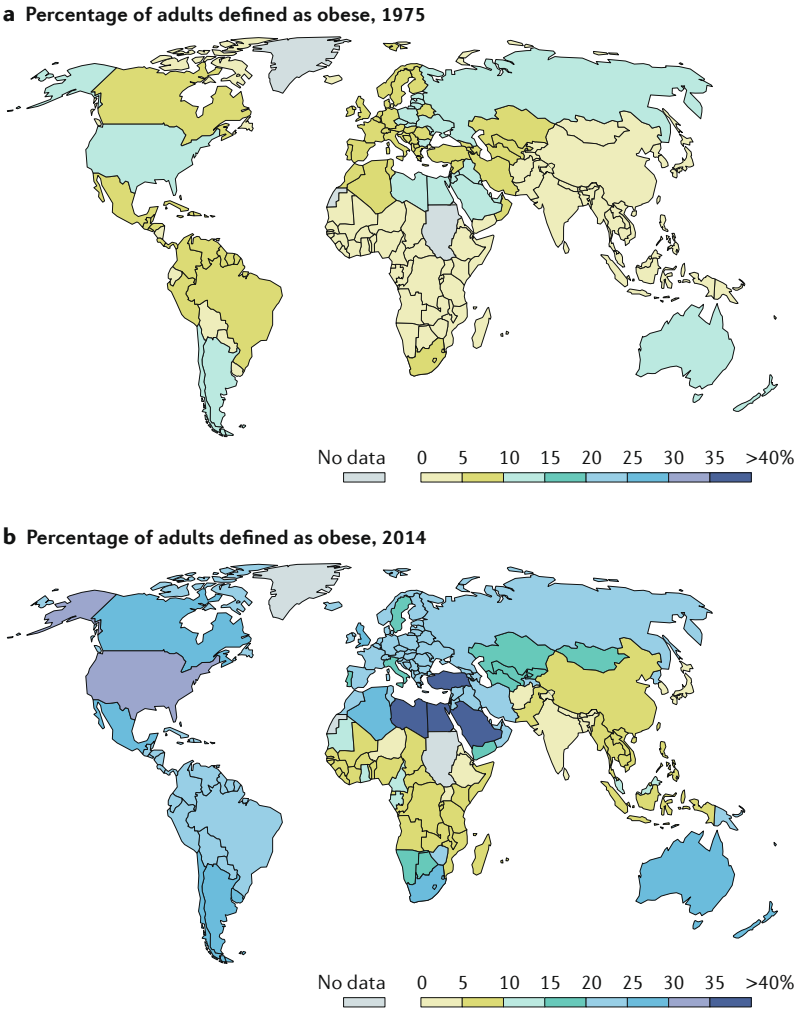

Fig. 4 | **Increase in prevalence of obesity over time.** Percentage of adults defined as obese by country in 1975 (part **a**) and 2014 (part **b**). The number of adults with obesity increased substantially between 1975 and 2014. Data from the WHO, Global Health Observatory.

These clusters include the following: physiology, individual psychology, individual physical activity, food consumption, food production, social psychology and physical activity environment.

Are changes in these clusters or individual factors equally important as underlying causes for the obesity pandemic? In the German Health Interview and Examination Survey for Children and Adolescents (KiGGS), the strongest risk factors for childhood overweight were parental obesity, low socio-economic status, migration background and high birthweight[60].

In a longitudinal birth cohort study among >8,000 children in the United Kingdom, the following factors were identified as being most strongly associated with the risk of obesity: parental obesity, very early adiposity (on the basis of standard deviation scores at 8 and 18 months; rapid weight gain during the first year), high television consumption, catch-up growth, birthweight and short sleep duration at an age of 3 years[61].

Although the importance of parental obesity might suggest the relevance of genetic factors, thus far obesity-associated genetic variants explain only a small proportion of BMI variance[26,27]. Therefore, it has been suggested that common obesity genetic variants do not directly cause obesity but might modulate an increased obesity risk under obesogenic environmental conditions[62]. For example, twin studies demonstrated that exposure to positive and negative energy balance results in body weight dynamics with greater similarity within than between twin pairs[63].

Susceptibility to food marketing. Food marketing promoting foods or beverages that are high in fat and sugar is also considered to be obesogenic as it modulates the behaviour of children[64]. In children, dietary intake and preference for energy-dense foods and beverages increases during or shortly after exposure to advertisements[64]. Interestingly, increased food intake as a response to exposure to food advertisements might affect children as a function of genotype[65]. Carriers of a high-risk single-nucleotide polymorphism in the fat mass and obesity-associated gene (*FTO*) were more responsive to food marketing than wild-type allele carriers[65]. Among genes identified by GWAS to account for BMI variability, the *FTO* gene was statistically the strongest genetic factor associated with obesity[66,67]. However, the mechanistic role of *FTO* and its overall contribution to the pathophysiology of obesity still need to be investigated in the context of other genes associated with obesity.

Modulation of food intake. Studies demonstrating that carriers of the *FTO* risk allele might have decreased satiety responsiveness and excess energy consumption[65,68,69] provide further evidence for the susceptible-gene hypothesis. These data also support the central role of the brain — where FTO is most highly expressed — in the modulation of food intake[70,71]. Modulation of individual choices by the genetic background might make it more difficult to find solutions to reduce obesity at the individual level. In fact, some individuals cannot control automatic or subconscious responses to food-related cues owing to the modulation of several neurophysiological pathways[72]. In addition, brain networks (including the dopamine mesolimbic circuit and the opioid, endocannabinoid and melanocortin systems) control not only appetite and satiety but also thermogenesis and spontaneous activity and can thereby very effectively defend body weight[73]. Important insights into the automatic and subconscious regulation of energy homeostasis[72–76] call into question the concept of targeting individual decision-making related to food and exercise choices as obesity prevention or treatment.

It is becoming clear that regulation of the food environment (for example, portion sizes and availability and advertising of unhealthy food) is a political task for societies aiming to reverse the obesity burden.

Dominant drivers of weight gain

The 'Westernization' of lifestyles. The potential main drivers of the obesity pandemic must be those that have changed substantially preceding or coinciding with the simultaneous rise in obesity prevalence across countries[10]. We live in increasingly obesogenic environments that profoundly influence our behaviour and lifestyle

choices. The increased prevalence of obesity over the past 50 years has coincided with a reduction in home cooking, greater reliance on convenience food, increased use of air conditioning (causing reduced energy expenditure to maintain body temperature), reduced physical activity, computer-based work dominating most occupations, leisure time entertainment becoming dependent on information technology, a growing habit of snack consumption, more persuasive food marketing and other changes[10,77,78]. In addition, the food industry aims to maximize profits and thus promotes large portions, frequent snacking and the normalization of sweets, soft drinks and fast food in our daily lives[79].

This 'Westernization' of lifestyles might lead to an increase in obesity levels more rapidly and to a greater extent in populations that did not have time to adapt to these changes. For example, the prevalence of obesity is much lower in Pima Indians living in Mexico than in those living in the United States (Arizona), indicating that even in genetically related populations[80] obesity development is determined mostly by environmental circumstances[81]. Moreover, people from Nigeria living in the United States have ~20–25% higher mean BMI than the average BMI of Nigerian men and women living in Nigeria[82]. Interestingly, the rise in obesity prevalence seems to be accelerated in middle-income countries in which shifts in environment and behaviour happen particularly rapidly. For example, obesity prevalence in Jamaica (a middle-income country) rose more rapidly between 1995 and 2005 than in the United States (a high-income country) and Nigeria (a low-income country)[83]. The significant difference in obesity prevalence between countries suggests a strong influence of the local environment on how key drivers of the obesity pandemic affect societies differently. However, there is wide consensus that changes in the global food system[7,10,44] combined with sedentary behaviours[84,85] seem to be the main causes of the worldwide rise in obesity prevalence over the past 50 years.

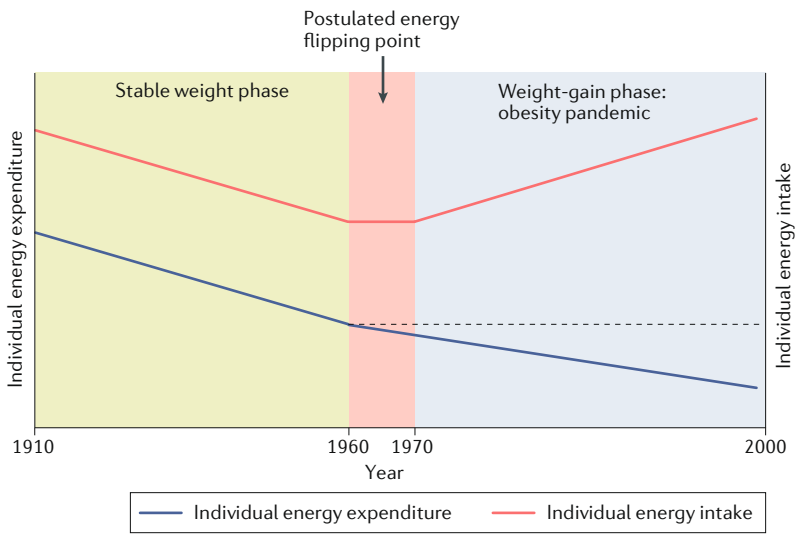

Fig. 5 | **The energy flipping point.** Food intake (red) and energy expenditure (blue) in the United States between 1910 and 2000. From 1910 to ~1960, energy expenditure reduced owing to technical changes in the workplace and growing motorization. This reduction in energy expenditure was matched by a parallel reduction in energy intake and resulted in a stable weight phase. Owing to an increase in the production of energy-dense, carbohydrate-rich and fat-rich foods in the United States, around the early 1970s an energy 'flipping point' marks the beginning of the weight-gain phase, in which increased energy intake was disproportional to either plateauing (dashed line) or further decreasing energy expenditure demands (accurate measurements of energy expenditure are unavailable)[10].

Role of the global food system. With a more than four times faster increase in obesity rates than the worldwide average, nations of the Pacific islands (including Nauru and the Cook Islands) now have the highest obesity prevalence in the world[38,39]. What can we learn from the extreme obesity rise in Micronesia and Polynesia regarding the mechanisms driving the global obesity pandemic? Obesity emerged very rapidly in Nauru and the Cook Islands in the second half of the past century[86,87]. Several factors have been hypothesized to underlie the high susceptibility to rapid weight gain in these nations, including genetic predisposition, their geographical isolation (with higher susceptibility to shortages in food supply) and their lack of capacity to produce sufficient food supplies for their own market[88]. The latter factors regarding food supply might expose the inhabitants of the Pacific islands more strongly to the global food system and food marketing than self-sufficient countries because there is a higher dependency on imported food (which tends to be affordable but also highly processed and energy dense)[89]. In addition, small, closely networking island communities seem to be more susceptible to social changes, global markets and food marketing[89], which may have facilitated the rapid social changes that have been well documented in Pacific islands[48,90]. The example of the fast-growing obesity prevalence in Nauru and the Cook Islands shows that obesity might develop when rapid social changes (in this case through colonization) are introduced to populations with a high degree of interdependence and interconnectedness[89]. This example, together with the observation that obesity prevalence in Cuba declined during the economic crisis of the early 1990s, suggests that obesity is not primarily a product of individual choice and independence[9,89].

The energy 'flipping point'. Worldwide, but particularly in high-income countries, the technical revolution of the past century with mechanization, new modes of transportation and computerization led to a decrease in human energy demands[10]. However, these changes had already started at the beginning of the 1900s, whereas the marked rise in obesity prevalence occurred only from the 1970s onwards[91,92]. Therefore, it has been postulated that in most high-income countries energy balance at the population level is characterized by an energy 'flipping point'[10]. In the United States (and presumably other high-income countries), this flipping point occurred at the time when the food supply for refined carbohydrates and fats markedly increased (1960s and 1970s)[93,94] (FIG. 5). In the first half of the past century, decreasing energy expenditure was paralleled by decreasing energy intake until the 1960s, followed by a phase of increased energy intake despite stable or decreasing energy demands[10]. The increasing availability of food from inexpensive

mass production is also reflected by a progressive increase in food waste (now estimated at ~1,400 kcal per person per day in the United States[95]). However, food supply and food waste data might provide only indirect evidence for the hypothesis that the global food system is the main driver of the obesity pandemic.

Theoretically, environmental and social mechanisms contributing to a continuous decline in energy demands might also contribute to a switch in a population's energy balance. Indeed, changes in body weight of children predicted from increased US food energy supply between the 1970s and 2000s were identical to the measured individual weight gain during that period[91]. Moreover, a study from the United Kingdom demonstrated that increased energy intake might entirely explain the observed increase in body weight, at least in women[96]. These data support the hypothesis that increased food supply is sufficient to explain the rise in average BMI and increased prevalence of obesity, at least in these countries[10]. Interestingly, nationally representative dietary surveys in the United Kingdom suggested that the increase in average body weight in men between 1986 and 2000 might be the result of both increased energy intake and reduced physical activity[96]. A study that estimated changes in energy flux in 1,399 adults proposed that increased energy intake is the predominant driver of higher BMI and therefore the main causal factor of increasing obesity in populations.

The beginning of the 'weight-gain phase' (FIG. 5) in the 1970s might also be seen as a response to policies drawn up to improve food supply. For example, the 1969 White House Conference on Food, Nutrition and Health addressed the problems of hunger and malnutrition and put policies in place that were required to combat undernutrition[97,98]. In response to the obesity pandemic, many countries, including the United States, now face the challenge of changing policies, agricultural regulations, the food industry and other sectors in a way that improves the food supply in accordance with nutrition recommendations and to make healthy choices more easily available[97].

As part of the positive energy balance at the population level, worldwide consumption of sugar-sweetened beverages has increased in parallel with the obesity pandemic[99,100]. Importantly, consumption of sugar-sweetened beverages has been linked to an increased risk of obesity[101,102]. Moreover, as an example of the role of gene–environment interactions in the pathogenesis of obesity, pronounced genetic predisposition to obesity in individuals has been associated with a greater consumption of sugar-sweetened beverages[103].

Why doesn't everybody develop obesity?

Given the worldwide spread of the 'Western diet' (containing high levels of sugar and fat, highly energy dense and low in fibre), one might expect that everybody should develop obesity under these conditions. These changes in the food system are clearly an important driver of the obesity pandemic. However, within a given environment —which might range from a country to a city, neighbourhood and even to families — body weight differs substantially[38–40]. Genetic and/or epigenetic effects as well as behavioural factors are suspected to be important modulators or moderators of energy balance. Some of the features underlying the heterogeneous biological response to shared environments are not unique to humans. For example, a certain substrain of the C57BL/6 mouse strain (which is frequently used as a control mouse) is resistant to obesity induced by a high-fat diet[104]. Genetic variation in only a few genetic loci might explain this variable response to obesity-inducing food triggers in this mouse model[104]. Of course, in humans the moderators might also include learned or adopted behaviour including meal rhythms versus snacking, food patterns (such as reward with sweets), preferring exercise or computer games and other factors. In addition to such behavioural differences, biological factors (including lack or low quality of sleep, psychological factors, weight stigma and discrimination) can have an important effect on weight gain[10,33,34]. Socio-cultural factors might also lead to epigenetic modifications in the pathogenesis of obesity, including older age of women at time of first birth, longer exposure of reproductive-age women to the obesogenic environment and social stressors that might lead to substantial epigenetic alterations in susceptibility to obesity in the offspring.

Genetic factors underlying BMI heterogeneity might have been overlooked for the following reasons[10]: monogenetic obesity causes are too rare to explain the obesity pandemic; small individual contributions of many genetic obesity risk loci might result in obesity; GWAS have been underpowered to detect some rare, but biologically relevant, gene variants; and the contribution of epigenetic modifications has not yet been fully elucidated[105–107].

Indeed, much of the BMI variability might be attributable to gene–environment or gene–behaviour interactions, including in the intrauterine environment. Intriguingly, maternal diet during pregnancy can affect DNA methylation patterns that can persist over decades in offspring and might even be inherited by future generations[107]. Chemical compounds in the environment (including ingredients of insect repellents such as *N*,*N*-diethyl-meta-toluamide (DEET), phthalates and dioxin) might affect epigenetic modifications even more acutely and thereby contribute to explaining variance in susceptibility to obesity[108].

Heritable epigenetic mechanisms might contribute to the worldwide rise in obesity[109]. Obesity is proposed to be a bimodal disease in which a TRIM28 (also known as TIF1β)-dependent network is capable of triggering obesity in a non-Mendelian, 'on/off' manner[110]. Rather than the idea that the current obesity pandemic is the result of a shift of the BMI distribution curve to the right, the bimodal disease model suggests that epigenetic mechanisms might 'switch on' obesity only in some people and other people might be protected[109,110]. An additional concept to explain BMI heterogeneity among humans is that genetically determined susceptibility differences exist in the central control of food intake that mediate the response to overeating. Supporting this concept, the regulator of G protein signalling 4 (*RGS4*) gene has been shown to regulate feeding and the response to diet-induced obesity[111]. The human *RGS4* gene locus is associated

with higher body weight and obesity susceptibility phenotypes, and increased levels of striatal RGS4 protein could be detected in people who are overweight (BMI ≥25 kg/m^2)[111]. In summary, we are still at the beginning of understanding the mechanisms defining susceptibility to obesity under obesogenic environments, but it is becoming clear that genetic factors and epigenetic mechanisms have an important — and yet to be fully explored — role.

Reversing the obesity pandemic

Despite country-specific attempts, thus far no country has succeeded in reversing the current obesity pandemic[44]. The WHO describes measures to prevent obesity, including shaping environments and communities in a way that an individual's choice of healthy foods and regular physical activity are the easiest, most accessible and affordable ones[7]. Indeed, at least one example from Cuba demonstrated that a return towards national poverty might substantially reduce obesity prevalence[9]. Caused by an economic crisis in the mid-1990s in Cuba, an average population-wide weight loss of ~5 kg led to rapid declines in rates of diabetes mellitus and heart disease, a phenomenon with a rapid rebound after mean body weight returned to pre-crisis numbers[9].

How can the individual responsibility[7] to limit energy intake from energy-dense foods, to increase consumption of healthy foods (such as fruits, vegetables and legumes) and to engage in regular physical activity (60 minutes per day for children; 150 minutes per week for adults) be facilitated? In principle, interventions aimed at motivating behaviour changes (such as education, health promotion, social marketing and incentives for healthy living) and/or enforcing actions that reduce the effects of the main causes of obesity (for example, laws, regulations and policy changes) might help. The latter approach might include policy interventions such as a tax on sugar-sweetened beverages, mandatory standards for meals at kindergartens and schools or banning unhealthy food advertisements aimed at children[112]. In Chile and Mexico, introducing a sugar-sweetened beverage tax in 2014 was associated with a substantially reduced purchase of sugary soft drinks, but health effects including reducing obesity cannot yet be evaluated[113,114]. Policy changes should also target the food industry by facilitating the development of processed foods that have reduced fat, sugar and salt content and restricting marketing of obesogenic foods particularly aiming at children[7,10,43].

Thus far, only a few governments worldwide have succeeded at introducing policy-led solutions to mitigate the causes of obesity because government officials are frequently reluctant to bring in laws restricting freedom of choice. In addition, the food industry, and other related industries, actively lobby against governmental regulation of the food market[115,116]. We are still a long way from reaching the goals of the WHO to achieve a 25% relative reduction in premature mortality from NCDs by 2025 (REF.[7]). The obesity epidemic will not be reversed without government leadership. A systems approach is required with multiple sectors involved and with basic population weight data and intervention outcomes accurately monitored and evaluated[43].

However, the number of healthy food policies implemented by governments, community organizations and food retailers has increased during the past few years[117]. Furthermore, centralized databases enable monitoring of the implementation, long-term maintenance and feasibility of healthy food policies; these databases include the World Cancer Research Fund's NOURISHING site[118] and the Global database on the Implementation of Nutrition Action (GINA)[119].

Several important barriers prevent progress in reversing the obesity epidemic, the most important of which is the almost absent pressure from society for political action. Restricted resources and funding, weak coordination and a lack of dedicated organizations also contribute to the slow progress in political changes[44,120].

Conclusions

The prevalence of obesity worldwide has nearly tripled since 1975 and continues to grow at a pandemic rate[38,39]. Remarkable regional differences exist in obesity prevalence and trends, which might help to identify societal causes of obesity and provide guidance for the most promising intervention strategies. Obesity has replaced tobacco consumption as the number one lifestyle-related risk factor for premature death; thus, it should be focused on intensively by public health policies. Whereas policy measures against tobacco consumption have been implemented in many countries and have been — at least partly — successful, analogous measures are obviously much more complicated in the case of obesity. Although the damaging effects of smoking have been very well established, many recommendations regarding nutrition and obesity-related behaviours are scientifically controversial and often cannot be translated into legislation prohibiting 'obesogenic behaviour'.

The WHO 'Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020' defines strategies that should be implemented to prevent a further increase in the worldwide prevalence of obesity. Thus far, progress in tackling obesity has been too slow and the WHO goals probably cannot be achieved within the near future. However, the main causes of obesity and their modulating factors have been characterized — the challenge remains to translate them into effective actions.

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