# Obesity

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Abstract | Excessive fat deposition in obesity has a multifactorial aetiology, but is widely considered the result of disequilibrium between energy intake and expenditure. Despite specific public health policies and individual treatment efforts to combat the obesity epidemic, >2 billion people worldwide are overweight or obese. The central nervous system circuitry, fuel turnover and metabolism as well as adipose tissue homeostasis are important to comprehend excessive weight gain and associated comorbidities. Obesity has a profound impact on quality of life, even in seemingly healthy individuals. Diet, physical activity or exercise and lifestyle changes are the cornerstones of obesity treatment, but medical treatment and bariatric surgery are becoming important. Family history, food environment, cultural preferences, adverse reactions to food, perinatal nutrition, previous or current diseases and physical activity patterns are relevant aspects for the health care professional to consider when treating the individual with obesity. Clinicians and other health care professionals are often ill-equipped to address the important environmental and socioeconomic drivers of the current obesity epidemic. Finally, understanding the epigenetic and genetic factors as well as metabolic pathways that take advantage of 'omics' technologies could play a very relevant part in combating obesity within a precision approach.

Obesity, considered by many as a 21st century epidemic[1], is defined as a disproportionate body weight for height with an excessive accumulation of adipose tissue that is usually accompanied by mild, chronic, systemic inflammation. Obesity is associated with the development of type 2 diabetes mellitus, cardiovascular diseases, some types of cancer and other adverse pathological conditions[2]. Some of these comorbidities are considered as features of the commonly named metabolic syndrome[3] — a prevalent risk factor for cardiovascular disease and type 2 diabetes mellitus (BOX 1).

Increased fat deposition, according to a simplistic view based on the first law of thermodynamics, results from an imbalance between the caloric intake and energy expenditure. According to this view, obesity is the result of low physical activity (a sedentary lifestyle) and the overconsumption of high-energy-yielding foods above the needs of the individual. However, in reality, the aetiology of obesity is more complex[4]. Indeed, circumstances such as socioeconomic status, environment and personal behaviours, and genotype–phenotype interactions have to be taken into account[5] to understand obesity, as all these factors affect food intake, nutrient turnover, thermogenesis, lipid utilization of fatty acids away from storage and towards oxidation, and also differential fat storage in regional adipose depots versus non-adipose tissues.

The control of body weight and composition has to consider energy intake, energy expenditure and fat deposition, which are interconnected and under an integral regulation by the neural and endocrine systems, where different neuropeptides and hormones participate[6]. Several agents modify these regulatory processes: environmental factors (for example, lack of sleep or shift work and ambient temperatures), overall diet quality, level of physical activity, the gut microbiota, endocrine disruptors (that is, chemicals that interfere with endocrine regulation), reproductive factors (such as greater fertility among people with higher adiposity and assortative mating (that is, mating between individuals with similar phenotypes)), drugs, and intrauterine and epigenetic intergenerational effects[7].

Another difficulty encountered in studying obesity is the marked heterogeneity of individuals with obesity. Examples of obesity types at both ends of the continuum are subcutaneous obesity, in which excess subcutaneous fat is found around the hip and thigh areas (pear-like body shape or gynoid obesity, which is more common in women), and visceral obesity, in which fat (mainly mesenteric adipose tissue) is mainly concentrated in the abdominal region (apple-like body shape or android obesity). Visceral obesity is more common in men and tends to be more pernicious in health terms, particularly affecting cardiovascular risk.

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To determine if and to what extent someone is obese, different methods have been designed and developed, including assessment based on anthropometry, bioelectrical impedance analysis, densitometry and imaging-based methods[8–10]. Even though the body mass index (BMI) is an imprecise tool, it is the most commonly used[11]. BMI grossly estimates adiposity and identifies overweight and obesity based on the weight of the individual expressed in kilograms (kg) and divided by the square height in metres ($m^2$). The WHO classification using BMI defines undernutrition as <18.5 $kg/m^2$, normal weight as 18.5–24.9 $kg/m^2$, overweight as 25–29.9 $kg/m^2$, obesity as ≥30 $kg/m^2$, and ≥40 $kg/m^2$ is considered extreme obesity[12]. Unless specifically mentioned, this classification will be used throughout this Primer. BMI could be complemented by also measuring waist circumference to discriminate between subcutaneous obesity and visceral obesity[13,14]. As it has been shown that low hip fat (adjusted for height or waist circumference) may protect against diseases, the ratio of waist-to-hip circumferences and the waist-to-height ratio have also been proposed to refine risk assessment. However, for practical reasons, comparability and ease to measure weight and height, the BMI still prevails as the most used indicator of adiposity worldwide.

Different approaches and treatments at the individual level have been developed and prescribed: dietary education and control, physical activity programmes, pharmacotherapy and bariatric surgery. Bariatric surgery has been associated with metabolic improvements (including halting or reversing the progression of type 2 diabetes mellitus) independent of weight loss, but adverse effects have also been reported[15].

At the present time, 39% of the world population is obese or overweight, despite decades of efforts to slow the progress of the epidemy[16] (FIG. 1). This prevalence translates into a global health cost equivalent to 2.8% of the world's gross domestic product, or approximately US$2 trillion[17]. To halt the epidemic, individualized treatment strategies such as precision lifestyle modifications should be complemented with wider population-based approaches and solutions, including prevention. Recently, several countries, such as the United States and the United Kingdom, have started lines of research in this area. The research will involve genotype analysis of >1 million people, which will be compared with their phenotypes. In addition, public health strategies have been implemented, such as taxation to reduce unhealthy fats and added sugar consumption, and personalized precision nutrition approaches[18,19].

In this Primer, we discuss obesity and its association with pathophysiological abnormalities that increase health risk, such as features of the metabolic syndrome.

## Epidemiology

### *Prevalence and trends*

According to the WHO, >2.1 billion adults were estimated to be overweight or obese globally in 2014 (REF. 16), of which 1.5 billion were overweight and 640 million were obese (FIG. 1). The estimated age-standardized prevalence (an epidemiological technique that is used to compare populations with different age profiles) of obesity in 2014 was 10.8% among adult men and 14.9% among adult women[1,20,21]. These data would indicate that female sex is associated with higher risk of obesity, whereas overweight is more prevalent among men[1]. However, the Global Burden of Disease Study 2013 reported a similar prevalence of overweight and obesity between men and women, being >36% in both[21].

In studies conducted in the United States, African Americans exhibited a higher prevalence of extreme obesity than other ethnicities[22]. Asian populations have lower BMI values than white individuals, but they have been shown to be prone to visceral fat deposition, making Asian populations more susceptible to developing type 2 diabetes mellitus at lower BMI levels than white individuals[23].

Between 1980 and 2008, the global age-standardized mean for BMI increased by 0.4 (in men) to 0.5 $kg/m^2$ (in women) per decade[24] (FIG. 2).The percentage of adults with a BMI of ≥25 $kg/m^2$ increased between 1980 and 2013 from 28.8% to 36.9%, and from 29.8% to 38% in men and women, respectively[21]. By 2030, estimates forecast that 57.8% (3.3 billion people) of the world adult population will have a BMI of 25 $kg/m^2$ or higher[25,26]. As such, the obesity-associated burden of disease is expected to increase in coming years. In many countries and regions, not only the United States and Europe, the number of adults who are overweight or obese is greater than that for normal-weight adults[1] (FIG. 1). The adverse health consequences of obesity represent greater threats for public health than hunger or malnutrition[5].

In 2013–2014, the worldwide number of children and adolescents (2–19 years of age) with obesity was estimated to be 110 million; this number has doubled since 1980. Furthermore, the estimated age-standardized prevalence of obesity in 2014 was 5% among children[21,27]. Available cross-national analyses of trends in overweight and obesity for both boys and girls (11–15 years of age)

in North America and countries in Europe from 2002 to 2010 evidenced stabilization in overweight prevalence, but overall rates of overweight in many countries are high[28]. Childhood obesity has been associated with metabolic complications and chronic disease in adulthood[29].

### *Metabolic imprinting*

Critical periods in the development of obesity exist in the prenatal period, infancy, childhood and adolescence (FIG. 3). Metabolic imprinting — defined as programming of metabolism during the prenatal and neonatal periods at the genomic and epigenomic level[30] — might permanently affect future disease risk and health, as proposed by the developmental origins of health and disease hypothesis[31]. Data from longitudinal birth cohorts are providing estimations of the development of obesity in childhood and adolescence, as well as about the genetic and environmental effects on BMI from infancy to the onset of adulthood.

In the prenatal period, excessive maternal gestational weight gain, especially in early pregnancy (first 20 weeks), is a risk factor for the development of overweight in children. Birth weight is a useful surrogate marker of fetal nutrition. Both overnutrition and undernutrition during fetal life can trigger pathways that are responsible for obesity later in life[32,33]. A high birth weight has been associated with higher risk of obesity[34], whereas a low birth weight has also been linked to a higher percentage of body fat, independent of BMI, and abdominal obesity in adolescents[35].

In infants, a rapid weight gain has also been associated with a high risk of overweight later in life; this was summarized in some systematic reviews and in at least one meta-analysis[36]. The type and amount of energy-yielding nutrients consumed by the mother during pregnancy and lactation, and even by both parents before pregnancy, have been associated with the development of metabolic complications in adulthood[37]. Longer duration of breastfeeding has been associated with a reduced prevalence of later life overweight[38]. Reduction of protein content in infant formulas was associated with a lower BMI and obesity risk at school age in one randomized clinical trial[39] and needs to be further investigated.

During childhood, an earlier adiposity rebound (FIG. 3) has been associated with a high BMI, a high amount of subcutaneous adipose tissue and a high waist circumference in adulthood[40,41]. Adolescence is a nutritionally vulnerable developmental stage because growth rate accelerates, as a consequence of high energy and nutrient needs. Pubertal timing influences BMI and is associated with BMI changes from childhood to adulthood, whereas early puberty increases the risk of later obesity development[42].

### *Risk factors*

At first glance, the major drivers of the obesity epidemic are overly simple: overeating and sedentary lifestyles[6]. A small daily positive energy balance seems to be an important contributor of cumulative weight gain[43], although the pathogenesis of obesity has proven to be more complex[44] (FIG. 4). State-of-the-art epidemiological approaches, such as integrated bioinformatics system analyses, need to be used to better understand the causes of obesity, including the intricate interplay between behavioural, environmental, physiological, genetic, social and economic factors[5].

One of the complexities to study risk factors in obesity is the remarkable differences in the way people accumulate body fat. An obvious example of such heterogeneity is the variation in body configuration and in regional accumulation of body fat at any given adiposity level. Such heterogeneity in the obesity phenotypes makes the study of what has been described in the past as a singular term (obesity) a challenge. Some have even suggested that we should refer to 'obesities' (REF. 45) rather than to obesity, as this condition cannot be considered as a homogeneous entity. In this regard, the development of imaging and integrative physiological technologies, including devices to better phenotype individuals with obesity and assess body composition and fat deposits (such as isotope labelling to determine brown fat presence), has been a major advance. Thus, it might become possible to identify large subgroups of individuals with obesity with common characteristics who would possibly share common aetiological factors.

The search for major gene effects in obesity has resulted in the successful identification of some monogenic forms of obesity. Although relatively rare, the prevalence may be higher in consanguineous populations[46]. Mutations in *MC4R* (which encodes melanocortin 4 receptor) account for up to 5% of extreme early-onset obesity and are the most prevalent genetic cause, together with *FTO* variants. Thus, genetics alone cannot explain the relatively recent (in the past 30 years) and rapid increase in the worldwide prevalence of obesity. Rather, it has become clear that obesity results from the interaction of several susceptibility genes (some of which have been identified) with diverse lifestyle factors[47]. In addition, the role of nutritional genomics including metabolomic issues, epigenomic signatures

Box 1 | **Metabolic syndrome**

According to the harmonized definition and clinical criteria given by the International Diabetes Federation, the American Heart Association and the US National Heart, Lung, and Blood Institute, metabolic syndrome is diagnosed when three of the following five criteria occur simultaneously[3]:

- Visceral obesity: a waist circumference of ≥94 cm in men and ≥80 cm in women in the West (exact value depends on country-specific definitions)
- Hypertriglyceridaemia: ≥150 mg per dl or on triglyceride-lowering medication
- Low levels of high-density lipoprotein cholesterol: <40 mg per dl for men and <50 mg per dl for women
- Elevated blood pressure: systolic blood pressure of ≥130 mmHg, diastolic blood pressure of ≥85 mmHg or antihypertensive drug treatment in a patient with a history of hypertension
- Increased glucose levels: fasting glucose levels of ≥100 mg per dl or drug treatment to lower increased levels of glucose

Metabolic syndrome is a concept that was introduced to provide clinicians with simple screening tools to identify individuals who are likely to have insulin resistance and related metabolic abnormalities, which are mainly associated with visceral obesity. However, the clinical use of the metabolic syndrome has been challenged by some specialists[201].

and metagenomic screenings are fields with increasing interest to unveil the origins, causes or consequences of obesity and for precision management of patients[48].

Several biological and environmental factors have an effect on energy intake and expenditure (FIG. 4). For example, eating behaviours are shaped not only by genetic factors and other biological factors but also by the opportunities to eat, food availability and affordability and the built environment (which affects, among others, access to food and physical activity). In this context, food companies have adopted powerful marketing strategies to induce people to eat more[49]. The food choices among energy-yielding food and snacking are enormous. Furthermore, eating away from home, which has been associated with obesity probably owing to the increase in portion size and other factors, has increased during the past several decades[50]. Physical activity, another behavioural component, is also conditioned by socioeconomic and cultural factors (for example, transportation type, videogame play, computer use and occupation). A conjoint secular trend in sedentary lifestyles coupled with increases in energy intake is able to greatly explain the observed increases in mean BMI in high-income countries[51], but also probably in most low-income and middle-income countries. The number of sleeping hours has been reduced, increasing tiredness during the activity hours and food overconsumption while awake, thereby predisposing to a sedentary lifestyle and obesity[52]. Interestingly, the 'Mediterranean siesta' was reported to be inversely associated with obesity risk if this sleeping period was <30 minutes[52]. Moreover, night-shift work is related with sleep deprivation and its consequences[7]. However, the question of whether obesity mainly results from an excess caloric intake or from a reduced energy expenditure still remains under debate in academic circles, but all components of the energy balance equation are likely to be important.

In addition to the quantity of calories, the type and quality (for example, saturated versus non-saturated lipids, as well as the source of fats, carbohydrates and proteins) of calories consumed also influence the energy balance and long-term body weight[53]. However, this area is still controversial; whether the dietary distribution of macronutrients on body weight, as well as the impact of a

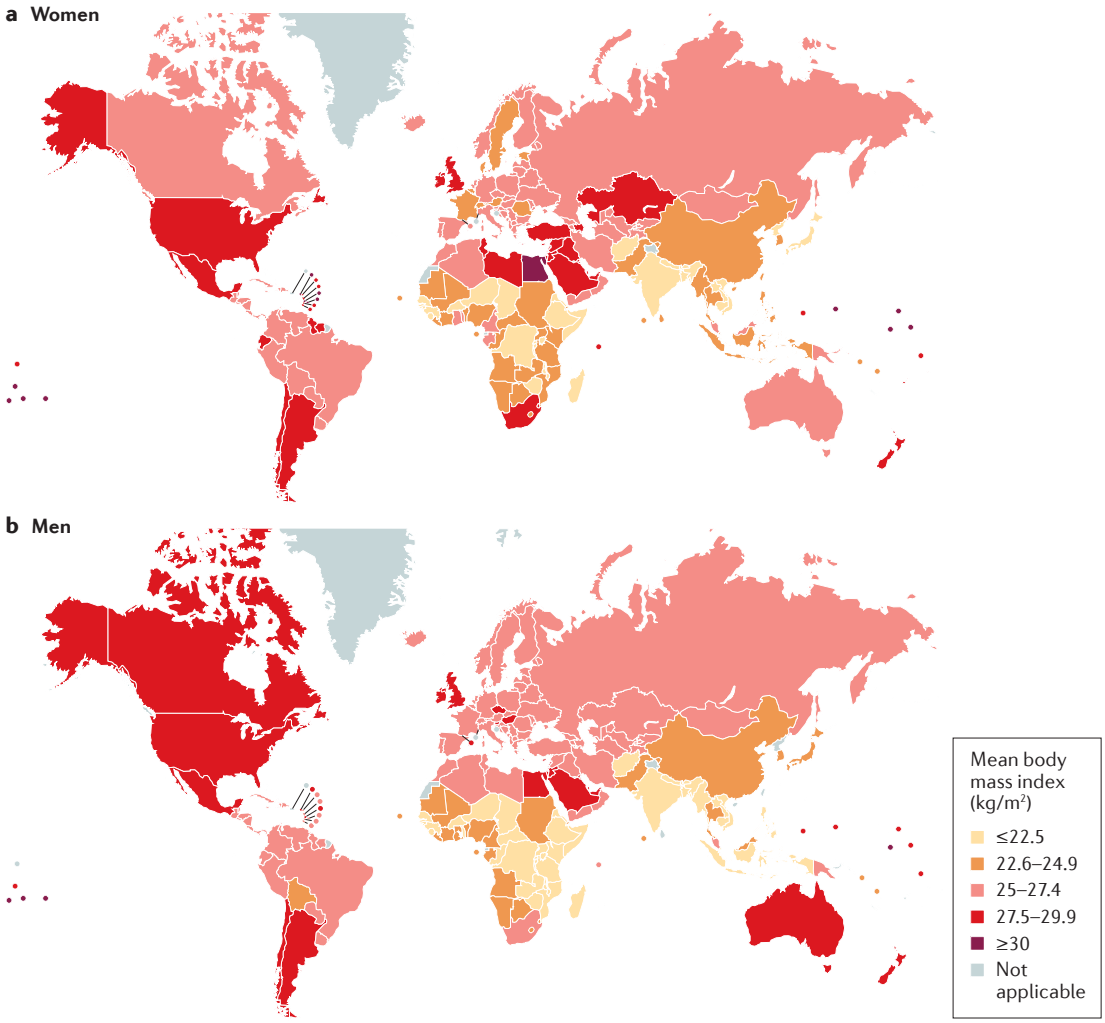


Figure 1 | **Global body mass index in men and women.** Age-standardized global body mass index for women (part **a**) and men (part **b**). Data obtained from the WHO (2014). Reproduced with permission of the World Health Organization.

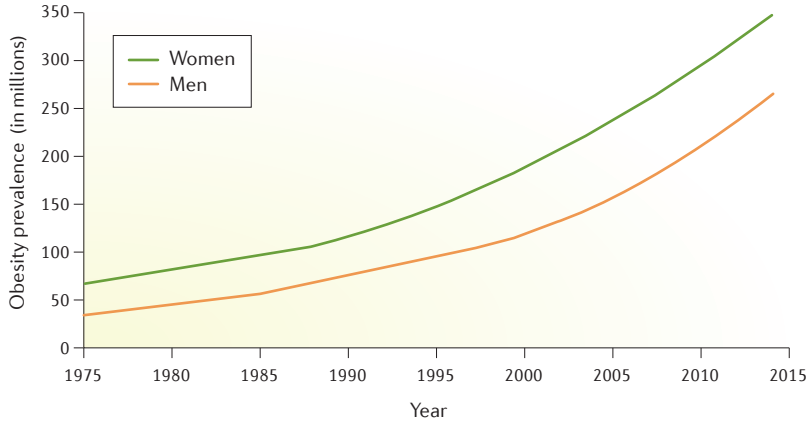


Figure 2 | **Evolution of obesity prevalence.** Since 1975, the global obesity prevalence has almost tripled. The prevalence of obesity is higher in women than in men. Figure obtained from smoothed regression analysis based on data provided in REFS 1,21,24.

particular nutrient (for example, the thermogenic effect of proteins), is important in obesity by promoting overconsumption of energy or by a direct metabolic effect is unclear[54,55]. A high-quality dietary pattern (defined by a balanced consumption of macronutrients, in which 10–20% of the energy is obtained from proteins, <30% from lipids and 50–55% from carbohydrates) is inversely associated with weight gain and the risk of developing obesity. This finding is also true for higher consumption of fruits and nuts, vegetables, whole grains, yoghurt and for adherence to the Mediterranean diet[56] (BOX 2). On the contrary, increased consumption of sugar-sweetened beverages, potato chips, French fries, red and processed meats, commercially baked goods, *trans*-fats, refined grains and added sugars have been associated with higher weight gain[57–60]. Carefully conducted longitudinal studies support the benefits of consuming meals with healthy foods and complex carbohydrates with low glycaemic index (a value given to foods as a reference on the speed at which they increase blood glucose levels) and the importance of high-quality, sustainable dietary patterns in preventing obesity[60–62].

### *Comorbidities and mortality*

Population studies have clearly shown that individuals with obesity are at greater risk of developing numerous health complications that contribute to premature death than normal-weight individuals[63,64] (FIG. 5). In addition to an increased risk of developing features of the metabolic syndrome (BOX 1), other common comorbidities are endocrine disorders (such as type 2 diabetes mellitus), respiratory problems (for example, sleep apnoea), cardiovascular diseases (for example, atherosclerosis and heart attack) and cancers (for example, endometrial, liver and kidney cancers)[65–68]. Moreover, obesity has negative impacts not only on psychological and mood issues but also on cognitive function[69].

Epidemiological research into comorbidities and complications associated with obesity is limited by several reasons. One difficulty encountered in large population studies has been to define the non-obese 'normal-weight' reference group. Although guidelines have suggested that a BMI range of 18.5–25 kg/m$^2$ was compatible with optimal health, a recent study pooling of individual data (about 4 million individuals from 189 studies who were followed-up on average for 13.7 years)[70] has revealed that the BMI range associated with lower mortality rates was around 20–25 kg/m$^2$, with values below that range being associated with an increased mortality rate. This report has shed light on the controversy resulting from a previous study[71] that proposed that individuals who are overweight and obesity class I (BMI: 30–34.9 kg/m$^2$) had reduced mortality compared with non-obese individuals. However, this study included individuals with a high degree of leanness (18.5–20 kg/m$^2$) in the non-obese 'normal-weight' group. These low-body-weight individuals were probably responsible for the high mortality rate reported in the non-obese group, as some were likely to be smokers and/or have pre-existing chronic diseases that caused weight reduction. When the Global BMI Mortality Collaboration international group excluded current smokers and those with pre-existing chronic diseases, it became clear that overweight and obesity class I are associated with an increased mortality risk[70]. In addition to the difficulties with determining the reference group, the study of obesity as a risk factor for all-cause mortality is methodologically challenging, especially during childhood[72], because of confounders, such as smoking and reverse causation (that is, low body weight is the consequence of a chronic disease rather than the cause), and non-confounders, such as overadjustment for intermediate variables in the causal chain.

Some studies have suggested that the lifetime maximum BMI has a stronger association with mortality than the BMI at the time a survey is taken[73]. In a meta-analysis[70] using individual participant data of 239 cohorts, overweight and obesity were significantly associated with total, cardiovascular and cancer mortality compared with the normal-weight group, after carefully addressing the issues of reverse causation and confounding by smoking. These associations were largely consistent between Asia, Australia, New Zealand, Europe and North America populations. In addition to mortality, obesity was also found to be associated with insulin resistance, hypertension and hypercholesterolaemia[74].

## Mechanisms/pathophysiology

Body weight — and ultimately obesity — is determined by the interaction of genetic, environmental and psychosocial factors acting through several physiological mediators of food intake and energy expenditure that affect fat deposition (FIGS 4,6).

### *Genetics and epigenetics*

Up to 70% of the inter-individual variation in body weight variability may be due to genetic differences between individuals[75]. Identification of genes that determine the susceptibility to obesity can provide insight into the pathophysiological mechanisms that underlie body weight regulation and fat distribution, which, in turn, can lead to new approaches for treatment and prevention.

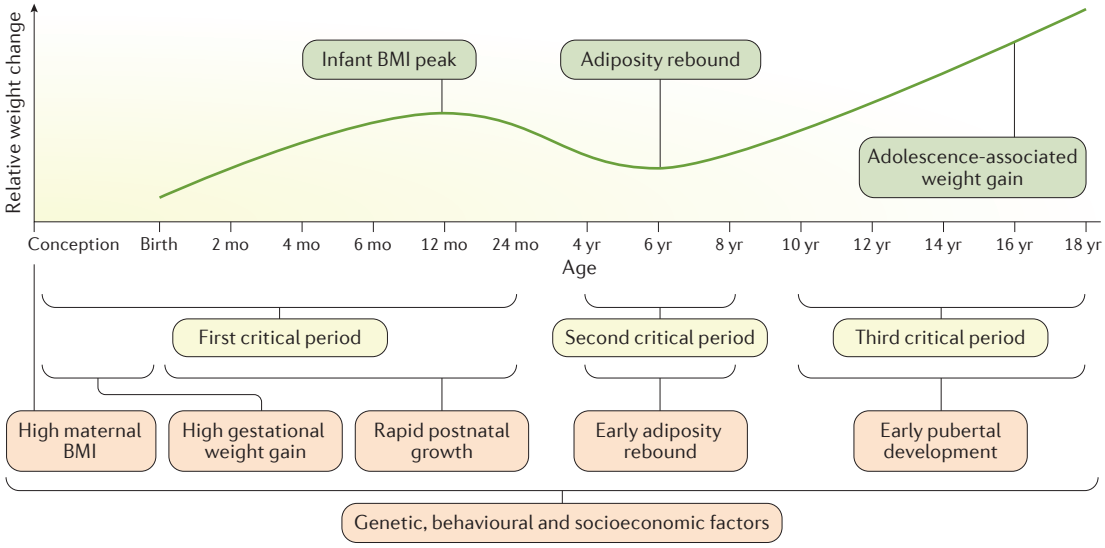


Figure 3 | **Critical periods in the development of obesity.** The first thousand days, from conception until the end of the second year of life, mark the first critical period in the development of obesity. Body mass index (BMI) usually increases until 7 months of age, when it reaches a temporary maximum (the so-called infant BMI peak). Between 5 and 7 years of age, the BMI reaches a minimum in children with adequate growth and development, after which it starts to rise again (that is, the adiposity rebound)[221]. During adolescence, BMI changes are substantially associated with puberty. Body weight at these critical periods is associated with later body composition[222].

Research into monogenic obesity has shed light on the biology of obesity in the general population. The molecular mapping of mutations causing monogenic obesity in mice was one of the first strategies to search for genes that control body weight. Prominent outcomes of this approach include genes encoding leptin (*Lep*) and its receptor (*Lepr*), the melanocortin 4 receptor (*Mc4r*) and pro-opiomelanocortin (*Pomc*), among others; these genes affect body weight through pathways in the central nervous system[76]. Mutations in the human orthologues of these genes cause monogenic obesity[77].

Large-scale genome-wide association studies (GWAS) that test the association of millions of common genetic variants without a prior hypothesis about their presumed role have identified >300 genetic loci for obesity traits. The first major success of GWAS was the discovery of the *FTO* locus[78,79]. A cluster of common non-coding variants in *FTO* showed a highly significant association with obesity risk[78,79]. The biology that underlies this association is only slowly getting resolved; the *FTO* locus may regulate the expression of nearby *RPGRIP1L* or distant *IRX3–IRX5* to influence body weight, by regulating appetite, thermogenesis, adipocyte browning and epigenetic mechanisms related to obesity[80,81]. Additional GWAS have identified genetic loci associated with adiposity traits, BMI and waist-to-hip ratio[82–84]. Pathway and tissue enrichment analyses applied to the BMI-associated loci provide further support for the role of the central nervous system in body weight regulation. Tissues with enriched expression of these genes include the hypothalamus, the pituitary gland and the hippocampus, and important pathways are those related to synaptic function and neurotransmitter signalling[82]. The same analyses applied to loci associated with the waist-to-hip ratio point to pathways implicated in adipogenesis, angiogenesis, insulin resistance and processes that affect fat distribution[83].

Despite highly significant associations, the effects of the established loci on the obesity outcomes are small. Of all established loci, *FTO* has the largest, but still small, effect on obesity susceptibility; each risk allele increases the risk of obesity by 1.20–1.32-fold, and BMI by 0.37 kg/m$^2$ (equivalent to ~1,060 g in body weight for a person who is 1.70 m in height). The effect of other BMI-associated variants range between 0.08 and 0.3 kg/m$^2$ (REFS 82,84). All BMI-associated variants combined explain <5% of the variation in BMI[82,84]. The effect sizes and explained variance of variants associated with the waist-to-hip ratio are of a similar magnitude[83,84]. However, interactions between genetic and environmental factors may explain important individual differences in body weight response to the same environmental exposures[84]. Research is needed to cover the gap with the epidemiological data indicating that genetics may contribute to 20–25% of body weight variability.

Epigenetic processes, including DNA methylation, histone modification and non-coding RNAs that switch genes on and off without changing the DNA sequence, are sensitive to external factors (for example, diet and physical activity) and internal factors (for example, hormones and genetic factors), are reversible and can be passed on to subsequent generations. Epigenetic processes are cell, time and tissue specific, which makes studying their roles in humans a major challenge. This statement is particularly true for obesity, given the central role of the brain in body weight regulation. Evidence for the role of epigenetics in obesity has come mostly from animal models[85], and only occasionally from studies in humans, although >600 articles have already been published in this area. For example, sons born to women who were starved

during the first half of pregnancy during the Dutch famine were at a significantly higher risk of developing obesity than comparable subjects; this was later related to epigenetic modifications[86,87]. This intergenerational study suggests that nutritional deprivation of pregnant mothers can have lasting non-genetic effects on body weight of the next generation. Although the methylation of the gene encoding hypoxia-inducible transcription factor 3A (*HIF3A)* was considered to be associated with higher BMI, this association was found to be the consequence and not the cause of higher BMI[88]. However, the HIF system has been shown to play a key part in energy expenditure and obesity[89]. Two other large-scale epigenetic studies, involving 10,000 and 7,800 individuals, respectively, identified large numbers of DNA methylation loci associated with BMI: 187 in the first and 83 in the second study[90,91]. Again, methylation at a substantial proportion of the loci was the consequence of obesity, rather than the cause. Clearly, more evidence for a (causal) role of epigenetic processes in obesity is needed, but assessing the epigenome at the right time in life and in the relevant tissues is a major barrier for studies in humans[92].

### *Adipose tissue*

***Types.*** The two major types of adipose tissues — white adipose tissue and brown adipose tissue — have a crucial role in sensing and responding to changes in systemic energy balance[93]. Adipocytes in brown adipose tissue contribute to energy expenditure via thermogenesis to maintain body temperature[94]. Brown adipose tissue is abundant in newborn babies and is located in the interscapular and supraclavicular regions, as well as around the kidneys, heart, aorta, pancreas and the trachea; these brown adipose deposits decrease with age, but can still be found in adults[95]. Brown adipose tissue has been negatively correlated with the BMI[96], although its precise role in the aetiology of obesity remains unclear. White adipocytes are the most abundant adipocytes in humans and have been long considered to have only an energy-storing function. However, recent research has revealed that these cells secrete various bioactive substances[97] (that is, adipocytokines or adipokines) (FIG. 6). Furthermore, a distinct (but minor) type of adipocytes known as 'beige or brite adipocytes' is recruited in white adipose deposits as a novel type of energy-dissipating adipocytes.

Adipose tissues are classified into subcutaneous adipose tissue and visceral adipose tissue based on their location in the body. Visceral adipose tissues include intra-abdominal (mainly mesenteric adipose tissue), perirenal and pericardial adipose tissue. Researchers and clinicians have been the most interested in intra-abdominal adipose tissue, as its accumulation closely correlates with the development of the constellation of metabolic abnormalities commonly referred to as the metabolic syndrome[98] (BOX 1).

***Pathological changes in adipose tissue.*** Although the list of clinical outcomes associated with obesity is rather extensive, the number and severity of these health complications seem to be dependent on the additional presence of excess fat stores in inner adipose deposits (such as the abdominal visceral adipose tissue) and in and around normally lean tissues such as the heart, the liver and the kidneys — a phenomenon referred to as ectopic fat deposition[74,99,100]. Consistent evidence shows that the way adipose tissue manages the energy surplus and the abnormal oxygen tension generated by the pathological growth of the adipocytes[101] has a profound effect on an individual's cardiometabolic risk profile, insulin sensitivity and dyslipidaemia (high levels of triglycerides or low levels of high-density lipoprotein cholesterol). For instance, if the subcutaneous adipose tissue handles this energy excess by causing adipose tissue hyperplasia (tissue growth owing to an increase in cell number), such properly expanding adipose tissue will then act as a 'metabolic sink', protecting lean tissues (for example, the heart, liver, pancreas and the kidneys) against harmful ectopic fat deposition[74,102]. Conversely, if subcutaneous adipose tissue cannot expand through fat cell hyperplasia (for poorly understood reasons that are under study), the stored triglyceride molecules will first contribute to adipocyte hypertrophy (tissue growth owing to an enlargement of individual cells) until these large adipocytes become saturated and are no longer able to expand, leading to either their rupture and macrophage invasion and/or increased release of pro-inflammatory adipokines and decreased release of anti-inflammatory adipokines, such as adiponectin by hypertrophied adipocytes. These phenomena contribute to a pro-inflammatory and insulin-resistant milieu. Furthermore, as the expanding capacity of these hypertrophied adipocytes becomes saturated, the excess triglyceride molecules will have no place to go in the subcutaneous adipose tissue and will be stored at undesired sites, such as the liver, heart, kidneys and pancreas — this ectopic fat deposition also generates an atherogenic, diabetogenic and inflammatory enviroment in the cell[99] (FIG. 7).

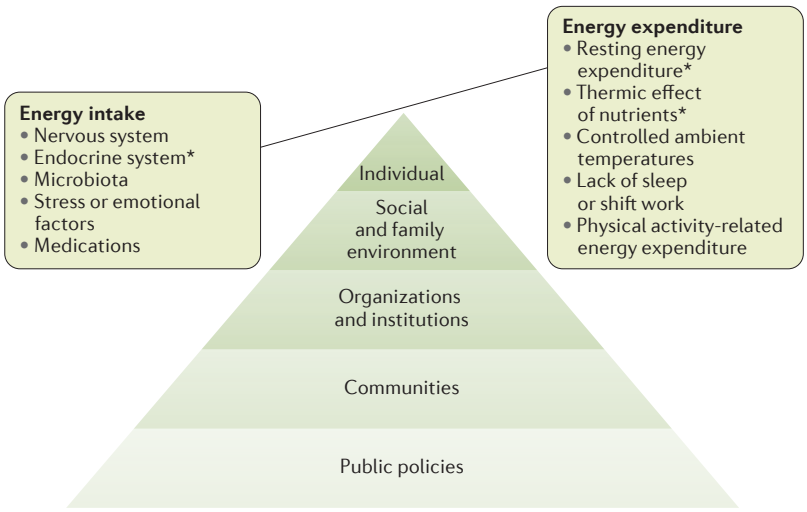


Figure 4 | **Key factors involved in the regulation of energy balance.** The energy balance is influenced by several biological factors. Although this balance indirectly relates to the first thermodynamic law, it cannot be translated to the level of causality. The pyramid holding the balance emphasizes the notion that we need to go beyond individual factors to ultimately have an optimal effect on the energy balance equation. *Could be affected by genetic and epigenetic factors.

Box 2 | **Healthy dietary patterns**

- The DASH diet: an eating plan that emphasizes eating fruits, vegetables and whole grains rather than refined grains. Fat-free or low-fat dairy products, fish, poultry, beans, nuts and vegetable oils are included, but foods that are high in saturated fats (such as fatty meats and full-fat dairy products), tropical oils (such as coconut, palm kernel and palm oils) and sugar-sweetened beverages and sweets should be limited.
- The Mediterranean diet: emphasizes eating primarily plant-based foods, such as fruits and vegetables, whole grains, legumes and nuts. Butter is replaced with healthy fats, such as olive oil. Herbs and spices are used as flavourings instead of salt. Red meat is limited to no more than a few times a month. Fish and poultry are eaten at least twice a week. Drinking red wine in moderation is optional.
- The RESMENA diet: a variant of the Mediterranean diet that considers the intake of fruit and/or vegetables with antioxidant capacity and the number of meals per day[202].

Imaging studies have now revealed that all these inner ectopic fat deposits tend to be correlated with each other, with some individual variation[103–105]. Thus, visceral obesity is often accompanied by excess fat in the liver, heart and kidneys, whereas the association is less evident for subcutaneous obesity[106]. Although excess visceral adipose tissue and excess liver fat often co-occur, some individuals with substantial visceral adipose tissue do not have excess liver fat, and vice versa[107]. Indeed, what the local drivers of regional differences in ectopic fat deposition are (genetic, hormonal and environmental), is a question that should receive further attention.

In addition, all subcutaneous fat deposits are not equal and available data indicate that the healthiest 'metabolic sink' may be the gluteal–femoral fat depot[102]. That is, lower body fat stores may not be neutral in terms of health risk; they may even be protective against several health outcomes including diabetes mellitus and cardiovascular disease[108]. In this regard, the severe dysmetabolic state of patients with lipodystrophy (that is, those who lack subcutaneous adipose tissue) shows the importance of healthy subcutaneous adipose tissue[109,110]. Genetic and environmental factors influence regional subcutaneous adipose tissue accumulation, but this issue would require extensive cardiometabolic imaging studies[111].

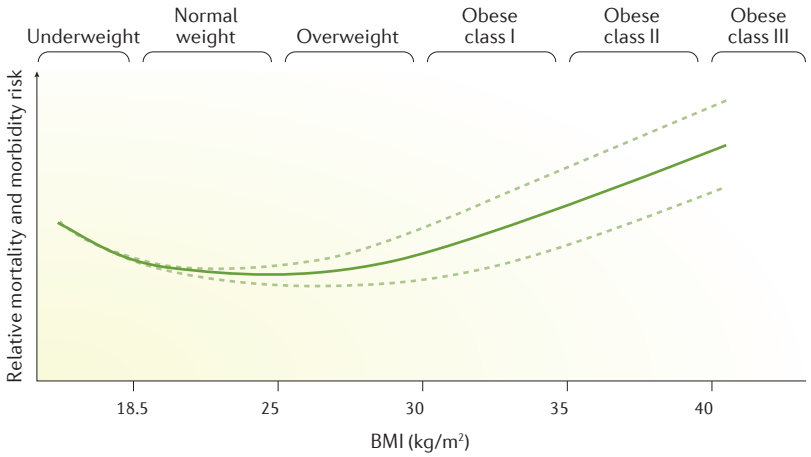


Figure 5 | **The relationship between the body mass index and mortality and morbidity risk.** The graph shows the increased health risk associated with extreme leanness and obesity. In addition, the upper and lower dashed lines illustrate the notion that a positive relationship between body mass index (BMI) and health outcome can be modulated by several factors. Factors that increase the risk for a given BMI include increased age, smoking, sedentary behaviours, diet of poor nutritional quality, excess of abdominal visceral adipose tissue and ectopic fat, and poor cardiorespiratory fitness. Factors that decrease the health risk for a given BMI are, for example, physically active lifestyle, high level of cardiorespiratory fitness, high-quality diet, and low levels of visceral adipose tissue or ectopic fat.

### *Regulation of the energy balance*

Food intake triggers gastrointestinal signals mediated by mechanical distension or paracrine hormones, and nutrient signals that modulate appetite involving different neurotransmitters, gut–brain peptides, amino acids and neuropeptides. The autonomic nervous system and several circulating hormones have also been involved in the metabolic response to food intake and nutrient metabolism, which affects appetite, thermogenesis and fat deposition, among other processes[112] (FIG. 6).

The role of microbiota is under considerable investigation, as it has been found that the microbiota of individuals with obesity is less diverse and have a differential proportion of firmicutes to bacteroidetes[113,114]. Although more studies are needed, it seems that this microbiota dysbiosis favours an inflammatory status, impairs the metabolism of some nutrients, influences energy extraction and affects the way this energy is expended and stored. Other endogenous factors associated with obesity might induce a disruption of appetite control, shifts in thermogenesis and futile cycles, adipogenesis impairments, inflammatory processes and lipid metabolism disturbances[7].

## Diagnosis, screening and prevention

### *Obesity phenotypes*

As mentioned before, patients with obesity with metabolic abnormalities, such as insulin resistance and dyslipidaemia, often have an excess of abdominal visceral adipose tissue[12]. CT and MRI can provide an estimate of the amount of fat stored in different adipose tissue compartments as this may greatly differ between individuals, but are not routinely used in the diagnosis of obesity[74]. The concomitant presence of high adiposity combined with low muscle mass (sarcopenia) may be associated with a greater prevalence of cardiometabolic abnormalities than individuals with the same BMI but higher muscle mass[115]; this diagnostic entity is known as 'sarcopenic obesity'. Sex-specific and BMI-specific reference curves for appendicular skeletal muscle index (that is, the sum of the muscle masses of the four limbs divided by the square height in metres) and fat mass index, which is measured using dual-energy X-ray absorptiometry (DXA) in adults, are available[116].

The metabolically healthy obese phenotype category is used to describe individuals with obesity who do not meet the clinical criteria of the metabolic syndrome[117,118] (BOX 1). During adulthood, the main predictor for the conversion of the metabolically healthy obese phenotype to the unhealthy phenotype is visceral abdominal fat accumulation[119]. However, controversy exists as the metabolically healthy obese phenotype is not well defined and also tends to be a transient phenomenon and, therefore, not a benign condition[117], as it is often only a matter of time until the individual develops complications.

Finally, the normal-weight obesity trait has also been described as a metabolic condition. Studies have pointed to clear health risks for individuals with this phenotype[120], especially among Asian populations[121], whose optimal cut-off values were approximately 24 and 23 kg/m$^2$ for BMI, for men and women, respectively[122]. Thus, BMI cut-off values need to be adapted according to ethnicity.

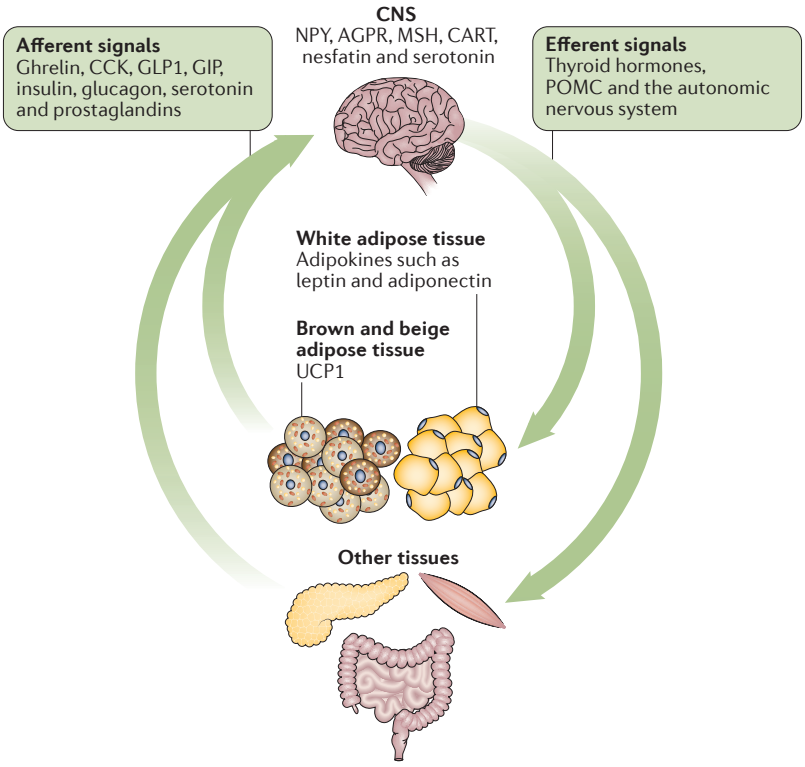


Figure 6 | **Control of hunger and satiety.** Hunger and satiety are controlled by complex interactions between the nervous system, nutrients, mechanical sensing, circadian rhythms and hormones. Several neurotransmitters and neuropeptides in the hypothalamus are involved in the regulation of food intake. Neuropeptide Y (NPY) and agouti-related peptide (AGRP) stimulate food intake, whereas melanocyte-stimulating hormone (MSH), cocaine- and amphetamine-regulated transcript protein (CART) and pro-opiomelanocortin (POMC) suppress food intake. Nesfatin 1 regulates hunger and fat storage. Thyroid hormones (triiodothyronine and thyroxine) are involved in several physiological processes, including the regulation of the basal metabolic rate and body temperature, but other efferent signals are also involved, such as the autonomic nervous system. Several adipokines (such as leptin, adiponectin, nicotinamide phosphoribosyltransferase (also known as visfatin), apelin, secreted frizzled-related protein 5, tumour necrosis factor, IL-6, prothrombin activator inhibitor 1 and angiotensinogen) produced by adipose tissues may mediate appetite, thermogenesis, inflammation and fat deposition. Leptin is also known as the 'satiety hormone' that regulates energy balance by inhibiting hunger; it opposes the action of ghrelin, the 'hunger hormone'. Adiponectin regulates several metabolic processes (including glucose homeostasis and fatty acid oxidation) and has potent anti-inflammatory, antidiabetic and anti-atherogenic properties. Mitochondrial brown fat uncoupling protein 1 (UCP1; also known as thermogenin) is involved in heat generation by inducing non-shivering thermogenesis. Gastrointestinal and pancreatic hormones (such as ghrelin, cholecystokinin (CCK), glucagon-like peptide 1 (GLP1), glucose-dependent insulinotropic peptide (also known as gastric inhibitory polypeptide (GIP)), insulin, glucagon and serotonin) are involved in the uptake of food, metabolism and the control of hunger. Some of these hormones increase food intake (for example, ghrelin) and others decrease food intake (such as GLP1, serotonin, CCK and insulin). CNS, central nervous system.

### *Evaluation*

The BMI should be measured in all individuals in clinical care settings[64]. The paradox of BMI in obesity assessment is that it is not a perfect index of adiposity, but is highly predictive of cardiometabolic risk[123]. The addition of the waist-to-hip ratio to BMI gives even a better prediction of cardiovascular disease[124]. BMI assessment should be accompanied by indices of body shape (such as waist circumference) and other features (such as blood pressure, and glucose and cholesterol levels) to define precisely the risk in individuals.

Overweight and obesity are defined using BMI criteria for adults. For children, the BMI Z-score (a score based on the BMI standard deviation) is often preferred to facilitate the analysis of different ethnic populations[125,126]. To overcome the limitations of BMI in clinical practice, in addition to measuring waist circumference, diverse obesity staging systems, taking into account other factors such as dyslipidaemia and glucose homeostasis, have been devised to help health professionals facilitate categorizing people according to weight-related health problems and to select appropriate treatments. Examples are the Edmonton Obesity Staging System, the Cardiometabolic Staging System, the ATPIII panel and the Framingham risk score, among others[127,128].

Skinfold thickness measurements and bioelectrical impedance analyses (BOX 3) can also be used in clinical practice to provide estimates of total body fat. However, measuring body folds and electrical conductivity are only proxies of the fat and lean mass owing to the imprecise assessment characteristics of these tools. Sex, age and ethnicity percentiles are currently available, based on fat mass measurements using DXA values in the NHANES study 1999–2004 (REF. 129).

Useful reference methods to measure total body fat exist, but their use is limited to laboratory settings; they mainly include densitometry and imaging-based methods, such as MRI and CT[8,9].

### *Prevention*

Obesity prevention should focus on maintaining weight loss or controlling excessive weight gain[130]. Potential preventive strategies are health promotion programmes or marketing, addressing lifestyle behaviours and policies that target the environment[131] (FIG. 4).

In general, the intervention should start as early as possible, even during the periconceptional period. However, experience in early interventions is limited. Thus, in a systematic review[132] on interventions during the first critical period (FIG. 3), only two prenatal interventions were included, with no effect on the BMI of the offspring. The first intervention included lifestyle interventions during gestation, such as dietary counselling, coaching and physical activity[133]; the second intervention consisted of monitoring and control of gestational diabetes mellitus using dietary advice, blood glucose monitoring and insulin therapy if necessary[134]. Of the six interventions that were implemented from pregnancy and infancy, only two were effective. In one of the effective studies, eight educational home visits by community health professionals focusing on infant diet, feeding and activity were

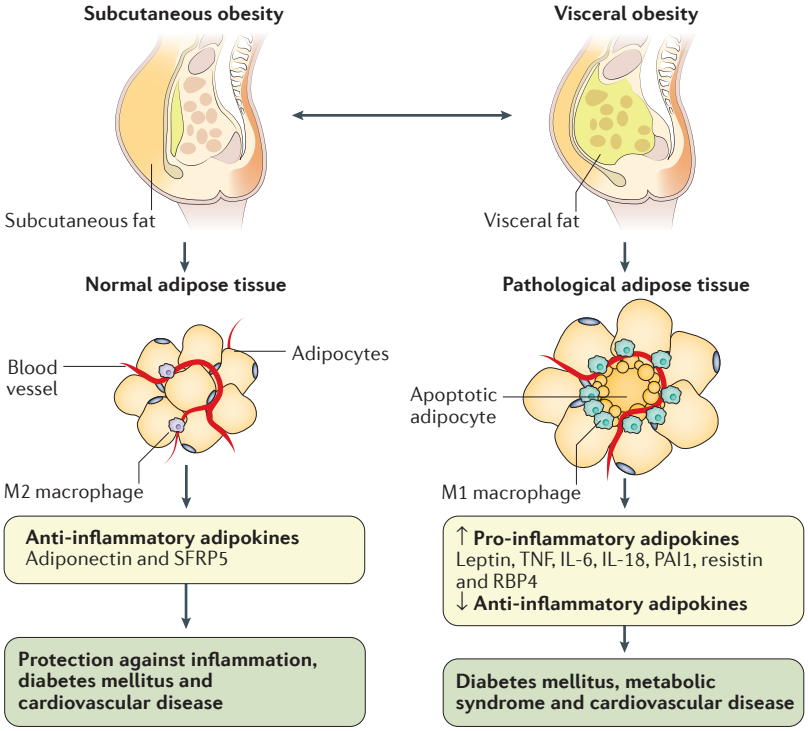


Figure 7 | **Pathological changes in adipose tissue.** A large-scale study revealed that the absolute value of visceral fat area correlated with obesity-associated cardiovascular risks, but cardiovascular risks did not increase with the increase of subcutaneous fat[223]. Accordingly, adipose tissues in subcutaneous fat obesity might function normally with the expected release of anti-inflammatory adipokines, whereas adipose tissues in visceral fat obesity release an increased amount of pro-inflammatory adipokines and suppress the secretion of anti-inflammatory adipocytokines, thereby creating low-grade inflammation, which contributes to systemic metabolic and cardiovascular impairment that is associated with obesity-related disorders[224,225]. Pathological changes in visceral adipose tissue show higher levels of adipocyte necrosis, owing in part to abnormal oxygen tension in the expanded fat depots, and the recruitment of macrophages with an inflammatory phenotype (M1 macrophages) that are arranged around dead cells in crown-like structures. PAI1, prothrombin activator inhibitor 1; RBP4, retinol-binding protein 4; SFRP5, secreted frizzled-related protein 5; TNF, tumour necrosis factor.

implemented before 24 months of age[135]; in the second study, community health workers provided education about maternal diet and infant feeding practices, combining home and group visits[136]. According to another systematic review[137], few studies were done in children <2 years of age; these studies were aiming to promote dietary behaviours or a combination of nutrition education and physical activity, but no intervention was apparently effective in terms of child weight status.

Although systematic reviews on the effectiveness of childhood obesity prevention programmes have shown diverse and often conflicting results, some strategies were found to be useful[138,139], such as the implementation of health education on nutrition, more physical activity lessons in the school curricula and the provision of healthy food at school. Limited evidence for the effectiveness of policies focusing on the child's environment and health information technologies focusing on children and parents is available. Performing interventions in primary care settings could improve parenting practices and promote healthy eating habits, but available studies showed only limited effect[140].

The complexity of obesity requires multilevel and multicomponent interventions that take a systems approach. Multilevel approaches focus on changing health behaviours by acting on multiple frameworks: in practice, going from the individual, often children or adolescents, schools or occupational environments and the communities. Multicomponent interventions incorporate more than one strategy to modify behaviours, within the same level[141]. For the development of the interventions, health promotion models should consider information on the determinants, such as the target population and opportunities in the corresponding societies. According to the WHO report 'Ending Childhood Obesity' (REF. 142), factors to be taken into account include maternal–child health, nutritional education and health literacy, parents' perceptions of healthy infant growth and development, peer pressure, family eating and physical activity behaviour, and the role of food and built environments. A broad perspective is necessary, as focusing just on one or a limited number of components or on the health sector alone is unlikely to be effective[142]. Despite the many identified limitations of obesity prevention programmes, policy efforts to prevent childhood obesity should continue[143]. Self-monitoring could be important in weight loss intervention[144].

## Management

Current management of obesity is aimed at weight loss by taking a risk-based approach using low-risk treatments, such as lifestyle interventions, dietary changes and exercise, as the first-line choice, followed by medication or surgery in selected cases. Several guidelines have been developed in the United States, the United Kingdom and Europe to aid the health care professional in treating the patient with obesity[145–150]. Response to any treatment is variable, and strategies to lose weight may be different from those for maintaining weight loss[151].

### *Lifestyle interventions*

Behavioural modification in lifestyle programmes has been an important part of programmes for weight loss for more than a quarter of a century[149,152,153]. A meta-analysis showed a mean weight loss of 3.01 kg (95% CI: 4.02–2.01) with behavioural changes[154]. Behavioural modification helps patients to understand and monitor[144] their eating behaviour, from the triggers that start it to the location, speed and type of eating, through to the consequences of eating and the rewards that can change it[155]. It also consists of strategies to help people to develop assertive behaviour, learn cognitive techniques for handling their internal discussions, and ways of dealing with stress. The newest innovation in the use of lifestyle interventions is implementation of online tools, including automated e-mail feedback, e-mail counselling and behavioural therapy[156].

### *Diets*

Diets for the management of body weight have only been rigorously tested in randomized controlled trials in the past 20 years[151]. Negative energy balance through caloric restriction is commonly used to produce weight

loss with diets, and all diets will on average induce this effect. A restriction of 500 kcal per day or an individualized –30% energy restriction, or a diet with 1,200 kcal per day for women and 1,500 kcal per day for men is generally recommended. Interestingly, improving overall nutritional quality without a direct energy restriction (for example, with the Mediterranean diet; BOX 2) can also be helpful to reduce weight[61,157]. However, adherence to the dietary programme is key[149]. In a meta-analysis of many popular diets, the low-carbohydrate diets produced a weight loss of 7.25 kg after 12 months compared with 7.27 kg low-fat diets, which is essentially no difference[158]. Inter-individual weight loss is high with all diets; some people lose a lot of weight and others actually gain weight[151]. Genetic variability may provide an explanation for some of the differential response to diets[151].

Differences in macronutrient composition do not always favour any one diet over another, which stresses the concept of involving the patient in the selection of a diet to increase compliance[149]. Preference should be given to one of several healthy dietary patterns such as the Mediterranean, the DASH or the RESMENA diets (BOX 2), which can be used as 'weight loss diets' in low-calorie versions[55]. Lower-fat diets are associated with lower levels of low-density lipoproteins, and higher-fat diets are associated with lower levels of triglycerides and higher levels of high-density lipoproteins in shorter-term weight loss studies, but these lipid effects generally disappear over the longer term when weight loss has plateaued and weights are not different according to diet group[151].

For long-term weight loss maintenance, adherence to the diet is important, but the macronutrient composition may have a role[159]. Higher protein intake, foods with a low glycaemic index and lower fat intake may benefit in maintaining weight loss, whereas higher-carbohydrate diets may favour weight regain[151,160]. Dietary recommendations for weight control should consider the overall quality of the diet and long-term health effects, as well as the role of specific amino acids, fatty acids, bioactive compounds, or the number of meals and timing of food consumption, and macronutrient distribution[161].

Box 3 | **Tools available to determine body composition**

- Anthropometry: the measurement of the physical properties of the human body, including body mass index (BMI), waist circumference, waist-to-hip ratio and skinfold thickness.
- Bioelectrical impedance analyses: determines the electrical impedance, or resistance to the flow of an electric current, through the body; this parameter can then be used to calculate an estimate of total body water. On the basis of the constant hydration of fat-free mass, total body fat can be calculated.
- Densitometry
  - Underwater weighing: determines body density by measuring the mass per unit volume of the body; density is used to estimate the total body fat.
  - Air displacement plethysmography: based on the same principle as underwater weighing, but uses air displacement rather than water immersion.
- Imaging-based methods
  - Dual-energy X-ray absorptiometry: a widely used method to study bone mineral density, from which the total body fat can also be estimated.
  - MRI or CT: mainly used to estimate abdominal fat in obesity research.

### *Physical activity*

As for all sedentary individuals, the current recommendation is to gradually increase aerobic physical activity in patients with obesity, by, for example, brisk walking, to reach a goal of >150 minutes per week[162,163]. This strategy has health benefits independent of weight loss, as moderate levels of physical activity lower the risk of developing diabetes mellitus and cardiovascular disease[163], which is maybe related to the fact that it has the potential to reduce harmful visceral adipose tissue and ectopic fat[12]. A meta-analysis indicated that physical activity results in 1–1.5 kg more weight loss over 12 months than with a dietary intervention alone[164]. For long-term weight maintenance, 60–90 minutes of exercise per day may be required[149,162,165]. In the Look AHEAD trial, the increase in activity at 1 year was not maintained at 4 years, and there was an increase in weight after year 1 in the intervention group, although they remained below their initial weight during an 8 year follow-up[166]. The type of physical activity (for example, aerobic versus resistance exercise or high-intensity versus low-intensity activity) does not seem to affect overall weight loss. However, more intense activity might be preferable for some individuals as it takes less time[167].

### *Medical management*

Drugs for use in treating patients with obesity are approved as adjuncts to diet and exercise and none has been approved for use in pregnancy, nursing or paediatric populations[145,152,168] (TABLE 1). The use of these drugs should be reserved for patients with moderate-risk or high-risk obesity (a BMI of >30 kg/m$^2$ or a BMI of >27 kg/m$^2$ if comorbidities are present)[145]. As they are intended for patients who are struggling to lose and maintain weight loss, a history of lack of success in the past is a prerequisite. All of these medications work through helping patients to better adhere to their diets, except orlistat and cetilistat (which is only available in Japan), which helps to enforce a low-fat diet. Thus, these medications should only be used with an effort of dieting. There is no ideal medication so far; in the right patient, any of them can be successful. If patients have not lost 4–5% of their body weight after 3 months, the drug should be stopped and another approach used[145]. The medications currently approved in the United States for chronic weight management are listed in TABLE 1; drugs availability in other countries may vary. Abuse of amphetamines, methamphetamine and phenmetrazine is well established, and these agents are approved by the US FDA for short-term treatment (usually considered <12 weeks), but not for long-term treatment, of the patient with obesity.

### *Bariatric surgery*

Use of bariatric surgery (also known as metabolic surgery) has become rapidly adopted as a treatment option for severe obesity, and this has increased with the advent of lower-risk laparoscopic procedures. The criteria for consideration are a BMI of >40 kg/m$^2$ or a BMI of >35 kg/m$^2$ with comorbidities, such as hypertension

or dyslipidaemia. Patients with pre-diabetes or recent-onset diabetes may qualify with a BMI between 30 and 35 kg/m$^2$ (REFS 169,170). Bariatric surgery can be performed on an individual basis in adolescents who are markedly overweight. Nearly half a million surgical procedures were performed worldwide in 2013 (REF. 152). There are a range of interventions that result in varying degrees of weight loss and each has its own risks and benefits that need to be considered carefully with each patient[171,172] (FIG. 8).

Outcomes following bariatric surgery have generally shown favourable results[173]. The Swedish Obese Subjects study has followed-up 2,000 patients for up to 20 years who were operated on with one of 3 surgical procedures: banded gastroplasty, gastric banding and Roux-en-Y gastric bypass (FIG. 8). Mortality was reduced by 24%, mainly owing to reduced risk of myocardial infarction and, in women, cancer compared with a control group receiving usual care[173]. Many other comorbidities, such as type 2 diabetes mellitus and sleep apnoea, are also improved, and patients report consistent improvements in quality of life. The weight loss averaged 23% at 1 year and 18% at 20 years.

Glucose control rapidly improves in patients with obesity who have type 2 diabetes mellitus, especially following bariatric surgery, suggesting that part of the metabolic improvement is independent of weight loss[173]. Head-to-head randomized controlled trials of surgical treatment against intensive medical treatment for type 2 diabetes mellitus have consistently shown greater improvements in glucose control in the surgical group[174]. Observational data also exist, which indicate that future risk of diabetes-related microvascular and macrovascular complications are also reduced following bariatric surgery[175]. Remission of diabetes mellitus is largely driven by weight loss, although several gastrointestinal hormones, including glucagon-like peptide 1, polypeptide YY and ghrelin, have also been implicated[176]. These encouraging data need to be put into the context of potential risks and adverse effects of surgery, which for some patients can be distressing or disabling. Among six studies in the Cochrane review, one death was reported with modern laparoscopic bariatric surgery, but re-operation rates ranged from 6.7% to 24% in the laparoscopic Roux-en-Y gastric bypass group and 3.3% to 34% in the laparoscopic banded group[177].

Table 1 | **US FDA-approved drugs for the treatment of obesity**

| Drug | Mechanism of action | Average weight loss (%)* | Approved use and DEA schedule‡ | Adverse effects and comments |
|---|---|---|---|---|
| Orlistat | Pancreatic lipase inhibitor, which blocks lipase in the intestine, thereby reducing fat absorption | 4 | Long-term oral use, not scheduled | Gastrointestinal adverse effects, such as bloating and diarrhoea, owing to undigested fat in the intestine; should be taken with a multivitamin, to compensate for the impaired absorption of fat-soluble vitamins[227] |
| Lorcaserin | Serotonin receptor (5-hydroxytryptamine 2C receptor) agonist, which acts in the brain to reduce food intake | 3 | Long-term oral use, schedule IV | Generally well tolerated with possible mild adverse effects, such as headache, dizziness, nausea, dry mouth and constipation; avoid use with other serotonergic drugs[228] |
| Liraglutide | Glucagon-like receptor 1 agonist, which reduces food intake and is marketed for diabetes mellitus at a lower dose | 6 | Long-term use by subcutaneous injection; not scheduled | • Nausea with vomiting are the principal adverse effects; acute pancreatitis or gall bladder disease can also occur; hypoglycaemia can occur when taken with other antidiabetic drugs; do not prescribe to patients with a personal or family history of medullary thyroid cancer, MEN2 or pancreatitis[229]<br>• Treatment is associated with 13% reduction in major adverse cardiovascular events and a 15% reduction in all-cause mortality[230] |
| Diethylpropion, phentermine, phendimetrazine and benzphetamine | Noradrenergic drug, which functions as an appetite suppressant | NA§ | Short-term oral use; schedule IV‖ | Dizziness, dry mouth, insomnia, constipation, irritability and cardiostimulatory effects[231] |
| Phentermine–topiramate extended release | Combinations of drugs act as appetite suppressants through the release of serotonin, noradrenaline and dopamine[168] | 9 | Long-term oral use, schedule IV | Larger weight loss, on average, than any of the other approved drugs. Adverse events are paraesthesia and change in taste (dysgeusia); metabolic acidosis and glaucoma are rare; do not use within 14 days of a MAOI antidepressant; obtain a negative pregnancy test before prescribing and avoid pregnancy |
| Naltrexone–bupropion sustained release | Combination of drugs that increase satiety and decrease appetite, inhibiting the reuptake of dopamine and noradrenaline, blocking μ-opioid receptor and activating pro-opiomelanocortin[168] | 6 | Long-term oral use, not scheduled | Nausea, constipation and headache; avoid in patients receiving opioids, MAOI antidepressants and those with a history of seizures; the cardiovascular safety of this treatment remains uncertain[232] |

MAOI, monoamine oxidase inhibitor; MEN2, multiple endocrine neoplasia type 2; NA, data not available. *The 1-year placebo-subtracted weight loss data. This parameter is used to compare the effectiveness of drugs between trials when placebo (that is, a substance with no active therapeutic effect) varies[233]. ‡The US Drug Enforcement Agency (DEA) evaluates drugs for potential abuse and classifies them from I (most hazardous) to V (least hazardous). §The 1-year placebo-subtracted weight loss for phentermine is 5%. ‖Benzphetamine is schedule III.

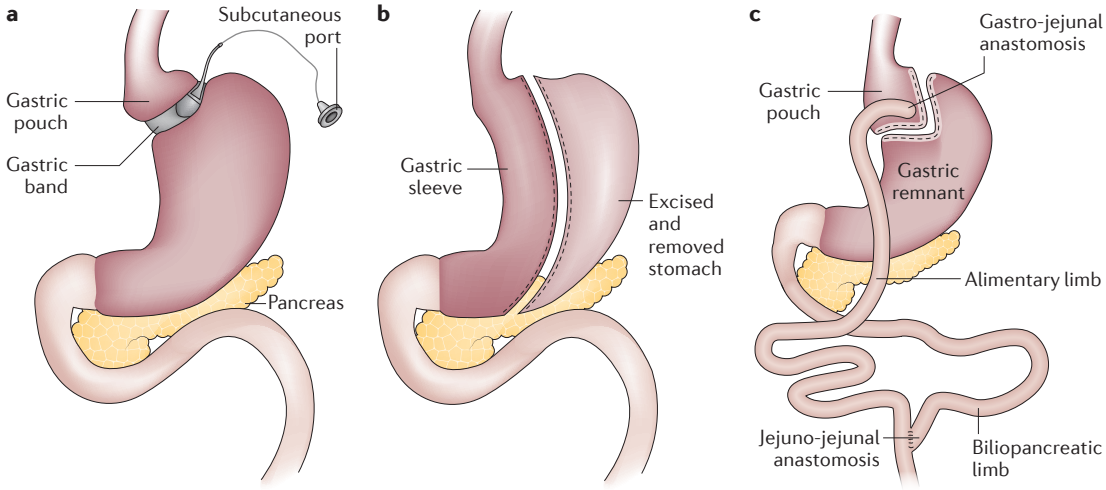


Figure 8 | **Bariatric surgery. a** | The abdominal gastric band is an inflatable silicone band placed just below the gastro-oesophageal junction to create a small gastric pouch with a narrow stoma. A subcutaneous port, which allows adjustment of the tightness, is attached to the band. Frequent follow-up is essential to achieve the optimal band tightness for each patient. This procedure is technically easy, but weight loss is less than with other bariatric procedures. **b** | The sleeve gastrectomy involves placement of a staple line along the greater curvature of the stomach, followed by the removal of the closed stomach. This produces an elongation from the oesophago-gastric junction to the pylorus. This procedure is now among the most widely performed, and the weight loss is comparable to the Roux-en-Y gastric bypass. **c** | The Roux-en-Y gastric bypass involves laparoscopic division of the jejunum approximately 50 cm from the ligament of Treitz, and the proximal end of the jejunum is anastomosed to the distal part of the jejunum about 150 cm below the site of transection, producing a jejunojejunostomy. The resultant 150 cm Roux limb of the proximal jejunum is brought up and anastomosed to the small proximal gastric pouch, providing a volume of about 15–30 ml. This procedure is more technically demanding, but competes with the sleeve gastrectomy. Reproduced with permission from REF. 226, Macmillan Publishers Limited.

Some patients find it hard to adapt to the profound changes in the amount and type of food they can eat following the procedure. Lifelong replacement therapy and monitoring are required for nutritional vitamin and mineral deficiencies, particularly after malabsorptive operations. Dumping syndrome, gastro-oesophageal reflux and hypoglycaemia can be very distressing and a challenge to treat. Weight regain can also be a problem, and revision surgery carries greater risks with no guarantee of success[178].

## Quality of life

The population burdens of obesity and overweight are substantial and represent priorities for public health[179]. By 2030, health care costs owing to obesity-related diseases are projected to reach $48–66 billion per year in the United States alone[68].

The increased risks for obesity-associated conditions, including type 2 diabetes mellitus, cardiovascular disease and certain types of cancer, account for a substantial part of this burden[20,65–68]. However, overweight and obesity are also known to have a substantial effect on emotional well-being, self-esteem and psychosocial health[180]. Overweight and obesity are usually associated with a lower health-related quality of life (HRQOL) than normal weight (BOX 4). Studies conducted in diverse settings (the United States, Canada, Europe and Australia) have reported a monotonic trend, showing that as BMI increases, HRQOL decreases[181]. For example, in the Rancho Bernardo cohort, California, USA (including community-dwelling), using the Quality of Well-Being Scale (BOX 4), the normal BMI group had the highest score, followed by the underweight, overweight and obese groups[182].

HRQOL estimates using the EQ-5D tool[183] (BOX 4) in the US Medical Expenditure Panel Survey[184] concluded that overweight men and women lost 270,000 and 1.8 million quality-adjusted life years, respectively, relative to their normal-weight counterparts. Men and women with obesity lost 1.9 million and 3.4 million quality-adjusted life years, respectively, per year. The authors of the study suggested that these sex differences might be explained by three facts: very fit men are more likely to be erroneously included in the overweight, or even obese, group; obesity in women tends to primarily affect morbidity instead of mortality, therefore, women have a longer lifespan than men; and psychological morbidity is a bigger burden in women than in men. Much of this burden of disease arose from lower HRQOL and shorter life expectancy.

A vicious cycle can occur in which poorer HRQOL and impaired mental health can act as triggers for subsequent weight gain[185,186], potentially adding to the enormous global problem of continually rising population obesity rates. Thus, quantification of the amount of weight loss that is needed to obtain a sufficiently large improvement in quality of life (that is, a clinically important difference) is required. For example, in the two large cohorts of the Nurses-I and Nurses-2 Health Studies, weight gains were associated with lower physical component scores, whereas weight losses were associated with higher physical component scores, role limitations

Box 4 | **HRQOL tools use in QOL research in obesity**

The two most frequently used tools to assess quality of life (QOL) in the field of obesity are the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and the Impact of Weight on Quality of Life-Lite (IWQOL-Lite)[203–205]. Other generic health-related QOL (HRQOL) measures used are the Quality of Well-Being Scale and the EQ-5D (EuroQOL). The SF-36 (one of the most frequently used tools to assess QOL) is a generic self-reported measure of HRQOL comprising 36 questions across eight domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health). The IWQOL-Lite[204,206] is a validated, obesity-specific, self-reported measure of QOL. The IWQOL-Lite assesses physical function, self-esteem, sexual life, public distress and work. Total scores on the IWQOL-Lite scales range from 0 to 100 (in which 0 indicates the poorest HRQOL). It is usually assumed that a threshold for change in a clinically important difference over time in the SF-36 is at least 5 points, and an improvement of 7.7–12 points (depending on baseline scores) in the IWQOL-Lite total score represents a clinically important difference in patients with obesity[207,208]. QOL measures for youth have also been reported in an IWQOL-Kids version, which has established minimal clinically important difference scores[209,210].

due to physical problems, bodily pain, general health and vitality. However, the relationship of weight change with mental health component scores, social functioning and role limitations due to emotional problems was small[187]. In the majority of people with severe obesity, minimally clinical meaningful improvements in HRQOL from a clinical point of view were only achieved after weight loss of ≥20% over 2 years[188].

Although it seems intuitive that weight loss would lead to improvements in HRQOL, the magnitude of weight loss needed for clinically significant improvements in HRQOL among individuals with obesity has been seldom quantified, and few publications have specifically aimed to assess the correlation between specific weight changes and changes in HRQOL. Recently, a systematic review of literature from the United States, including 20 publications that analysed publications using the 36-Item Short-Form Health Survey (SF-36) and/or the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) to measure quality of life, showed that clinically relevant weight loss (usually >5%) after bariatric surgery may be associated with improvements in HRQOL. In non-bariatric studies with weight loss of 5%, improvements in some aspects of HRQOL were noted, although the causal nature of the relationship was uncertain. In both bariatric and non-bariatric studies, many domains of the usual tools (SF-36 or IWQOL-Lite) increased, but improvements were mainly significant for physical domains, and not so often for mental dimensions of the quality of life[179]. The vitality domain of the SF-36 apparently was the most sensitive score to weight loss.

In children and adolescents, overweight and obesity do not usually lead to major immediate comorbidities, but they are associated with more-sedentary lifestyles, lower levels of self-esteem, social exclusion, suboptimal achievements in education and also with lower quality of life[189–192].

## Outlook

### *Pathophysiology*

A deeper understanding of appetite and food preferences is needed, which should include satiety, taste receptors, neuronal circuits and neurotransmitters. The thermogenic capacity of brown adipose tissue with the latest discovery of beige adipocytes is also gaining interest[193]. In this regard, better understanding of the transformation of white adipocytes into beige and finally brown adipocytes to increase thermogenesis is crucial.

### *Individualized precision nutrition*

The role of genetics, epigenetics, nutrigenomics (the study of the interaction between nutrition and genes founded on 'omics' technologies) or personalized nutrition remains to be better understood to improve obesity management[194]. However, it is important to balance the individual and the epidemiological values of the personalized approach versus population-based strategies. Precision nutrition based on phenotypical and genotypical data holds some promise but seems unlikely to solve the global obesity epidemic, which is largely a societal problem. The following information for precision medicine and feeding should be considered to individualize the treatment: family background; clinical history and lifestyle; food preferences, allergies and intolerances; epigenetics; culture and religion; socioeconomic status; hours of sleep or work shift; extensive working hours; and chronobiology (a science speciality based on the study of biological rhythms), among others. Indeed, precision nutrition depends on integrating genetic and epigenetic data with phenotypical information about the individual[48]. New genetic and omic approaches, including nutrigenetics, transcriptomics, metabolomics, metagenomics (microbiota) and epigenetics, among others[194], under the umbrella of omics technologies, are relevant for the future implementation of individualized nutrition together with more precise body composition measurements, big data

Box 5 | **New treatment strategies under investigation**

**Lifestyle interventions**

- New educational programmes
- City urbanism affecting lifestyle

**Diets**

- New diets for weight loss or weight maintenance based on macronutrient distribution and/or the nutrigenetic advances[55]
- Specific nutrients that help to reduce metabolic impairments, such as the mitochondrial-related metabolic impairments[211]

**Other treatments**

- Precision drugs based on pharmacogenetic and nutrigenetic approaches[168]
- Antibody drugs or vaccines against mediators such as ghrelin[212,213]
- Bioactive compounds that affect digestion or metabolism (such as fibre, curcumin, spices, omega-3 fatty acids, resveratrol and quercetin[214,215])
- Oxygen therapy to reduce appetite and improve inflammatory and cardiorespiratory status[216,217]
- Gene therapy of specific genes related to metabolism, for example, *UCP1* and *UCP2* (REFS 218,219), or isocitrate lyase and malate synthase, which are two enzymes involved in the glyoxylate cycle[220]

analytics, bioinformatics and integrated interpretation of all this information. Indeed, it is necessary to define obesity more precisely, improving the measurement of body composition and defining obesity subtypes. As obesity rates continue to increase worldwide, new therapeutical approaches or tools are needed (BOX 5).

### *Prevention*

Undoubtedly, more attention and financial support should be paid to the prevention of obesity[19]. At the population level, public policies and economical strategies are needed to improve food and physical environments, the food system and the health system to curb the global obesity epidemic. For example, some efforts have been enacted for higher taxes on sugary drinks, unhealthy fats and fast foods, and calorie labels on menus, for example, in Mexico, France, Finland, Hungary and Denmark[18]. In addition, many communities are working on facilitating physical activity and more sleeping hours by changing TV programming and increasing the green areas, sidewalks, and biking lanes in the cities[195,196]. Furthermore, living at higher altitudes seems to prevent weight gain[197] and the metabolic syndrome[198]. One hypothesis is that the decreased oxygen availability at higher altitudes increases the calories burnt for the same activity compared with lower altitudes, and this extra effort improves cardiorespiratory health in the long term. Several behavioural approaches, including motivational interviewing techniques, focus groups and multicomponent programmes involving cognitive strategies, have been designed for adults[199], and incentive-based behavioural changes targeting children have been investigated[200], suggesting that public health nutrition should coexist with precision individualized nutrition.


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