Clinical Medicine 2023 Vol 23, No 4: 284–91

Causes of obesity: a review

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ABSTRACT

Obesity research is advancing swiftly, but the increase in obesity prevalence is faster. Over the past three decades, researchers have found that biopsychosocial factors determine weight gain much more than personal choices and responsibility. Various genes have found to predispose people to obesity by interacting with our obesogenic environment. In this review, we discuss the impact of physical inactivity, excessive caloric intake, intrauterine environment, postnatal influences, insufficient sleep, drugs, medical conditions, socioeconomic status, ethnicity, psychosocial stress, endocrine disrupting chemicals and the gastrointestinal microbiome, on the occurrence of obesity.

KEYWORDS: obesity, genetics, environment, modifiable, causes, genetics, epigenetics, modifiable factors

DOI: 10.7861/clinmed.2023-0168

Introduction

The World Obesity Federation estimates that 800 million people are currently living with obesity, of whom 39 million are children under 5 years (2020) and 340 million are children and adolescents between the ages of 5 and 19 years. Moreover, there are at least 1 billion more people at risk of becoming overweight or obese.

The impact of obesity on individuals and society is evident by considering the chronic diseases resulting from obesity (type 2 diabetes mellitus (T2D), hypertension, dyslipidaemia, osteoarthritis, sleep apnoea and various cancers) and the associated disabilities, which can lead to decreased productivity.

Although efforts to treat obesity are underway with increasing success, we have failed to control the relentless increase in obesity. Determining the exact causes of obesity and understanding their pathophysiology is a major stumbling block. This was fully addressed in the landmark foresight report first published in 2007, which identified the complex drivers of obesity and outlined a plan to prevent and treat it.[1] This report envisions the obesity occurrence and goals up to 2050 and suggests appropriate measures to achieve a sustainable decrease in the prevalence of obesity.[1]

The causes of obesity are multipronged and inter-related. To simplify we describe them here as non-modifiable and modifiable factors.

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Non-modifiable factors

Genetic

There have been several studies over the past 20 years on genetic obesity, which have found that genetic mutations (abnormal changes in DNA sequence), polymorphisms (normal variation in a DNA sequence, which is common in the population) and changes in gene expression (the process by which information encoded in a gene is turned into a function), all have a role in predisposing individuals to obesity.

Initially, candidate gene studies (ie those that look at the genetic variation associated with disease in *specified* genes) identified certain genes to be pathogenic for severe early-onset obesity or monogenic (rare) obesity (Table 1).[2–26] Later, genome-wide association studies (GWAS), which help identify new genes associated with particular diseases identified additional genes (Table 1).

There are three types of genetic obesity: monogenic, polygenic and syndromic. Monogenic obesity results from a mutation or deficiency of a single gene and is a rare but severe cause of obesity. It occurs when there is a mutation in one of the genes involved in the leptin–melanocortin pathway (see below). Genes associated with this type of obesity are detailed in Table 1. Typical features of monogenic obesity are hyperphagia (insatiable hunger) and early-onset obesity (age 3–5 years). Polygenic obesity results from the simultaneous presence of multiple gene variants, which have an accumulative effect. There are several genes associated with this type of genetic obesity, some of which are detailed in Table 1. The third type is syndromic obesity, it is associated with other signs of a developmental disorder, and may or may not be accompanied by a congenital malformation syndrome; typical signs are dysmorphic features and organ abnormalities.[27] Examples of syndromes associated with obesity are Prader-Willi, Cohen and Bardet-Biedl among others,[28]; their respective genes are detailed in Table 1.

GWAS enabled researchers to discover that it is the accumulation of gene variants that predisposes individuals to common or polygenic obesity (Table 2).[29] Genes found to be more common in individuals with obesity were then assessed for association with the risk of developing obesity, body mass index (BMI) and other body composition traits, such as body fat percentage;[15,16,30] fat free mass;[31] imaging derived adipose tissue;[32] circulating leptin levels and leptin receptor (LEPR) levels.[33] These studies established the role of epigenetics in obesity (discussed in detail below).

The leptin–melanocortin pathway

Most research on genetic obesity has revealed that the leptin–melanocortin circuit in the hypothalamus has a key role in

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Table 1. Genes associated with genetic obesity

Gene	Encoding protein	Type of genetic obesity
LEP[2]	Leptin	Monogenic
LEPR[3]	Leptin receptor	Monogenic
PCSK1[4]	Proprotein convertase subtilisin/kexin enzyme 1	Monogenic
MC4R[5–7]	Melanocortin-4 receptor	Monogenic, polygenic
POMC[8–10]	Pro-opiomelanocortin neuropeptide	Monogenic
ASIP[11]	Agouti signalling protein	Monogenic
BDNF[12,13]	Brain-derived neurotrophic factor	Monogenic, polygenic
FTO[14,15]	(Fat-mass & obesity associated gene); Fe^{2+}-α-ketoglutarate-dependent dioxygenase	Polygenic
SIM1[16]	Single-minded 1 transcription factor	Monogenic
NTRK2/TRKB[17]	Neurotrophic tyrosine receptor kinase 2 (receptor for BDNF)	Monogenic
KSR2[18]	Kinase suppressor of Ras 2 protein	Monogenic
NPY[16]	Neuropeptide Y	Monogenic
SH2B1[19,20]	SH2B adaptor protein 1	Monogenic
ADCY3[21,22]	Adenylyl cyclase 3	Monogenic
INSIG2[23]	Insulin-induced gene 2 protein	Polygenic
MKRN3, *MAGEL2*, *NDN*, *NPAP1* and *SNURF-SNRPN*[24] (in Prader–Willi syndrome critical region)	Makorin ring finger protein 3, MAGE family member L2, necdin protein, nuclear pore-associated protein, SNRPN upstream reading frame–small nuclear ribonucleoprotein polypeptide N	Syndromic (Prader–Willi syndrome)
COH1/VPS13B[25]	Vacuolar protein sorting 13 homolog B	Syndromic (Cohen's syndrome)
BBS 1–26[26]	BBSome proteins	Syndromic (Bardet–Biedl syndrome)

appetite regulation and that genes expressed exclusively in this pathway have a pivotal role in obesity.[34] Leptin is an appetite-regulating hormone secreted by fat cells, which circulates at levels proportional to the mass of fat.[35] In obesity, an excess of leptin is secreted, which eventually leads to leptin resistance (similar to insulin resistance). When cells in the hypothalamus become resistant to leptin, the signal for satiety is not received and the person remains hungry. Leptin levels decrease with food deprivation ie during fasting and increase after eating.

Leptin activates LEPR expressed in different areas of the central nervous system.[36] In the arcuate nucleus of the hypothalamus, LEPRb (an isoform of the leptin receptor) is found on two types of neurons, which have a pivotal role in the melanocortin pathway; one type expresses pro-opiomelanocortin (POMC) and the other expresses agouti-related protein (AGRP).[37] POMC neurons in the arcuate nucleus connect with melanocortin-4 receptor, (MC4R) neurons in the paraventricular nucleus via melanocortin, which signal to decrease food intake.[36] In contrast, AGRP neurons act on MC4R neurons to increase food intake.[37,38] A balance between the action of these two types of neurons is found to control eating behaviour.

The hypothalamus receives signals via peptides and hormones (peptide Y, glucagon-like peptide-1, cholecystokinin and ghrelin[39,40]), which are released by the gut in response to food (varying with the composition of macronutrients), signals from adipose tissue (leptin) and visceroceptive information from the vagus nerve.[41] Although this signalling is entirely subconscious, hypocretins (melanin-concentrating hormone and orexins[42] secreted from the lateral hypothalamic area) act on the medial hypothalamus and affect reward-related brain areas, thus forming a vital loop between the homeostatic and hedonic system; it is this 'cross-talk' between metabolism and the pursuit of pleasure that makes it difficult to control appetite and lose weight.[43]

Table 2. Key features of monogenic and polygenic obesity.[36]

Monogenic	Polygenic
Early-onset, severe obesity	Common obesity
High genetic contribution	Modest genetic contribution
Single mutation in one gene	Hundreds of variants in or near many genes
Large genetic effect	Each variant has a small effect
Rare	Common
High penetrance	Low penetrance
No environmental influence	Environment is a key determinant

Hypothalamic obesity

The leptin–melanocortin pathway is involved in other rare causes of non-genetic obesity, best described as hypothalamic obesity. Lesional hypothalamic obesity results from either an anatomic change in the hypothalamus (usually affecting the

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ventromedial and arcuate nuclei), as occurs in the case of cranial tumors, such as craniopharyngioma (most common), glioma or other tumours, involving the hypothalamus. Treatment of such tumours with surgery and radiotherapy, and pathologies involving the hypothalamus, such as neurosarcoidosis, tuberculosis and Langerhans cell histiocytosis,[27] can also result in hypothalamic obesity. Rapid Onset of Hypoventilation Hypothalamic Autonomic Disorder (ROHHAD) syndrome is likely autoimmune mediated and has positive anti-pituitary and anti-hypothalamic antibodies.[27] Rapid Onset of Hypoventilation Hypothalamic Autonomic Disorder with Neuroendocrine Tumours (ROHHADNET) syndrome can be considered a paraneoplastic syndrome in which hypothalamic obesity occurs in association with neuroendocrine tumours (NETs).[27]

Modifiable factors

Epigenetics

Epigenetic changes are those that affect genetic expression without changing the sequence of DNA; these are acquired through interaction with the environment and, interestingly, are also heritable. Certain obesity syndromes, such as Prader-Willi syndrome, result from imprinting failures.[44] GWAS studies forming the basis of international collaborations, such as the Genetic Investigation for Anthropometric Traits (GIANT) Consortium, found associations between obesity-related genes and traits. The GIANT meta-analysis reported 32 single-nucleotide polymorphisms (SNPs) related to with obesity, which were then used by other researchers to generate a genetic risk score for obesity.[45] The Early Growth Genetics (EGG) Consortium was founded to analyse genetic data from different studies and to improve understanding of underlying mechanisms causing weight gain in early life, childhood and young adulthood. Twin, family and adoption studies estimate the heriability of obesity to be between 40% and 70%.[46] Having a high-risk genetic profile makes a person more susceptible to an obesogenic environment. Studies concluded that the presence of these genes increases the risk of obesity but does not necessitate obesity. This risk can be ameliorated by healthy food choices, increased physical activity and avoiding other causes of obesity mentioned in this review.

Physical inactivity

In one study of 109,000 people in the UK Biobank, the relationship between physical activity and the genetic risk score for obesity was analysed and showed that physical activity decreased the risk of obesity. In fact, those with higher genetic risk scores benefited the most despite light exercise.[47] According to a World Health Organization survey, more than 28% of the world's adult population and 81% of adolescents were physically inactive in 2016. Increasing use of passive modes of transportation have led to reduced physical activity. Lockdown during the Covid19 pandemic has contributed significantly to decreased activity levels world over.

Excessive caloric intake

Historically, the central dogma of the science of obesity has been that it is simply an energy balance disorder: calories in, calories out. If this energy-based model (EBM) of obesity, was true, then essentially exercising more and eating less should work for everyone. However, this is not the case. Many researchers believe that the pathophysiology of obesity is more complex. The carbohydrate–insulin model (CIM) of obesity, first suggested by Gary Taubes in his book *Good Calories, Bad calories* in 2007 and then later endorsed in 2018 by Ludwig and Ebbeling,[47] proposes that a high carbohydrate diet (with predominantly large amounts of sugar and starch) induces postprandial hyperinsulinaemia; the high insulin level shifts the calories into fat cells rather than into lean tissues and this leads to an overall sense of starvation in the body, whereby the person has a reduced metabolic rate and feels hungrier.

Interestingly, this model was challenged by Hall and colleagues in 2022,[48] whereby they countered that the CIM is inaccurate, and that EBM is a 'more robust theory of obesity than CIM'. They argued that it is the brain that is responsible for body-weight regulation via a complex interaction between metabolic, endocrine and nervous system signals that respond to the intrinsic energy requirements of the body in combination with external environmental influences. According to Hall and colleagues, adipose tissue acts as an endocrine organ and the secretion of leptin and other adipokines is directly responsible for increased food intake.

Alongside the intrinsic mechanism of obesity, we must recognise external influences, such as the rapid emergence of fast-food chains, meal deals, upsized drinks and the easy availability of inexpensive ultraprocessed food as part of the problem; we also ought to take a step back and analyse why such a significant part of the world's population suddenly has an energy balance disorder. According to the Foresight report on *Tackling obesities*,[1] although genes, energy intake, early growth pattern and diet have an important role in the development of obesity, it is the obesogenic environment that has modified human behaviour and interacted with human physiology to cause the increase in obesity rates. Today, there are numerous opportunities to eat high-calorie food. Other aspects include: the lower cost of food and drinks; increased marketing of food products; technological advances (such as the improved quality of television and computer screens, increased variety of video games and virtual reality simulators that encourage sedentary behaviour); increased rates of sedentary employment; longer working hours; and improved accessibility of food (convenience stores and vending machines), which result in decreased overall movement.

The intrauterine environment

Obesity in mothers has long been known to be the strongest risk factor for obesity in childhood.[49,50] One prospective study carried out at the University of Southampton concluded that there was a strong association between adiposity of mothers and their daughters, but not their sons.[51] By contrast, there was no such association between the adiposity of fathers and their offspring in this study. Therefore, a stronger association of mother–offspring fat mass suggests a possible role of the intrauterine environment in the development of obesity later in life. However, currently, evidence linking the mother's diet during pregnancy with birth weight is insufficient.

The warm rich environment of the womb has a profound effect on early development. A meta-analysis of 14 studies found that maternal smoking during pregnancy was associated

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with a 50% higher risk of childhood obesity.[52] Maternal weight gain during pregnancy leads to insulin resistance and gestational diabetes, which manifests as large birth size.[53] Furthermore, several studies have found a direct association between birth weight and BMI later in life.[54–56] We now know that gestational weight gain and gestational diabetes contributes to obesity in the offspring.

Postnatal influences

The postnatal environment is just as crucial to setting the pace of weight gain throughout life. Modifiable postnatal factors that affect weight in later life include: (1) Sleep duration: interestingly, there is a direct association of short sleep duration in babies with weight gain in infancy as well as adulthood.[57] A meta-analysis of 42 studies concluded that short sleep duration is a risk factor for development of obesity at any ages.[58] Research found antenatal depression, introduction of solid foods before 4 months and infant television viewing to be responsible for decreased infant sleep duration[59]; (2) Breastfeeding duration: a meta-analysis of 17 studies reported that a longer duration of breastfeeding was associated with a lower risk of weight gain in the baby, with each month of breastfeeding reducing the risk by 4%[60]; and (3) rate of weight gain in infant: the speed at which a baby gains weight has also been associated with obesity in later life. A systematic review of 10 studies reported a link between rapid early growth and the risk of obesity in later life.[61]

Insufficient sleep

Sleep regulates glucose metabolism and neuroendocrine function. Lack of sleep reduces glucose intolerance, insulin sensitivity and leptin levels and increases the levels of cortisol and ghrelin (and, therefore, appetite).[62] Sleep and exercise are mutually beneficial because exercise has long been known to contribute to a good night's sleep and recent research has shown that poor sleep results in low levels of physical activity.[63] One study also found that a change in the mean duration of sleep increased the risk of obesity by modifying the effects of fat mass and obesity-associated gene (FTO) variants on BMI.[64]

Drugs

Certain therapeutic drugs cause significant weight gain in some people. These are detailed in Table 3 along with the most probable pathophysiology causing the weight gain.[65–69]

Medical conditions

Medical conditions may cause weight gain via different mechanisms. For example, insulinoma is a rare neuroendocrine tumour of the pancreas, which is mostly benign and presents with weight gain and symptoms of hypoglycaemia because of oversecretion of insulin by the tumour cells. It can occur in isolation or as part of the multiple endocrine neoplasia (MEN-1) syndrome. Insulinomas are very rare, with an occurrence of between 1 and 32 per million per year.[70] Obesity can also be related to hormonal disbalance. For example, decreased levels of thyroxine associated with hypothyroidism cause the overall metabolism to slow down and, hence, cause weight gain. In Cushing's syndrome, increased serum cortisol levels cause higher serum insulin levels, which increase glucose metabolism and fat synthesis. High cortisol also increases appetite and cravings for sweet and salty food. A similar mechanism related to high insulin levels causes weight gain in patients with polycystic ovarian syndrome. Metabolic syndrome is another condition which refers to the co-occurrence of hypertension, insulin resistance, impaired glucose tolerance, abdominal obesity, elevated triglycerides and low high-density lipoproteins. Weight gain results mainly from high insulin levels in this condition. Weight gain-especially around the neck-causes airway narrowing, sleep apnoea and disturbed sleep (known as obstructive sleep apnoea). If left untreated, this condition hinders weight loss because the disturbed sleep cycle results in higher cortisol levels. Finally, conditions causing oedema, such as congestive heart failure and hypoproteinaemia because of malabsorption or deranged liver and kidney function, can cause overall weight gain. However, it can be argued that this is not true weight gain because it relates to fluid rather than fat build-up.

Table 3. Drugs associated with obesity

Drugs causing obesity	Reason
Antidepressants	Increased levels of serotonin, dopamine, norepinephrine increase appetite and possibly interfere with metabolism[25]
> Amitriptyline	
> Nortriptyline	
> Phenelzine	
> Citalopram	
Antipsychotics	Increased appetite and possibly increased craving for sweet or fatty food[65]
> Lithium	
> Clozapine	
> Quetiapine	
> Haloperidol	
Antidiabetics	
> Thiazolidinediones	Increased fat mass and fluid retention[66]
> Sulfonylureas	Increased insulin release, increased glucose absorption; excess glucose is converted to fat[67]
> Insulin	Fear of hypoglycaemia causing increased food intake[67]
α_2-adrenergic agonists	Fluid retention[68]
> Clonidine	
β_2-adrenergic agonists	Decreased metabolism and altered energy homeostasis[69]
> Atenolol	
Steroids	Increased cortisol levels lead to raised serum glucose levels and, consequently, raised insulin levels

Socioeconomic status

According to the 2021–22 National Child Measurement Programme in England, there is a strong link between deprivation and children living with obesity.[71] The prevalence of severe obesity in reception-aged children was nearly three times as high in the most deprived areas (ie 4.6% as opposed to only 1.3% in children

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living in the least-deprived areas). Similarly for older children, ~31.3% year 6 children (age 10–12 years) from the most-deprived areas were living with obesity compared with 13.5% in the least-deprived areas.[71] Socioeconomic status is also an important determinant of obesity in adults.[72]

Among ~9,000 non-Hispanic Europeans, low and/or decreasing socioeconomic status increased the genetic risk score for obesity, whereas high/improving socioeconomic status dampened this association. Spinosa and colleagues linked this association to psychosocial distress and emotional eating.[73] This contrasts with another study that explored the relationship between obesity, gross national product and socioeconomic status from 67 countries. According to this study, obesity increased with the increase in the economic development of a country.[74] Moreover, an interesting trend was noticed: in lower income countries, those people with higher socioeconomic status were more likely to be obese, whereas, in higher income countries, those with higher socioeconomic status were less likely to be obese. The authors attributed this phenomenon to the fact that, in the former, improving socioeconomic status led to eating high-calorie foods and avoiding physical activity, whereas, in the latter, individuals responded with increased physical activity and healthy eating. Certain lower income countries, such as India, face the conjoint challenge of an increase in obesity along with malnutrition.[75]

Ethnicity

Certain ethnicities are more predisposed to gaining weight than others. Data show that, in November 2021, ~63.5% adults were overweight or living with obesity.[76] Out of these, 72% adults were of Black ethnic origin, 64.5% were White British, 57% were Asian, 57.9% were 'other'–White, and 59.5% were mixed ethnic groups. Only 37.5% adults of Chinese ethnicity were living with excess weight or obesity.

Psychosocial stress

According to one study of 2,983 adults from a community in Chicago, USA, multiple stressors were found to increase the risk of obesity.[77] Other studies have discovered that chronic psychosocial stress can interact with genetic predisposition to determine adiposity. Stress increases chronic exposure to glucocorticoids (promoting abdominal obesity) and contributes to emotional/comfort eating.

Endocrine disrupting chemicals

Environmental chemicals that disrupt the hormone action in the human body are called endocrine-disrupting chemicals (EDCs).[78] EDCs have lipophilic structures and, thus, can interfere with hormonal action and upset normal endocrine functions. Some EDCs interfere with steroid and thyroid hormones, whereas others disrupt metabolism and upset the function of adipocytes (which secrete hormones and act as an endocrine organ).[79] EDCs interfering with adipocyte function can lead to obesity[80–82] and, thus, are also referred to as obesogens.[82,83] Foetuses and neonates are most susceptible to obesogenic EDCs.[83,84] One study found that exposure to diethylstilbesterol (DES) during the neonatal period predisposed mice to becoming obese at 4–6 months of age.[85] EDCs include several chemicals in our environment, the most relevant of which are detailed in Table 4.[86–88]

Table 4. Endocrine-disrupting chemicals[80]

Chemical	Description
Tributylin	Used to paint ship hulls; inhibits aromatase (enzyme converting testosterone to oestrogen)[86,87]
Diethylstilbesterol (DES)	Synthetic oestrogen that is no longer used in humans but still used to enhance fertility in farm animals[88]
Persistent organic pollutants	
Dichlorodiphenyltrichloroethane (DDT)	Insecticide
Dichlorodiphenyldichloroethylene (DDE)	Breakdown product of DDT
Polychlorinated biphenyls (PCBs)	Industrial persistent organic pollutants
Bisphenol A (BPA) and phthalates	Used in the manufacture of plastics
Polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls	Used as flame retardants
Parabens (alkyl esters of p-hydroxybenzoic acid)	Used as antimicrobial agents for preservation of food, drugs and personal care products
Phyto-oestrogens	Naturally present in soybeans, legumes, lentils and chickpeas

Gastrointestinal microbiome

Gastrointestinal microbes were termed 'friends with benefits' by John F. Cryan (a key figure in research on the gut microbiome). The normal human gut microbiome, ~100 trillion in number,[89] comprises *Firmicutes*, *Bacteroides*, *Proteus*, *Actinomycetes and Fusobacteria*.[90] Two phyla are predominantly seen to inhabit people with obesity: Firmicutes and Bacteroides. Turnbaugh and colleagues[91] found that Firmicutes were abundant in the microbiota of obese mice. Other studies found a link between obesity with *Akkermansia muciniphila*; its supplementation resulted in improved metabolism, insulin sensitivity and plasma triglycerides.[92,93]

Bifidobacteria has been used to treat obesity in young people, also improving insulin sensitivity.[94] Factors affecting the gut microbiome include the mode of delivery (normal vaginal birth or Caesarean section), duration of breastfeeding, age at which solid food is introduced, diet and the use of antibiotics throughout life.[95]

Approach of healthcare professionals

Obesity management is directly influenced by the approach of healthcare professionals to obesity and, therefore, it is imperative to evaluate our approaches to patients living with obesity.

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The attitude of the general public also needs to be modulated toward children and adults with obesity. The stigma associated with increased weight strongly impacts mental and physical health and leads to a lifetime of low self-esteem. According to the World Obesity Federation, weight bias eventually leads to weight stigma. There is a general weight bias where people associate laziness, low intelligence, poor hygiene and lack of will-power with obesity.[96] Although this is not a direct cause of obesity, it can be argued that it leads to increasing obesity prevalence as people with obesity are disheartened and avoid seeking medical advice. In one study, the motivation to lose weight was studied in 10,854 people with obesity and it was found that support from healthcare professionals and a positive interaction with them helped engage patients and motivated them to lose weight.[97]

The importance of involving a multidisciplinary team for obesity management in underlined by some clinicians. Obesity is a product of multiple factors and, therefore, requires input by multidisciplinary team and support from specialist obesity nurses and dietitians to develop a personalised plan for each patient.

Conclusion

The causes of obesity are a nexus of communal and individual factors. Although most of these are modifiable, controlling all contributing factors is a real challenge. The Foresight report [1] describes these risk factors as 'interconnected' and grouped them into different clusters on an 'obesity map' to enable easier understanding and management of obesity. These groups include the physical activity environment, food consumption, food production, individual psychology and social psychology. Understanding these risk factors individually and appreciating their interconnection is key to understanding the causes of obesity and working toward a plausible solution to curb this worldwide pandemic.

Key practice implications

- The causes of obesity are manifold and cannot be attributed to one single cause, such as overeating.
- In most cases, including polygenic obesity, the factors causing obesity are modifiable.
- A multidisciplinary team is necessary to decide upon a personalised plan and help support people living with obesity.
- Healthcare professionals must appreciate the complexity of obesity and acknowledge that it is best managed with a multidisciplinary, patient-centred approach.
- Efforts to prevent and treat obesity must be made by individuals as well as governments to promote a healthy environment. ■

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