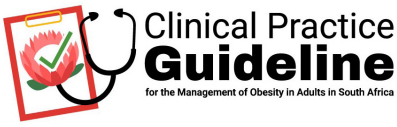
The science of obesity



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Cite this chapter: May W, Goedecke JH, Conradie-Smit M. The science of obesity.
S Afr Med J 2025;115(9b):e3600. https://doi.org/10.7196/SAMJ.2025.v115i9b.3600

KEY MESSAGES

- Obesity arises from a complex interplay of genetic, biological, behavioural, psychosocial and environmental factors.[1]
- Obesity has a strong genetic component, with twin studies indicating a 50 - 80% concordance in body mass index (BMI) and regional fat distribution. A Swedish study on identical twins raised apart found no correlation between BMI and their adoptive families but a strong correlation with their biological twin, despite being raised in separate households.[1]
- The regulation of appetite, body weight and energy balance is highly complex, governed by a network of hormonal signals from the gut, adipose tissue and other organs, as well as neural signals that shape eating behaviours. Many of these signalling pathways are disrupted in people living with obesity.[1]
- Since body weight is homeostatically regulated, weight loss triggers physiological adaptations that promote weight regain. These include a decrease in energy expenditure, and hormonal changes that enhance appetite while reducing satiety.[1]
- Adipose tissue influences the central regulation of energy homeostasis, and excess adiposity can become dysfunctional, with production of proinflammatory cytokines and associated metabolic health complications.[1]
- Individual variations in body composition, fat distribution and function result in a highly variable threshold at which excess adiposity begins to negatively affect health.[1]
- Emerging research in obesity science has widened to include brown fat, the gut microbiome, immune system regulation, and the intricate mechanisms that regulate body weight.[1]
- Obesity can be classified as primary, secondary and genetic obesity.
- In the current management of primary obesity, prevention (the path in) and treatment (the path out) need to be distinctly separated.
- Effective primary obesity treatment requires an integrated approach that addresses the non-modifiable cause (increased appetite) together with modifiable contributors (poor diet quality, increased stress, poor sleep, reduced physical activity and increased sedentary behaviour). Behavioural modification and psychological support provide additional benefit.
- Effective treatment in genetic and secondary obesity requires treatment of the underlying causes along with modification of the contributors.

Introduction

Obesity is a complex chronic disease in which abnormal or excess body fat (adiposity) impairs health, increases the risk of long-term medical complications, and reduces lifespan. However, owing to individual differences in body composition, body fat distribution and function, the threshold to which adiposity impairs health is highly variable among adults.[2] Epidemiological and population studies define obesity using the body mass index (BMI), calculated as weight in kilograms divided by height in metres squared (kg/m^2). The BMI is a fairly reliable anthropometric measurement to stratify obesity-related health risks at the population level. However, at an individual level it can both underestimate and overestimate adiposity and provide inadequate information about the health of an individual.[3]

Obesity is a chronic disease caused by the complex interplay of genetic, metabolic, behavioural and environmental factors; the latter are thought to be the proximal cause of the dramatic rise in the prevalence of people living with obesity (PLWO).[4] The increased availability of processed, affordable and effectively marketed food, an abundance of sugar-sweetened beverages, economic growth, behavioural changes, and rapid urbanisation in low- and middle-income countries are some of the key drivers that promote overconsumption of food.[5] Concerning energy expenditure, the level of physical activity for leisure has been relatively stable or slightly elevated over the past 50 years.[6] This chapter attempts to address the cellular and molecular pathogenesis of obesity to inform a rational approach to the management of this complex disease.

The neurobiology of appetite control and energy balance dysregulation

In states of energy imbalance, where food intake exceeds energy expenditure, the energy surfeit is converted into fat and stored in adipose tissue. Body weight is meticulously regulated for survival

during unpredictable periods of feast and famine. Even a small surplus of caloric intake (less than 1%) over energy expenditure can accumulate over years to cause weight gain.[4]

The brain and obesity

The brain probably plays the most important role in PLWO and energy balance. A simple approach to understanding the neurobiology of PLWO may be to divide the brain into three main areas that regulate weight: the hypothalamus, the mesolimbic area, and the frontal lobe. Understanding the regulation of each area and the importance of the connections between these areas creates a greater understanding of obesity.

The hypothalamus (homeostatic area)

The brain, notably the hypothalamus, has long been known to play a central role in energy homeostasis by regulating energy intake and expenditure. Recent advances have provided new insights into the complex control of appetite, with major implications for body weight regulation.[7-9]

The arcuate nucleus of the hypothalamus, often termed the hunger centre, controls feeding behaviours. There are two sets of neuronal populations that reside in the arcuate nucleus. Neurons co-expressing agouti-related protein (AgRP) and neuropeptide Y (NPY) in the arcuate nucleus, when activated by hormonal and neural signals from the gut, adipose tissue and peripheral organs, stimulate hunger sensation and trigger food-seeking behaviours.[10]

The activity of these neurons is rapidly reduced upon access to food. These neurons are primarily involved in food seeking or the homeostatic control of appetite. They mediate their downstream effects via the Y1 and melanocortin-4 receptors located in the nearby paraventricular nucleus. The AgRP/NPY neurons project directly to the second set of neurons co-expressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), which suppress food intake by firing through the downstream inhibitory Y1 and gamma-aminobutyric acid receptors.[10] The homeostatic control of appetite in the arcuate nucleus is influenced by a number of factors: the nutritional status of the organism, nutrient sensing and availability, taste, smell and food preferences.

The mesolimbic (hedonic) area

In addition to the homeostatic appetite control centre in the hypothalamus, other neural systems are involved and provide the emotional, pleasurable and rewarding aspects of eating, also known as hedonic eating. Hedonic eating is based on the feelings of reward and pleasure that are associated with seeing, smelling or eating food.[11] This pathway means that the brain can crave food, or enjoy food, even when the person is completely satiated. Signals are transmitted by the dopaminergic, opioid and endocannabinoid pathways via the respective receptors in downstream targets.[12] Dopamine is released in the brain, signalling a desire to eat, in response to emotional triggers, such as sadness, or environmental triggers, such as the smell or sight of delicious food.[13] Opioid and endocannabinoid signals are released when food is consumed, and are responsible for the feeling of pleasure associated with eating.[14] Some PLWO may have a heightened anticipation (wanting) of the pleasure of food driven by a dysregulation of dopamine.[15] Unfortunately, the pleasure of eating the food (liking) is also dysfunctional and is downgraded compared with the anticipation, resulting in a need to overeat to achieve the level of the anticipation.[16] This leads to a vicious cycle and can create an environment of constant overeating. Controlling this dysregulation between wanting and liking with medications, hormonal regulation and cognitive behavioural therapy is a target for the treatment of PLWO.

The lateral hypothalamus is a brain region that is tied to consummatory behaviours and mediates positive reinforcement.[17] These circuits drive food consumption and hedonic eating. Hedonic eating is also regulated by the corticolimbic system, which consists of the cortical areas, basal ganglia, hippocampus and amygdala in the midbrain.[9]

The frontal lobe (cognitive functioning)

The frontal lobe (cognitive functioning) is responsible for executive functioning and overriding primal behaviours driven by the mesolimbic system.[18] Cognitive functioning works well under optimal conditions (rest, oxygen, support, and decreased stress) that help to deal with adverse situations. Excessive eating often occurs in the evening, during suboptimal conditions, following the accumulation of stressors throughout the day, fatigue, and lower levels of willpower.

There are also other areas of executive dysfunction in some PLWO, primarily in decision-making, response inhibition and cognitive flexibility.[19] PLWO may have a dysfunctional connection between the cognitive lobe and the rest of the brain that leads to the inability to control eating behaviours.[18]

Current research indicates that there is a significant crosstalk between homeostatic and hedonic eating, which is mediated by many of the endocrine and gut-derived signals. Leptin, insulin, ghrelin and glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) also act on the dopaminergic neurons in the midbrain to modulate food reward and hedonic eating.[20]

Another appetite-suppressing network involves calcitonin gene-related peptide (CGRP) neurons in the parabrachial nucleus (PBN) that potently suppress eating when activated, but do not increase food intake when inhibited. PBN-CGRP neurons are activated by signals associated with food intake, and they provide a signal of satiety that has negative valence when strongly activated.[9]

Recent data highlight that the hypothalamic circadian clock network is actively involved in the alignment of fasting and feeding with the sleep/awake cycle through the AgRP neurons by co-ordinating the leptin response and glucose metabolism with arousal.[21] Cognitive areas in the prefrontal cortex exert executive control on the decision to eat and the food choices.

In summary, the biological control of appetite is complex and involves the integration of the central neural circuits with signals from the gut, adipose tissue and other organs to influence homeostatic and hedonic eating, and executive control by higher brain centres on the decision of when and what to eat. These neural networks have also been shown to be altered in PLWO.

Adipose tissue and food intake

Leptin and insulin are the two key hormones that communicate to the homeostatic control concerning the long-term energy reserve and nutritional status of the body. Leptin is a fat-derived hormone that is secreted by white adipose tissue in proportion to the body's fat mass. Leptin and insulin bind to their respective receptors in the arcuate nucleus to decrease food intake and increase energy expenditure. In states of decreasing body fat stores, circulating leptin levels fall and signal the hypothalamus to inactivate the POMC/CART-expressing neurons to promote feeding, while simultaneously lowering its inhibitory effect on the AgRP/NPY-expressing neurons to increase appetite and decrease energy expenditure. As adiposity increases, leptin levels increase in circulation and exert negative feedback to

suppress appetite to prevent further weight gain. However, leptin resistance can also occur in some people who have excessive adiposity, which can perpetuate the vicious cycle of fat mass accretion.[22]

Gut-derived signals on nutrient availability

GLP-1, a powerful incretin, and peptide YY3-36 (PYY), which delays gastric emptying, are potent anorexigenic gut hormones that are secreted by enteroendocrine L cells in the small bowel in response to food ingestion. They both promote satiation (meal termination) and satiety by activating the POMC/PYY neurons while reducing hunger via the AgRP/NPY neurons. They communicate to the homeostatic system the prandial state and nutrient sensing and availability.[23] Oxyntomodulin enhances satiety and decreases food consumption.[24]

Several other gut hormones, such as glucose-dependent insulinotropic polypeptide, are also involved in the control of appetite and energy expenditure. Cholecystokinin (CCK) is secreted in response to fat and protein ingestion. CCK stimulates gallbladder contractility and pancreatic enzyme secretion and slows gastric emptying. CCK also mediates fat and protein satiation, as well as having glucose-regulatory effects on the hypothalamus via the vagal afferent fibres. Pancreatic polypeptide is secreted by the F cells in the pancreatic islets under vagal control and is released during the postprandial phase to enhance satiety.[24]

In contrast, ghrelin is an orexigenic hormone produced in the gastric fundus that increases hunger and stimulates food intake. The ghrelin level rises in the fasted state and falls rapidly following meal ingestion.

Upon food ingestion, sensory information on the volume and composition of the meals, and notably satiation, is relayed to the nucleus tract solitarius (NTS) in the brainstem by vagal afferent fibres. The NTS in turn integrates and transmits the signals to the homeostatic control pathways in the hypothalamus, primarily influencing satiety and meal termination.[8]

Genes associated with obesity

The genetic and epigenetic variability among individuals influences how they self-regulate food and explains why not all people exposed to obesogenic factors develop obesity. Many genes have been linked to the development of PLWO, and more than 140 genetic regions are now known to influence obesity traits.[25] Studies with twins have shown a relatively high degree of concordance of body mass and eating behaviours (50 - 80%).[26] Linkage studies in rodents with obesity caused by single-gene mutations and candidate gene-based approaches in humans with severe obesity have identified a number of mutations in genes involved in appetite control.[27] Loss-of-function mutations in leptin, leptin receptors, pro-opiomelanocortin and melanocortin-4 receptors are examples where individuals display intense hyperphagic and food-seeking behaviours. Correction of these rare defects, such as the treatment of leptin-deficient PLWO with recombinant leptin, can result in significant weight loss.[28] Eleven monogenic forms of obesity have been discovered. They are rare, and the most common cause, heterozygous mutation in *MC4R*, accounts for about 2 - 5% of severe obesity in the paediatric population.[29] Most of these obesity-associated genes are found in the central nervous system and are mainly involved in the functional and structural aspects of neurotransmission. Syndromic forms of obesity are also uncommon; they include Prader-Willi, Bardet-Biedl and Cohen syndromes. Endocrine causes of obesity, such as Cushing's disease, hypothyroidism and pseudohypoparathyroidism, are also rare and make up fewer than 1% of all cases of obesity.[30]

Adipose tissue and excess adiposity

Adipose tissue has long been viewed as a passive energy repository to store fat in the form of triglycerides, so that it can be released during periods of energy demand such as starvation or exercise. Adipose tissue is a dynamic organ that can respond to alterations in energy stores through adipocyte hypertrophy and hyperplasia. Adipose tissue can be as high as 50% of total body composition.[31] In adults, subcutaneous fat accounts for about 85% of total body fat, and intra-abdominal or visceral fat accounts for the rest. Within each fat depot, white adipose tissue is comprised of large mature adipocytes, which account for about half of all cells, while preadipocytes, endothelial cells, macrophages and inflammatory cells account for up to 10% of cells. Adipose tissue expansion is accomplished via adipocyte hypertrophy, where cell size can increase up to seven-fold. Adipocyte hyperplasia relies on adipogenesis, which involves recruitment, proliferation and differentiation of preadipocytes to acquire the phenotype of mature adipocytes. Regulation of adipogenesis is meticulously controlled at the transcriptional level. The key players are CCAAT enhancer-binding proteins and peroxisome proliferator-activated receptor gamma.[32] These transcription factors are subject to modulation by circulating hormones and nutrients, and they largely determine body fat distribution. Adipogenesis is associated with the production of a large number of proteins; many of these function as important signalling molecules in glucose and lipid metabolism, and energy homeostasis. Visceral fat is different from that of subcutaneous adipose tissue with regard to decreased insulin sensitivity, increased lipolytic activity, lower angiogenic potential, increased expression of proinflammatory adipokines, and decreased production of 'good' hormones and cytokines.

Adipose tissue-derived hormones and cytokines

Among the adipose tissue-derived proteins, leptin and adiponectin have been extensively studied and provide new insights into adipose tissue biology and regulation. Leptin is secreted by adipocytes, and its plasma levels increase with weight gain and decrease with weight loss, in keeping with its key role as a signal of adipose tissue stores. Leptin binds to specific receptors, which belong to the interleukin-6 receptor family of class I cytokine receptors, and exerts an inhibitory effect on food intake and appetite. Its effect is not limited to appetite regulation and energy homeostasis; it also exerts a wide array of endocrine and metabolic influences in the body. It suppresses insulin secretion from pancreatic beta cells and plays a role in insulin resistance.[33]

Adiponectin is a hormone abundantly produced by adipocytes. It exerts pleiotropic effects on a broad array of physiological processes, including energy homeostasis, vascular function, systemic inflammation and cell growth. One of its most important functions appears to be an insulin-sensitising agent that stimulates insulin gene expression and secretion. Adiponectin levels are inversely correlated in PLWO and insulin-resistant states and reflect whole-body insulin sensitivity. Circulating adiponectin levels are lower in PLWO and in individuals with polycystic ovarian syndrome, impaired glucose tolerance or type 2 diabetes. A decreased adiponectin level, or hypoadiponectinaemia, is associated with an increased risk of developing type 2 diabetes in otherwise healthy people.[22]

Adipose tissue dysfunction

Adipose tissue dysfunction may develop under conditions of continuous positive energy balance in people with an impaired expandability of subcutaneous adipose tissue. The inability to store excess calories in healthy subcutaneous fat depots can lead to increased visceral fat accretion and ectopic fat deposition in the

liver, muscle and epicardium of the heart. Adipose tissue expansion often leads to dysfunctional changes, which are characterised by inflammation, inappropriate extracellular matrix remodelling, and insufficient angiogenic potential. Cellular hypoxia is thought to be the driver for adipose tissue dysfunction.[34] A consequence of dysfunctional adipose tissue, especially in the visceral depots, is augmented production of fat-derived proinflammatory cytokines, or adipokines. These adipokines, which include tumour necrosis factor alpha, interleukins, C-reactive protein and monocyte chemotactic protein-1, in turn can accelerate the progression to fibrosis, accelerated angiogenesis, apoptosis and autophagy by promoting the migration of immune cells into adipose tissue. Importantly, dysfunctional adipose tissue can lead to the development and progression of a myriad of adiposity-related comorbidities, such as type 2 diabetes, hypertension, dyslipidaemia, metabolic disease-associated liver disease, cardiometabolic risks and atherosclerotic cardiovascular disease.[35]

Brown and beige fat

Emerging data indicate that, in addition to white adipose tissue, brown adipose tissue, which is involved in whole-body energy homeostasis through non-shivering thermogenesis, also exists in small quantities in adult mammals and humans. Beige adipocytes, which are inducible forms of thermogenic adipocytes, have also been reported in white adipose tissue. Recruitment of beige adipocytes, or 'beiging' of white fat, can be induced by chronic exposure to cold temperatures and, to some extent, exercise.[36] Further elucidation of the potential roles of brown/beige fat in the regulation of whole-body energy metabolism and glucose/lipid homeostasis may open new avenues for the management of PLWO in the future.

Gut microbiome and obesity

The gut microbiota is the collection of all the micro-organisms in the gastrointestinal tract.[37] Recent data suggest that the gut microbiota may influence weight gain and insulin resistance through various pathways, including energy harvesting from bacterial fermentation, short-chain fatty acid signalling, and bile acid metabolism.[38] Gut microbiota composition and function may also affect hunger pathways, but their precise role in regulating food intake has yet to be determined.[39]

The majority of the research into gut microbiota has been conducted in animal studies. These studies have determined that certain bacteria are responsible for promoting energy retention, and others for energy expenditure.[40] Earlier human studies indicated that the primary bacteria involved in weight homeostasis are the firmicutes that promoted weight gain and the bacteroidetes that are more often present in lean individuals.[41] However, a recent systematic review found the Proteobacteria to be the most consistent phylum associated with obesity.[42] Faecal transplants from lean individuals to PLWO have been conducted, but are in their infancy and require more research. A recent closer analysis of the trials concerning the role of microbiota in mice and humans revealed that although earlier studies initially appeared to show a significant effect, their impact was less substantial upon scrutiny. Furthermore, later research, including human trials, has not provided evidence supporting the gut microbiota's role in manipulating body weight.[43,44] The use of prebiotics to alter gut flora in favour of bacteria that promote weight loss is being investigated.[45] Metabolic and bariatric surgery and medications may have an effect on the gut microbiome, potentially explaining some of the reasons for success with these interventions.[46,47] More data are leading us to understand how the gut microbiota interacts with brain neurochemistry to influence weight changes.[48] The field of microbiota is still a developing one and may result in new interventions, but as yet there are few practical applications. Research into the role of other gut organisms including archaea, viruses, fungi and protozoa is needed.

Adiposity-related medical complications

Adipose tissue dysfunction and excessive adiposity predispose to the development of many medical complications. The most common metabolic complication is insulin resistance and, in susceptible individuals, type 2 diabetes. The predominant theory explaining the link between obesity and cardiometabolic risk is described as obesity inducing an insulin-resistant state through two primary mechanisms: a defective insulin signal, and chronic tissue inflammation with increased adipose tissue macrophages.[49] Adipose tissue is a source of increased levels of circulating free fatty acids due to increased lipolysis. In the liver, increased free fatty acid flux results in increased glucose production, triglyceride synthesis and secretion of very low-density lipoprotein. Other lipid abnormalities include reductions in high-density lipoprotein and increased levels of small dense atherogenic low-density lipoprotein particles. High levels of circulating free fatty acids are also taken up by muscle and the pancreas and can lead to the development of ectopic fat. Free fatty acids impair insulin secretion in the pancreas and diminish insulin signalling in muscle and the liver, giving rise to insulin resistance in these organs.

It appears that adipose tissue from the visceral depot is more important as a source of excessive circulating adipokines and inflammatory mediators than the subcutaneous depots.[50,51] Importantly, inflammatory cells, such as macrophages and monocytes, migrate to visceral fat of PLWO, further augmenting the inflammatory state, and impairment of insulin sensitivity.

Adiposity is also linked to increased risk of many forms of cancer through the release of hormonal growth factors and inflammatory adipokines.[52]

Benefits of modest weight loss

Obesity management, as well as cardiorespiratory fitness, are critically important in improving the overall cardiovascular health of PLWO. Indeed, obesity management benefits all PLWO, regardless of the amount of weight loss. Patients able to achieve a weight loss of 5 - 10% of their initial weight will experience a reduction in their cardiovascular disease risk factors, improvement in lipid profiles, reductions in blood glucose and glycated haemoglobin, and a decreased risk of developing type 2 diabetes and other obesity-related complications.

The benefits of modest weight loss (5 - 10%) are worth emphasising with regard to the prevention and management of type 2 diabetes. In the landmark National Institutes of Health-sponsored multi-centre Diabetes Prevention Program, 3 234 PLWO who also had impaired glucose tolerance were randomised to usual treatment (control) or to intensive behavioural intervention.[53] The aim was to achieve and maintain a reduction of 7% of their initial body weight through a –500 kilocalorie/day deficit hypocaloric diet and 150 minutes or more per week of moderate-intensity physical activity. A third group received metformin 850 mg twice daily. After a 2.8-year follow-up, the behavioural lifestyle intervention group had lost 5.6 kg (6%), whereas the metformin group lost 2.1 kg (2.2%) and the control group lost 0.1 kg. Compared with the control group, the incidence of diabetes was reduced by 58% with behavioural intervention and by 31% with metformin.[53] The benefits of modest weight loss

from the 2.8 years of intensive behavioural intervention persisted in the 10-year Diabetes Prevention Program Outcomes Study.[54] The researchers concluded that each kilogram (1.1%) of body weight loss through intensive behavioural modification was associated with a 16% relative risk reduction in the development of type 2 diabetes in individuals with impaired glucose tolerance and delayed the onset of disease by 4 years.[54] Metformin treatment was half as effective as intensive behavioural intervention and weight loss. A meta-analysis of 17 randomised clinical trials on the effectiveness of behavioural intervention to prevent or delay diabetes found that in over 8 000 trial participants with impaired glucose tolerance, the pooled hazard ratio was 0.51 for behavioural intervention against standard counselling; this corresponded to numbers needed to treat for benefit of 6.4.[55]

Rational approach to obesity management

To best understand the modern management of PLWO, it is worthwhile trying to gain insight into our current, evolving understanding of PLWO. As mentioned earlier in the chapter, obesity is defined as a chronic disease associated with abnormal or excess body fat that impairs health and increases mortality. The recent Lancet Commission report on the definition and diagnostic criteria of clinical obesity[3] categorises obesity into three types: genetic, secondary, and primary obesity. While genetic obesity stems from both monogenetic disorders (as opposed to polygenetic disorders) such as melanocortin-4 receptor mutations and leptin deficiency, as well as non-monogenetic disorders such as Prader-Willi syndrome, and secondary obesity arises from medical conditions or medications, primary obesity – the most prevalent form – has no clear identifiable underlying cause. Managing primary obesity requires recognising that currently the path into obesity differs from the path out, and that for effective treatment the path out requires identifying both the causes and contributors in the treatment regimen. The subsequent discussion will focus on primary obesity and attempt to clarify the underlying processes. It is by no means a comprehensive overview, but serves to highlight our current incomplete understanding of the disease, as well as explain our current management approach.

Obesity can be seen as two distinct, overlapping issues, namely the personal fat threshold and the global rise in body weight. These two key concepts have often been conflated, but require separate attention.

The personal fat threshold

The **first key concept** concerns the **personal fat threshold (PFT),** first coined in 2015.[56] This concept refers to an individual's susceptibility to developing obesity-related conditions, such as type 2 diabetes, once they surpass a certain level of fat accumulation. Essentially, crossing this threshold triggers metabolic complications. The most compelling evidence supporting this concept comes from the work of Roy Taylor and colleagues and is based on his original twin cycle hypothesis.[57] This hypothesis proposes that chronic excess calorie intake leads to fat accumulation in the liver, which eventually spills over into the pancreas. The resulting interaction between the liver and pancreas disrupts insulin secretion and action, leading to hyperglycaemia. This hypothesis was tested in the Counterpoint study,[58] which showed that individuals with newly diagnosed type 2 diabetes (within 4 years from diagnosis) could achieve normal fasting glucose levels within just 7 days of starting a very low-calorie diet. During this period, liver insulin sensitivity returned to normal and liver fat decreased by 30%. Interestingly, while liver function improved rapidly, insulin secretion took about 8 weeks to return to normal.

In the Counterbalance study,[59] the transition from the initial low-calorie diet to a more sustainable eating plan was carefully managed, with participants receiving intensive education. This study showed that weight loss and improved metabolic function were maintained long term, especially in those with a shorter duration of diabetes. By 6 months, diabetes remission was maintained in those with no weight regain, along with improvements in liver and pancreas fat, while stable insulin secretion was sustained.

Further clinical confirmation of the PFT came from the Diabetes Remission Clinical Trial (DiRECT), which found that significant weight loss was key to achieving diabetes remission in people living with diabetes for less than 6 years. Participants with a BMI ranging from 27 to 45 kg/m^2 who lost 15 kg or more had an 86% remission rate at 1 year and 70% at 2 years.[60,61] The Reversal of Type 2 diabetes Upon Normalisation of Energy intake in the non-obese (ReTUNE) study tested the PFT across a lower BMI range (21 - 27 kg/m^2) and showed a 70% remission rate at 1 year with a median weight loss of 6.5% (5.5 - 10.2%), further validating the concept of the PFT.[62] These studies provide compelling evidence for the existence of organ-specific fat thresholds, which are specific to each individual and vary across the BMI range, and which can be reversed with timely intervention.

The global rise in body weight

The **second key concept** in the obesity landscape is the **global rise in body weight**. While this phenomenon is linked to PFTs, it primarily concerns the factors driving individuals' weight towards and beyond these thresholds. In other words, although each person has distinct organ-specific fat thresholds, these thresholds may not be reached without external forces promoting weight gain. Notably, these PFTs may be achieved with a normal BMI as described above in the ReTUNE study,[62] highlighting the complexity of the disease. In addition to driving an individual toward their PFT, excessive fat mass can also lead to mechanical complications, either on their own, concurrently with, or in combination with PFT-related problems.

Understanding why the world is gaining weight requires us to examine two key questions: (*i*) how does the body regulate its weight? and (*ii*) how are these regulatory systems compromised?

Models of body weight regulation

While the mechanisms of weight regulation are still not fully understood, some of the current theories include the **set-point model,**[63] the **dual-intervention point (DIP) model,**[63,64] and the **Leeds model of appetite regulation**.[65] The set-point model of body fat regulation suggests that the body maintains fat levels within a specific range, adjusting energy intake and expenditure when fatness deviates from this point. The set-point model is based on the 1953 article by Kennedy,[66] in which he introduced the concept of 'lipostasis', a feedback mechanism aimed at stabilising body fat stores via hypothalamic regulation.

Despite its popularity, the set-point model has three major flaws. First, weight stability can result from factors other than a set point, such as passive feedback from energy expenditure influenced by fat-free mass, as described in the Leeds model of appetite regulation (discussed further below).[65] Second, the model's prediction of gradual weight gain conflicts with real-world patterns, where weight can fluctuate significantly during holidays or weekends.[67-71] Third, population averages mask individual variations, challenging the idea of a stable set point. Additionally, the theory's evolutionary basis is weak; fat storage's impact on survival is likely to have varied across different environments, making a universal set point improbable.[63]

The discovery of leptin, a hormone produced by fat cells, has provided a molecular basis for the set-point model by linking fat stores to appetite regulation.[72] However, as previously discussed, leptin's role is more complex than simply signalling fat levels. In individuals without leptin mutations, elevating leptin levels exogenously does not trigger the same response, invoking the concept of 'leptin resistance'.[73] In summary, careful examination of the set-point model, as well as evolutionary considerations, raise doubts about its existence.[63]

In contrast, the DIP model[63,64,74] proposes a more flexible system, where the body tolerates a wide range of fat levels but triggers a response when thresholds are breached, either too high (upper intervention point, UIP) or too low (lower intervention point, LIP). This system is postulated to have evolved as a survival mechanism: at the lower end, to prevent starvation and support reproduction; at the higher end, to avoid excess fat that could increase the risk of predation. It is important to understand that these two points are proposed to be entirely separate and independently regulated processes, with leptin being important at the LIP and an as yet unidentified hormone/system at the UIP. Between the upper and lower intervention limits lies a 'zone of biological indifference', where fat mass can fluctuate freely until it nears the intervention points. Variations in individual UIP, particularly higher UIPs, explain differences in weight gain. This model also helps account for the previously unexplained issues around a fixed set point, such as weekly weight changes from weekdays to weekends, as well as annual holiday weight gain followed by incomplete weight loss afterwards.

The DIP model, however, has several flaws.[63] First, it cannot explain the surge in obesity rates since the 1960s. The 'drifty gene' hypothesis, explored in more detail below, helps explain the selection of genes over long periods but does not account for the recent spike in obesity. Second, some captive animals become obese despite facing predators, suggesting that they should have stricter fat regulation if the DIP model were correct.[63] Third, the model suggests that the body only responds to weight loss below a certain point (LIP). However, PLWO on calorie-restricted diets show metabolic changes, such as reduced energy use and increased hunger, that seem to defend fat stores, contradicting the DIP model.[63]

The Leeds model of appetite regulation introduces yet another layer of complexity, suggesting that body composition influences appetite regulation through two main mechanisms: firstly, fat-free mass (as opposed to fat mass in the above two models) drives energy intake (appetite) through resting metabolic rate, and secondly, fat mass (via leptin) acts as an inhibitory force on energy intake. In PLWO, the concept of leptin resistance is once again highlighted, as seen in the set-point model. This implies that in PLWO, appetite increases due to higher fat-free mass, while leptin resistance reduces appetite suppression, ultimately contributing to further weight gain. These systems are influenced by complex neuronal processes that integrate signals from the gastrointestinal system, especially after eating.

In summary, despite ongoing research it remains unclear which mechanism or combination of mechanisms predominantly controls body weight. What has become clear, however, is that these regulatory systems have been disrupted by long-term genetic changes, which have been compounded by the recent exposure to a toxic environment and poor diet quality, currently reflected in the global rise in obesity rates.[75]

Genetics

Firstly, with regard to genetics, and excluding the previously well-described monogenetic defects, three of the evolutionary theories that potentially explain our vulnerability to modern diets and environments are the 'drifty gene' hypothesis,[64,74] the 'thrifty gene' hypothesis,[74] and the climatic adaptation hypothesis for obesity.[76]

The DIP model introduces the idea that the UIP has shifted over evolutionary time, as suggested by the drifty gene hypothesis. In this model, the genetic basis of obesity is viewed as a non-adaptive consequence of the elimination of predation risks deep in our evolutionary past. This lack of selection pressure causes an erosion of the UIP with a subsequent elevation of the UIP. Since these mutations are not adaptive but instead occur due to genetic drift over evolutionary time (about 2 million years),[77] this concept is referred to as the 'drifty gene' hypothesis.[64,74]

In contrast, the thrifty gene hypothesis, initially proposed by Neel,[78] proposes that humans evolved to store fat as a survival mechanism against famines. However, current evidence contradicts this idea.[74] Firstly, early humans, such as *Homo erectus*, thrived as apex predators with access to abundant large animals. The overkill hypothesis suggests that they overhunted large herbivores, contradicting the notion of constant food shortages. Mastery of fire further increased caloric intake through the ability to cook food items. Even after the introduction of agriculture (8 000 - 10 000 years ago), famines were infrequent. Survivors of famines were not systematically fatter; mortality was more linked to age (the young and old tend to die) and social status. The rarity of famines and the relatively short period of 8 000 - 10 000 years are not considered strong enough selective pressures to drive genetic variations for fat storage. Additionally, humans show no consistent seasonal fat accumulation, unlike hibernating species. Instead, human fat storage is better explained by disease resistance, as fat reserves support survival during illness-induced anorexia. Fat also plays a crucial role in reproductive success, with leptin regulating fertility. In conclusion, the thrifty gene hypothesis lacks empirical support. Human adiposity is better explained by disease resistance and reproductive investment rather than an evolutionary response to famine.[74]

The climatic adaptation hypothesis for obesity proposed by Sellayah *et al*.[76] suggests that the modern obesity pandemic is linked to historical human migration and climatic adaptation. It challenges the thrifty and drifty genotype hypotheses, arguing that selection pressures varied across ethnic groups based on ancestral exposure to different climates. Populations that migrated to colder regions developed enhanced brown adipose tissue thermogenesis, increasing metabolic rates and reducing obesity risk. In contrast, populations in warmer climates retained heat-adaptive traits that may predispose them to obesity in modern environments. This perspective highlights the role of evolutionary selection in shaping obesity susceptibility across geographical regions.

More recently, epigenetics,[79,80] the study of heritable changes in gene expression in the absence of changes in the nucleotide sequence of genes, has emerged as an important player in the gene-environment interaction. Advances in DNA research and its modifications have greatly enhanced our knowledge of how epigenetic changes influence energy metabolism and expenditure in obesity and metabolic disorders. Crucially, their reversible nature presents exciting opportunities for therapeutic and corrective strategies.

Fetal programming,[74,81] itself linked with epigenetics, is also increasingly recognised as a significant factor in rising obesity levels. Researchers Barker and Hales were the first to establish a link between birthweight (a marker of prenatal nutrition) and future health outcomes. Recent research indicated that maternal obesity early in pregnancy was linked to an increased likelihood of obesity in the offspring during young adulthood.[82] This risk may then be transmitted across generations.[83] These findings imply that maternal

nutrition could play a significant role in the obesity crisis, emphasising the lasting impact of prenatal environments on health, succinctly captured by the saying 'you are what your mother ate'.[74] Phrased differently, 'genes load the gun, early-life factors take aim, and the environment pulls the trigger'.[81]

Dietary factors influencing body weight

In terms of dietary intake, three dominant theories – the energy balance model (EBM),[84-86] the carbohydrate-insulin model/fuel partitioning (CIM),[84-87] and the more recent OBS/REDOX model[88] – offer insights into how dietary intake has compromised the underlying systems that control weight.

The EBM argues that the increase in obesity is due to a positive energy balance, where the consumption of calorie-dense, ultra-processed foods in large portions leads to an excess of energy intake for a given energy expenditure. These ultra-processed, energy-dense, large-portion foods, often low in fibre and protein and high in salt and sugar, disrupt the body's normal signalling processes, increasing appetite. This increase in appetite is seen as a primary problem of the appetite centre, and the focus of the EBM is therefore about the quantity of food. The EBM, however, does not explain why some individuals are more prone to weight gain than others, or how early-life exposures influence later-life obesity.[84-86]

On the other hand, the CIM suggests that obesity is caused by a shift in how the body partitions energy. Rather than burning fat for energy, the body stores it under the influence of insulin in the face of high-glycaemic carbohydrates. This is then interpreted by the brain as a lack of energy, leading to an increased appetite. This increase in appetite is seen as a secondary issue, as opposed to the EBM seeing appetite as a primary issue. This model points to an altered metabolic pathway that drives weight gain, and the focus of the CIM is therefore more about the quality of food as opposed to the quantity of food as in the EBM. However, there are only rodent data and no human data to support the CIM.[87]

A third theory, the OBS/REDOX model,[88] proposes that certain environmental chemicals, called obesogens, contribute to obesity by disrupting the body's hormonal signalling and metabolic regulation. These chemicals are present in air, food, packaging, and household products. The theory integrates four key models, the EBM, the CIM, the oxidation-reduction model (REDOX) and the obesogens model (OBS), as each model by itself does not explain all aspects of weight gain.

These four models provide complementary perspectives on the mechanisms driving obesity, each highlighting different but interconnected pathways. The EBM suggests that weight gain results from an imbalance between calorie intake and expenditure. The CIM builds upon this by emphasising the role of insulin in energy storage. The REDOX adds another layer, proposing that reactive oxygen species influence metabolic signalling and energy regulation. Finally, the OBS highlights the role of environmental factors, such as endocrine-disrupting chemicals, in altering hormonal signalling. These substances can interfere with appetite regulation, metabolism and fat storage, compounding the effects described by the other models. Together, these models illustrate that obesity is not simply a matter of calorie excess but rather a complex interplay of hormonal, metabolic and environmental factors that collectively drive weight gain. Increased appetite, as in the other two models, is again highlighted as a major issue. Of note is that according to this model, not just individuals but even future generations may potentially be influenced through epigenetic effects. It highlights the importance of reducing exposure to obesogenic chemicals as a strategy for preventing obesity.

All three theories mentioned (EBM, CIM and OBS/REDOX) highlight an increase in appetite as a central factor in obesity, although they attribute this increase to different mechanisms (primary or secondary). Regardless of the cause, this heightened appetite drives increased calorie intake and excess fat accumulation. As this cycle progresses, the individual's capacity to regulate appetite gradually deteriorates, rendering it a non-modifiable cause for obesity. These mechanisms, along with the appetite-related factors previously discussed in this chapter, which affect the homeostatic, hedonic and executive regions of the brain, highlight excessive appetite as a central issue in PLWO. It is also important to recognise additional factors influencing individuals' dietary behaviours, as discussed in other chapters of this guideline ('Reducing weight bias in obesity', 'Epidemiology of adult obesity', and 'The role of mental health in obesity management'). These factors include socioeconomic status, cultural norms, the food environment and food accessibility, mental health, trauma or stress-related eating, and weight stigma – all well-established contributors to obesity that can influence both what and how much is consumed.

Obesity management

The path in and the path out

It is important to recognise that the path into obesity differs from the path out. While factors such as genetics, epigenetics, early fetal programming, poor diet quality, and environmental toxins contribute to obesity development – primarily by increasing appetite – these same factors are difficult to reverse once obesity is established. This challenge arises from our still limited understanding of the mechanisms and the lack of effective interventions to counteract these influences after obesity has developed. In other words, regardless of how one becomes obese, once there, a different path out is required to lose weight and improve obesity-related disorders. In keeping with this, although we cannot address the factors that lead to an increased appetite (the path in), we can address the final cause of an increased appetite directly (the path out), which will be the focus of treatment below. Addressing the factors themselves that lead to an increased appetite can only be tackled by public health systems, as part of a prevention strategy. Potential strategies are not discussed here, as they still need to be developed. The key takeaway from this concept is that preventive strategies, which address the path in, are required for the broader population, while treatment strategies, which focus on the path out, are tailored to the individual.

Causes and contributors

Effective treatment – the path out of obesity – requires distinguishing between its underlying causes and contributing factors. As mentioned earlier, excessive appetite (driven by genetics, epigenetics, early fetal programming, poor diet quality and environmental toxins) is seen as a final common pathway (cause) for weight gain that is not modifiable by PLWO. In contrast, modifiable contributors such as stress, poor sleep, poor diet quality, physical inactivity and increased sedentary behaviour offer potential intervention points for managing PLWO. These contributors are not seen as the main reason for weight gain, but rather as aggravating factors. This framework of causes and contributors[89] highlights that while the root causes of obesity are beyond an individual's control, contributing factors can still be managed by the individual, albeit with a more limited impact. This perspective underscores the importance of addressing the underlying cause of weight gain, predominantly an increased appetite, in achieving effective long-term weight loss and maintenance. This is largely why metabolic and bariatric surgery and GLP-1 RA medications

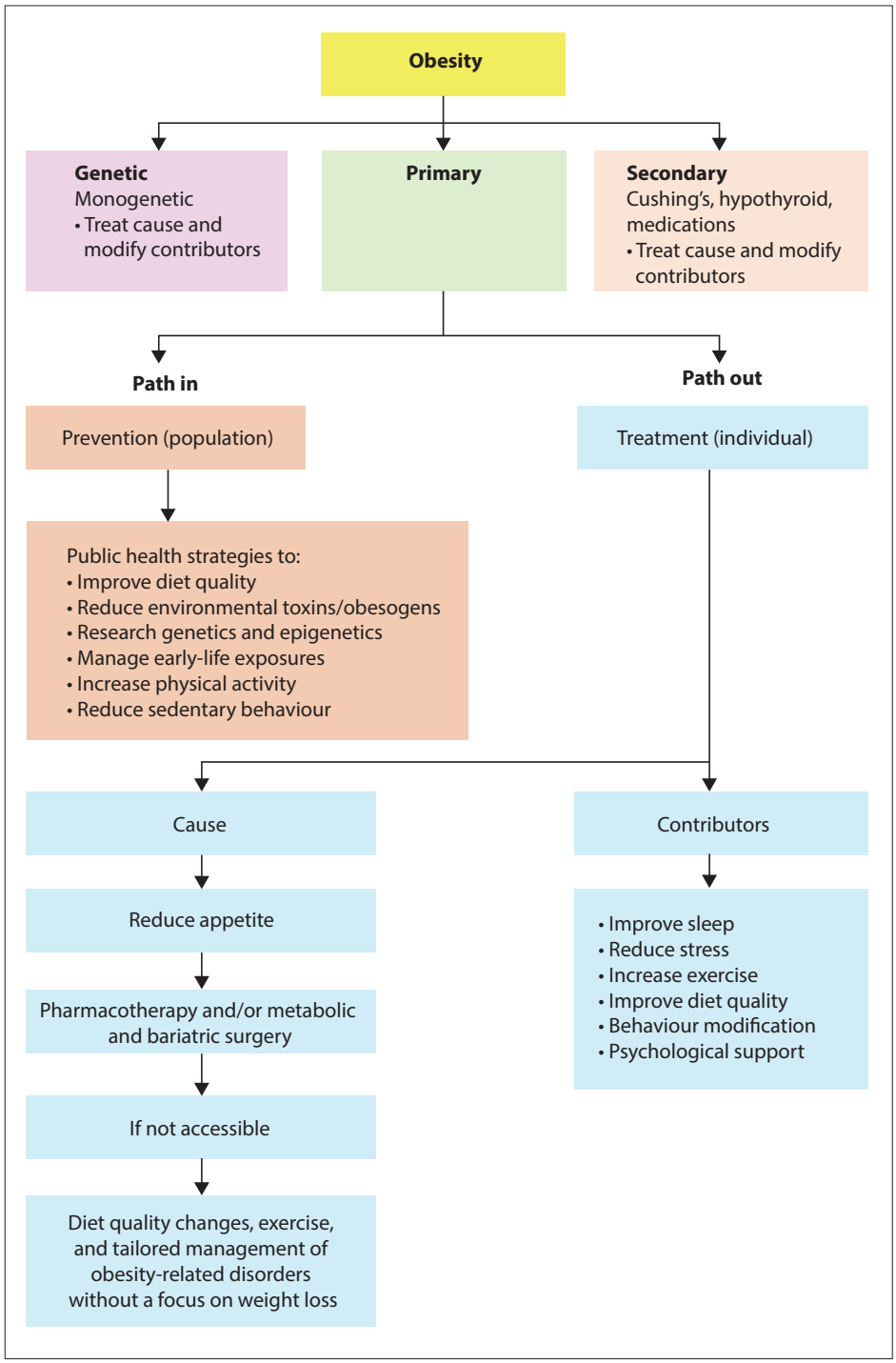

Fig. 1. Rational approach to obesity management.
Obesity is a complex chronic disease in which abnormal or excessive body fat (adiposity) impairs health, increases the risk of long- term medical complications, and reduces lifespan. Its management follows a rational, structured approach based on classification into genetic, primary and secondary causes. Genetic obesity, including monogenetic forms, and secondary obesity – resulting from conditions such as Cushing's disease, hypothyroidism, or certain medications – require targeted treatment that addresses both the underlying cause and contributing factors. These contributing factors are shared with primary obesity. In primary obesity, prevention efforts (path in) focus on population-level public health strategies aimed at improving diet quality, reducing exposure to environmental factors and obesogens, promoting physical activity, minimising sedentary behaviour, managing early-life exposures, and advancing research into genetic and epigenetic influences. Treatment (path out) targets excessive appetite using pharmacotherapy and/or metabolic and bariatric surgery, alongside modification of contributors. When pharmacotherapy and/or metabolic and bariatric surgery are not accessible, the focus shifts to enhancing diet quality, increasing physical activity and managing obesity-related conditions through a personalised approach, without an emphasis on weight loss.

have shown such success.[90-93] It is important to recognise that while increased appetite is the primary final common pathway (cause) in primary obesity, genetic and secondary obesity have distinct underlying causes that can be directly targeted, such as leptin replacement therapy in leptin deficiency or treatment for Cushing's disease.[89]

For a long time, the traditional 'eat less, move more' approach has been promoted for weight loss. However, this method has proven largely ineffective for achieving sustained weight loss and maintenance.[94,95] A significant issue with the 'eat less, move more' approach is that reducing food intake is challenging for individuals with an underlying problem of an excessive appetite. Along with this, the body's counter-regulatory measures – such as decreased basal metabolic rate and heightened hunger – also complicate efforts to lose weight and maintain weight loss, favouring weight regain.[96] Notably, an increased appetite has a stronger influence on weight regain than reduced energy expenditure. For each kilogram lost, appetite rises by ~95 kcal/day, while energy expenditure drops by ~25 kcal/day.[96] The greater impact of an increased appetite, rather than a slower metabolism, during weight loss underscores why medication and metabolic and bariatric surgery are effective. Beyond addressing the root cause of an increased appetite, they also help counteract the body's compensatory increase in appetite. Of concern is that without the use of medications and metabolic and bariatric surgery to manage appetite, along with the counter-regulatory mechanisms initiated by weight loss, PLWO are prone to yo-yo dieting, with potential harm.[97]

Finally, to reconcile the interconnected issues of PFT and excess body weight, we need more robust research into the factors – beyond overall weight gain – that influence how and where fat is stored in the body. Understanding these mechanisms may allow us to better target and manage PFT-related disorders independently

of weight loss. In the meantime, weight loss remains our primary therapeutic strategy to reduce excess body fat and thereby improve issues related to PFT. This strategy also addresses other obesity-related complications like osteoarthritis that have additional mechanisms beyond PFT, such as those related to the mechanical effects of excess fat mass itself.[98] Complicating the picture are new medications such as GLP-1 RAs, which provide cardiovascular benefits beyond their effects on weight loss.[99]

In summary, effective treatment of primary obesity for weight loss and improvement of obesity-related disorders requires an integrative path-out strategy. This approach combines lifestyle modifications with targeted interventions such as medication and metabolic and bariatric surgery to address both a heightened appetite and the body's counter-regulatory mechanisms. Managing contributors such as stress, poor sleep, physical inactivity and poor diet quality, along with behavioural modification as well as psychological assistance, serves as supportive therapy rather than the primary treatment.[90-95,100] Interestingly, it appears that when using more powerful appetite-suppressing treatments such as GLP-1 RAs and metabolic and bariatric surgery, the contribution of other options like behavioural treatments does not seem to add benefit for weight loss.[101-104] With the current powerful appetite-suppressing treatments available to us, behavioural treatment is, however, still important for dietary quality changes, adhering to exercise, and the psychological adaptation to weight loss. (See the chapter 'Effective psychological and behavioural interventions in obesity management'.) Despite the lesser effect of lifestyle changes on weight loss and maintenance, of great importance is that improving diet quality, along with increasing physical activity and reducing sedentary behaviour, remain markedly beneficial for overall health and longevity regardless of weight loss. (See the chapters 'Medical nutrition therapy in obesity management' and 'Physical activity in obesity management'.)

Conclusion

Obesity, a chronic disease characterised by excessive body fat, can be caused by genetic, secondary or primary factors. It encompasses two inter-related challenges: the PFT and the global rise in body weight. While several theoretical models attempt to explain body weight regulation, a definitive answer remains elusive. However, modern environmental and dietary factors have disrupted these regulatory systems in genetically susceptible individuals, contributing to widespread weight gain.

The path into primary obesity differs from the path out. Preventing obesity – the 'path in' – must be the priority of public health strategies. It requires improving diet quality, eliminating dietary and environmental toxins, and focusing on early-life interventions, particularly during the perinatal period, as well as increasing physical activity and reducing sedentary behaviours. Advances in genetics and epigenetic research also hold promise in addressing the predisposition to obesity. Conversely, the 'path out' of obesity demands targeted interventions addressing its underlying causes and contributors, with excessive appetite playing a pivotal role in primary obesity. Managing primary obesity necessitates an integrative approach, combining lifestyle modifications with medical and/or surgical treatments. In cases where medical and/or surgical treatments are inaccessible owing to availability or cost, the focus shifts to optimising health through improvements in diet quality and increased physical activity, together with tailored management of obesity-related disorders, without a focus on weight loss.

Acknowledgement. 'The science of obesity' is adapted from the Canadian Adult Obesity Clinical Practice Guideline (the 'Guideline'), which Obesity Canada owns and from whom we have a licence. SAMMSS adapted the Guideline having regard for relevant context affecting South Africa using the ADAPTE Tool.

SAMMSS acknowledges that Obesity Canada and the authors of the Guideline have not formally reviewed 'The science of obesity' and bear no responsibility for changes made to such chapter, or how the adapted Guideline is presented or disseminated. Therefore, such parties, according to their policy, disclaim any association with such adapted materials. The original Guideline may be viewed in English at: www.obesitycanada.ca/guidelines

Author contributions. WM rewrote a significant proportion of the adapted chapter following extensive review of the literature, including drafting the figure. JHG and MC-S contributed to editing, and all authors approved the final version of the chapter.

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