



Obesity in adults

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Obesity has increased in prevalence worldwide and WHO has declared it a global epidemic. Population-level preventive interventions have been insufficient to slow down this trajectory. Obesity is a complex, heterogeneous, chronic, and progressive disease, which substantially affects health, quality of life, and mortality. Lifestyle and behavioural interventions are key components of obesity management; however, when used alone, they provide substantial and durable response in a minority of people. Bariatric (metabolic) surgery remains the most effective and durable treatment, with proven benefits beyond weight loss, including for cardiovascular and renal health, and decreased rates of obesity-related cancers and mortality. Considerable progress has been made in the development of pharmacological agents that approach the weight loss efficacy of metabolic surgery, and relevant outcome data related to these agents' use are accumulating. However, all treatment approaches to obesity have been vastly underutilised.

Introduction

Obesity is defined by WHO as abnormal or excessive fat accumulation that might impair health. This condition is also defined by BMI (weight [kg] divided by height squared [m^2]) of 30 kg/m^2 and more, a cutoff mainly pertinent to the White population. BMI is a convenient but flawed means of estimating fat mass that is mainly useful as a screening tool for obesity and for epidemiological purposes.¹

As defined by BMI of 30 kg/m^2 or more, obesity affects more than 890 million (13%) adults globally.¹ This number underestimates the true prevalence of obesity considering that most non-White populations have obesity at lower BMI ranges. The prevalence of obesity has nearly tripled since 1975 and is projected to increase to 1·02 billion (18% of adults) by 2030.² Obesity is more common in women than men, and there are marked regional variations in prevalence and trends from less than 5% prevalence and small increases over time in south and southeast Asia (eg, Viet Nam and Bangladesh) and sub-Saharan Africa (eg, Ethiopia and Rwanda), to more than 35% prevalence and rapid increases in Oceania (eg, Nauru and Samoa), the Middle East (eg, Qatar and Kuwait), and the USA.³ Substantial disparities exist in the prevalence of obesity across groups of different socioeconomic status, especially in women.⁴

More than half of the global rise in mean BMI between 1985 and 2017 was due to increases in rural areas. Except

among women in sub-Saharan Africa, BMI appears to be increasing at the same rate, or more quickly, in rural than in urban areas in low-income and middle-income regions.⁵

Pathophysiology

Despite variations in energy intake and physical activities from day to day, most adults maintain a stable bodyweight over months to years. This stability is not a result of conscious control, but by coordinated regulation of energy intake and expenditure, mediated by communication between peripheral organs (particularly adipose tissue, gastrointestinal tract, and pancreas) and brain areas involved in energy homeostasis, reward, and executive functions.⁶

Intentional attempts to lose weight by reducing food intake lead to a cascade of neuroendocrine changes, including a reduction in the adipocyte hormone leptin, reduced energy expenditure (skeletal muscle work efficiency, autonomic nervous system tone) beyond that expected for the reduction in body mass, and increased appetite (increased hunger, food preoccupation and reward, and reduced satiety).⁶ Many of these changes persist after weight stabilisation and would be expected to limit weight loss and oppose its maintenance.

Weight gain leading to obesity can only result from a sustained positive energy balance, but the underlying causes of this imbalance are complex and involve interactions between our biology and environmental, behavioural, sociocultural, and economic factors.

Environmental changes, often referred to as an obesogenic environment, are likely to be the primary reason for the sharp rise in obesity prevalence over the last five decades. Among the proposed drivers of increased food consumption are commercial determinants of health, such as increased food availability, food marketing, food pricing, portion sizes, energy density, ultra-processing of foods, and prioritisation of profitable by-products (eg, corn, soy), and other societal and environmental changes including inadequate sleep, increased stress, and exposure to endocrine-disrupting chemicals.^{7–14} Environmental changes that favour reduced energy expenditure through

Search strategy and selection criteria

We used the terms “obesity” and “adult” to search the Cochrane Library, MEDLINE, and Embase for manuscripts published in English or Spanish in peer-reviewed journals between Jan 1, 2001, and Nov 15, 2023. We largely selected relevant publications from 2021 onwards but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by our broad search strategy and selected those we judged relevant. Our reference list was modified based on comments from coauthors and reviewers focusing on high-quality publications.

physical activity, such as less time spent in occupational physical activity and increased sedentary activities, have been associated with population weight gain and a decline in basal energy expenditure over several decades, which has also been proposed to contribute to the increase in obesity rates.^{15–17}

Not all people exposed to obesogenic environments develop obesity. Differences in predisposition to obesity are related to genetic variations. Common obesity is associated with many genes with small individual effect sizes on BMI and adiposity, most of which are predominantly expressed in the central nervous system. Collectively, these genes can confer large differences in susceptibility (eg, 13 kg difference in weight and 25-time gradient in risk of severe obesity between the lowest and highest deciles of polygenic risk score).¹⁸ A few genes with large effect sizes on BMI (monogenic obesity) have also been identified, including genes encoding components of the leptin-melanocortin pathway, an essential neural circuit regulating food intake.^{19,20} Heterozygous loss-of-function mutations in the melanocortin-4 receptor gene are the most common cause of monogenic obesity. These mutations are found in 5% of children with severe obesity and approximately 0·3% of the general population.¹⁹ This observation has given rise to the concept that common obesity might in fact not be one disease but the consequence of several subtypes of or even different diseases resulting in excess adipose tissue, which contributes to a deterioration in health.²¹

Consequences of obesity on health and wellbeing

Obesity has wide-ranging consequences on the health and wellbeing of individuals affected (figure 1). For simplicity, the effects of obesity can be categorised as metabolic, anatomical, and psychological, although there is an overlap between these categories. Most people with obesity experience stigma and discrimination related to their body size, leading to decreased quality of life and social wellbeing.

Metabolic consequences of obesity include (but are not limited to) type 2 diabetes, metabolic dysfunction-associated steatotic liver disease, hypercholesterolemia, chronic kidney disease, and atherosclerotic cardiovascular disease. These conditions share common pathophysiology, whereby the chronic need for storage of excessive nutrients leads to adipose tissue dysfunction, manifestations of which include an increase in circulating fatty acids and increased production of proinflammatory cytokines. These abnormalities promote oxidative, mitochondrial, and endoplasmic reticulum stress, leading to β -cell dysfunction, multi-organ insulin resistance, endothelial dysfunction, hypercoagulability, and abnormal lipid metabolism, ultimately leading to the clinical manifestations.^{22–25} Chronic inflammation and hyperinsulinemia are also proposed to underlie the increased risk of several cancers conferred by obesity.²⁶

Excess adipose mass can interfere with the function of various organs and tissues. Common examples include increased wear and damage to weight bearing joints leading to osteoarthritis, pain, and impaired mobility, increased abdominal pressure causing gastroesophageal reflux disease, venous stasis, increased work of breathing, restricted diaphragmatic movement, and pharyngeal collapsibility leading to respiratory insufficiency and obstructive sleep apnoea.

Implicit and explicit weight bias are pervasive across most societies and people with obesity are often subject to stigmatisation.²⁷ This stigma manifests in many ways including employment discrimination²⁸ and lower earning potential,²⁹ posing risks to psychological and physical health, fuelling health disparities, and interfering with implementation of effective obesity prevention programmes and treatment.³⁰ Obesity and depression commonly co-exist and have a reciprocal relationship, with depression being a risk factor for obesity and obesity increasing the risk of depression.³¹ Quality of life is often decreased in people with obesity, with individuals who have a higher BMI reporting lower physical and mental quality of life.^{32,33}

Obesity's association with excess mortality is well established, although the relationship might not be linear.³⁴ Effective treatment of obesity improves the adverse effect of obesity on health and wellbeing, with larger treatment effects associated with greater improvements. Weight loss of 5–10% of bodyweight improves many aspects of health, including insulin resistance, blood glucose and lipid concentrations, blood pressure, liver fat content, the need for glucose lowering medications, and in some people, renal disease, obstructive sleep apnoea, urinary incontinence, and depression.³⁵ Weight loss of 10% or more can lead to remission of type 2 diabetes³⁶ and lower

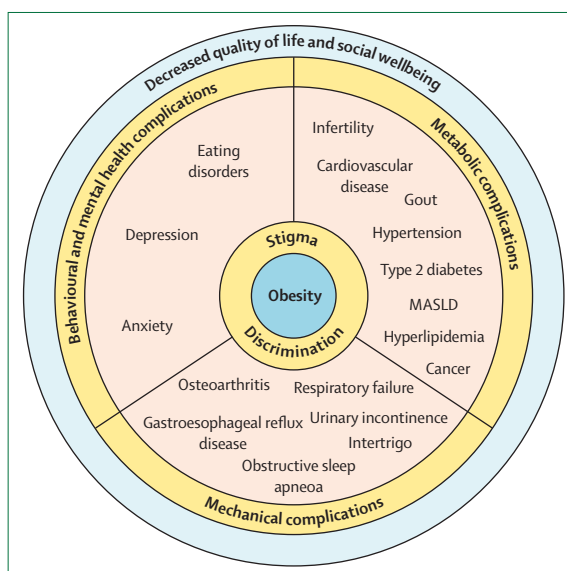


Figure 1: The wide-ranging complications of obesity

risk of asthma, atrial fibrillation, dyslipidaemia, heart failure, chronic kidney disease, osteoarthritis, and cardiovascular events.³⁷ Larger weight loss of 15% or more has been shown to further reduce the risk of renal disease progression, prevent or improve heart failure outcomes, improve metabolic-associated steatohepatitis, and reduce risk of cardiovascular events (myocardial infarction, stroke, revascularisation procedures, and heart failure), obesity-related cancers, cancer mortality, and all-cause mortality.^{38–41}

In people with obesity, health-related quality of life improves proportionally with the degree of weight loss, especially in individuals with higher baseline weight.³³ Greater improvements are usually noted in physical functioning, pain, and general health than in mental health domains (figure 1).^{42–45}

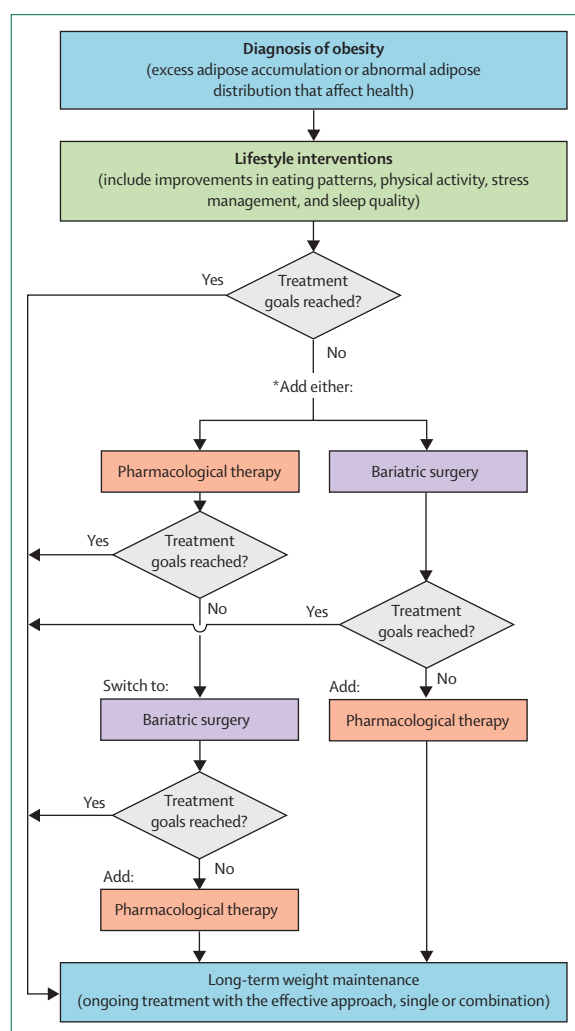


Figure 2: Conceptual approach to the treatment of obesity

*For individuals with severe disease (as defined by either very high BMI or presence of severe obesity-related co-morbidities) combination approach with lifestyle interventions and either pharmacological therapy or bariatric surgery should be considered first line, as appropriate.

Diagnosis

Obesity is a chronic and heterogeneous metabolic condition characterised by excess adiposity or abnormal adipose function that is associated with health consequences. To satisfy the current definition of obesity by WHO, clinicians must make an individualised assessment of the patient, which includes quantification of excess adipose tissue and identification of all deleterious consequences of obesity on the individual. Both criteria rely on imprecise measures and hence clinical acumen is required. The commonly used BMI-based definition of obesity has been widely adopted due to its ease of implementation; however, this definition has important shortcomings.⁴⁶ BMI is an imperfect measure of adipose mass, as it overestimates adipose mass in muscular individuals and underestimates it in frail individuals. BMI does not reflect fat distribution, inter-individual differences in fat metabolism, or susceptibility to adipose tissue dysfunction. Furthermore, a BMI-based definition does not consider the presence of the consequences of obesity on health or wellbeing, a defining tenet of any disease.

A large multi-specialty group has been tasked with developing a clinical definition of obesity, publication of which is expected in 2024.⁴⁶ In the meantime, if the presence of excess adipose mass is in doubt, clinicians are recommended to obtain additional anthropometric measurements including waist-to-hip ratio or waist-to-height ratio, to estimate adipose tissue mass and distribution, and interpret the results in the context of any associated health consequences.⁴⁷ Assessments of adipose tissue mass and distribution, along with associated health consequences should be monitored at least annually, or more frequently in individuals at high risk of obesity, to guide strategies to prevent, diagnose, and treat its complications.

Goals of care

The primary goal of care when treating obesity is health gain, with weight loss being a surrogate marker of treatment effectiveness. This approach is analogous to blood glucose lowering as a marker of the effectiveness of treatment of type 2 diabetes, where the goal is to minimise the risk of microvascular complications, and ultimately, to improve health and quality of life.

Most chronic diseases (eg, type 2 diabetes, hypertension, hypercholesterolemia) are treated to a target. These targets do not necessarily represent normality, but rather the level where the benefits of treatment optimally outweigh the risks. For obesity, we do not yet know how to define these targets because the diversity of complications of obesity makes it difficult to identify a single realistic and healthy goal that would be suitable for all patients. However, 15% weight loss appears a reasonable starting point to effectively improve most obesity-related complications and conditions.⁴⁸

Management

Management of obesity in adults follows the same principles as management of other chronic metabolic conditions. Lifestyle interventions are the initial approach and remain foundational even when additional interventions are needed to control the disease. A conceptual treatment approach for obesity is described in figure 2. As is the case for other chronic metabolic conditions, two important frameworks apply to the treatment of obesity: frequent monitoring of achievement of treatment goals and avoiding treatment inertia by adjusting or intensifying treatment when needed; and life-long treatment is needed even after reaching treatment goals to prevent deterioration.

Lifestyle interventions

Lifestyle interventions, consisting of nutritional therapies with or without exercise therapies, are the cornerstone of chronic disease management. For people with obesity, the strongest evidence of health benefits from lifestyle interventions aimed at weight reduction comes from structured, multimodal interventions, focusing on improving nutrition (with or without the use of meal replacements) and increasing physical activity. These

interventions are delivered by a multidisciplinary team, and are typically intensive to improve engagement and adherence, including frequent, face-to-face (group or individual) contact with clinicians (at least 14 sessions over 6–9 months) and continued follow-up for at least 12 months.^{49–51} Randomised controlled trials with more than 5-year follow-up data (table 1) consistently show that intensive lifestyle interventions are more effective than usual care. The overall effect on weight loss is modest (4–9% at 1 year and 1–3% at 5–10 years). As with all obesity treatments, response rates are variable, with 10–20% of the cohort reaching weight loss of more than 10%.

The Diabetes Prevention Program explored the effects of lifestyle intervention aimed at 7% bodyweight loss in preventing type 2 diabetes in people with impaired glucose tolerance. The programme showed a reduction in incidence of diabetes by 58% and 34% at 3 and 10 year follow-ups compared with standard care.⁵⁰ Very similar results were found in the Finnish Diabetes Prevention Study, which aimed at weight loss of 5% or more.^{53,54}

In people with type 2 diabetes, the Look AHEAD (Action for Health in Diabetes) study examined the effects of an intensive lifestyle intervention aimed at

	Diabetes Prevention Program ^{*52}	Finnish Diabetes Prevention Study ^{53,54}	Look AHEAD ⁵⁵	DIRECT ⁵⁶	WRAP ^{57†}
Participants	3234 participants with impaired glucose tolerance; 68% women, mean age 51 years; mean BMI 34 kg/m ²	522 participants with impaired glucose tolerance; 67% women, mean age 55 years; mean BMI 31 kg/m ²	5145 participants with type 2 diabetes; 59% women, mean age 59 years; mean BMI 36 kg/m ²	298 participants with type 2 diabetes <6 years duration; 41% female, mean age 54 years; mean BMI 35 kg/m ²	1269 participants; 68% women, mean age 53 years; mean BMI 34 kg/m ²
Intervention	Low-calorie, low-fat diet, moderate intensity physical activity ≥150 minutes/week, 16 individual counselling sessions over 24 weeks then monthly group sessions	Low-fat diet (<30% kcal from fat and <10% from saturated fat), ≥15 g of fibre per 1000 kcal/day, moderate intensity physical activity ≥30 min/day, 7 individual sessions over 52 weeks, plus optional supervised exercise training	1200 to 1800 kcal/day (<30% from fat and >15% from protein), moderate intensity physical activity ≥175 minutes/week, one individual and three group sessions monthly for the first 6 months, followed by one individual and two group sessions per month for the next 6 months, then two individual sessions per month in years 2 through 4, then one individual session monthly for the remainder of the follow-up	Withdrawal of medications for diabetes and hypertension; 825 to 853 kcal/day total diet replacement for 3 months then structured food reintroduction and maintenance; physical activity up to 15 000 steps/day; individual sessions every 2 weeks for 20 weeks then monthly for 2 years	Given vouchers and asked to attend local WW (formerly Weight Watchers); weekly meetings and access WW web tools for 52 weeks
Goal reduction in % bodyweight	7%	≥5%	7%	≥15 kg	Not stated
Follow-up (years)	Mean 10.0 years	Median 9.0 years	Median 9.6 years	Mean 5.0 years	Mean 5.1 years
Mean weight loss % at 1 year and end of follow-up	At 1 year: 7.4 (control 0.1%); end of follow-up: 2.0% (control 1.0%)	At 1 year: 4.7% (control 0.9%); end of follow-up: 1.0% (control 0.6%)	At 1 year: 8.6% (control 0.7%); end of follow-up: 6.0% (control 3.5%)	At 1 year: 9.9% (control 1.0%); end of follow-up: 5.5% (control 4.7%)	At 1 year: 7.1% (control 3.4%); ⁵⁸ end of follow-up: 2.8% (control 0.5%)
Glycaemic outcomes	Reduction in incidence of type 2 diabetes by 58% and 34% vs standard care at 3 and 10 years	Reduction in incidence of type 2 diabetes by 58% and 38% vs standard care at 3 and 9 years	Partial or complete type 2 diabetes remission‡ in 11.5% and 7.3% (vs 2.0% and 2.0% standard care) at 1 and 4 years	Type 2 diabetes remission§ in 46% and 7% (vs 4% and 3% standard care) at 1 and 5 years	No difference between groups in HbA _{1c} or in progression from normoglycaemia or non-diabetic hyperglycaemia at baseline to type 2 diabetes at 5 years

HbA_{1c}=glycated haemoglobin. *Outcomes provided for lifestyle intervention vs standard care arm. †Outcomes provided for 12-month vs brief intervention arms. ‡Partial remission of diabetes defined as a transition from diabetes to prediabetes (fasting plasma glucose 100–126 mg/dL, HbA_{1c} 5.7–6.5%) with no diabetes medication. Complete remission was defined as transition from diabetes to normoglycaemia (fasting plasma glucose <100 mg/dL and HbA_{1c} <5.7%) with no diabetes medication. §Remission of diabetes defined as HbA_{1c} <6.5% after at least 2 months with no diabetes medication.

Table 1: Summary of randomised controlled trials of lifestyle intervention for weight loss with at least 5 years' follow-up

7% weight loss on cardiovascular outcomes. The intervention resulted in 6·0% weight loss (vs 3·5% with standard care) after 10 years, and numerous health benefits but no change in cardiovascular events.^{35,59} The DiRECT trial⁵¹ used a total meal replacement strategy aiming for weight loss of 15 kg or more in people diagnosed with type 2 diabetes in the last 6 years. At 5 years, the 85 (57%) of 149 intervention participants with data available had 5·5% weight loss. Only 11 were in remission, these 11 participants having had an average weight loss of 9%.⁵⁶

Due to their success in clinical trials, structured, intensive lifestyle interventions are recommended in treatment guidelines, but are challenging to implement in routine care due to the resources required, insufficient funding models or reimbursement for their delivery, and the substantial time commitment and engagement these interventions require to be successful. The National Health Service Diabetes Prevention Programme was introduced in the UK in 2018, showing a reduced population incidence of type 2 diabetes of 7%.⁶⁰

When treating obesity, a goal of at least 150 min per week of moderately vigorous aerobic activity is recommended, such as brisk walking. Regular aerobic activity has many benefits, including improvements in blood pressure, blood glucose, and physical fitness.^{61,62} The expected weight loss from physical activity alone is minimal, therefore combination with dietary changes is important. However, high levels of physical activity have been found to correlate with better maintenance of weight loss.⁶³

No single best dietary approach for weight loss and health improvement exists.^{64,65} Adherence to the intervention is the strongest correlate of its success.⁶⁶ Weight loss is variable and not everyone will reach weight loss of more than 5% at 12 months, even with a structured lifestyle intervention.^{66,67} Moreover, as with all obesity treatments, when the treatment is stopped, weight regain is common. Should goals of care not be reached with lifestyle interventions alone, additional treatments, such as medications and bariatric surgery, are recommended to facilitate long-term control of obesity. For approximately 20% of the patients who can maintain a specific nutritional and exercise therapy in the long term, the benefits are substantial, especially for individuals who reach more than 10% weight loss.⁶⁸ As increasingly effective obesity treatments make substantial weight loss more achievable, the goal of lifestyle interventions might shift from assisting weight loss towards optimising health gain through eating patterns, physical activity, stress management, and sleep quality. Clinicians treating people with obesity should be familiar with the locally available behavioural therapy programmes and their outcomes.

Pharmacotherapy

A few medications are available for long-term obesity management, including the combinations of naltrexone

plus bupropion, phentermine plus topiramate, as well as orlistat, liraglutide, semaglutide, and tirzepatide.^{69–73} Orlistat, liraglutide, naltrexone plus bupropion, and phentermine plus topiramate have been proven to be safe and effective treatments for the disease of obesity, providing 5–10% weight loss in patients who respond to them (table 2). However, the latest generation of medications for obesity (including semaglutide and tirzepatide) are transforming the way the disease can be treated.

Semaglutide, a GLP-1 receptor agonist, results in 10–17% weight loss in people with obesity, with and without type 2 diabetes.^{78,84,86} The exploratory secondary endpoints in the regulatory trials (STEP trials) revealed beneficial effects on blood pressure, glycaemic, lipid, inflammatory, and anthropometric parameters. Overall, semaglutide's safety concerns, including rate of serious adverse events and proportion of adverse effects leading to drug discontinuation, are those known for the GLP-1 receptor agonist class of medication. The most common drug-associated adverse events were mild to moderate gastrointestinal symptoms (nausea, vomiting, diarrhoea, and constipation). Rates of hypoglycaemia, acute pancreatitis, gallbladder-related events, and injection site reactions were low in participants treated with semaglutide and often comparable with rates in the placebo groups. These side-effects will, however, need to be monitored in post-market surveillance schemes.

SELECT was the first randomised cardiovascular outcome study powered for superiority evaluating an obesity pharmacotherapy.⁸⁷ The study randomly assigned 17604 participants with a BMI equal to or greater than 27 kg/m² and a prior myocardial infarction, stroke, or peripheral vascular disease, but without diabetes, to treatment with semaglutide 2·4 mg weekly versus placebo, both in conjunction to standard of care.⁸⁸ Over a mean follow-up of 39·8 months, a major cardiovascular event (myocardial infarction, stroke, or cardiovascular death) occurred in 6·5% and 8·0% of participants in the semaglutide and placebo groups, respectively (hazard ratio [HR] 0·80, 95% CI 0·72–0·90, $p < 0·001$).⁸⁹ Although the cardiovascular death secondary endpoint was not statistically significant (HR 0·85, 95% CI 0·71–1·01, $p = 0·07$ [nominal significance level for superiority of 0·023]), the HR for the heart failure composite endpoint (heart failure hospitalisation and cardiovascular death) was 0·82 (95% CI 0·71–0·96), and the HR for all-cause death was 0·81 (CI 95% 0·71–0·93). Furthermore, the risk of progression to diabetes was 73% lower among individuals treated with semaglutide compared with placebo (HR 0·27, 95% CI 0·24–0·31). This landmark study was the first to show that pharmacological treatment of obesity can reduce cardiovascular events. The occurrence of serious adverse events in SELECT was lower in the semaglutide group (33·4% of participants) than in the placebo group (36·4% of participants), and no new risks were identified in this large cohort.

	Naltrexone plus Bupropion	Phentermine plus topiramate extended release	Orlistat	Liraglutide 3 mg	Semaglutide 2-4 mg	Tirzepatide
Dosage form and dosing	8 mg naltrexone–90 mg bupropion; starting at one tablet daily; increasing by one tablet daily once per week over 4 weeks to maximum two tablets twice daily	3.75 mg phentermine–23 mg topiramate once daily, oral for 14 days; then 7.5/46 mg; after 12 weeks when <3% weight loss, can increase to 15/92 mg	60–120 mg three times a day, with meals, oral	Starting at 0.6 mg daily, subcutaneous; increasing every week: 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg (maximum)	Starting at 0.25 mg weekly, subcutaneous; increasing every 4 weeks: 0.5 mg, 1.0 mg, 1.7 mg, and 2.4 mg (maximum)	Starting at 2.5 mg weekly, subcutaneous; increasing by 2.5 mg weekly after at least 4 weeks; maintenance 5, 10, or 15 mg weekly
Mechanism of action for weight reduction	Dopamine and noradrenaline reuptake inhibitor (bupropion); opioid receptor antagonist (naltrexone)	Sympathomimetic (phentermine); GABA receptor activation, and carbonic anhydrase inhibition (topiramate)	Inhibition of gastric and pancreatic lipase	GLP-1 receptor agonism in appetite and reward centres; slowing gastrointestinal transit	GLP-1 receptor agonism in appetite and reward centres; slowing gastrointestinal transit	Dual GIP/GLP-1 receptor agonism
Contraindications	Chronic opioid use, acute opioid withdrawal, uncontrolled hypertension, seizure disorder, abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiseizure drugs, and monoamine oxidase inhibitors use	Glaucoma, hyperthyroidism, monoamine oxidase inhibitors, hypersensitivity to sympathomimetic amines, and pregnancy	Chronic malabsorption syndrome, cholestasis, and pregnancy	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, pregnancy	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, pregnancy	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, pregnancy
*Side-effects	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhoea, and sleep disorders	Elevation in heart rate, mood and sleep disorders, cognitive impairment, metabolic acidosis, paraesthesia, and dry mouth	Oily rectal leakage, abdominal distress, abdominal pain, flatulence with discharge, faecal urgency, steatorrhea, faecal incontinence, and increased defecation	Increased heart rate, constipation, diarrhoea, nausea, vomiting, and headache	Nausea, vomiting, diarrhoea, abdominal pain, constipation, and headache	Nausea, diarrhoea, vomiting, constipation, dyspepsia, and abdominal pain
Mean placebo-subtracted weight loss (%) in participants without diabetes	5% ⁷⁴ (at 1 year)	9% ⁷⁵ (at 1 year)	4% ⁷⁶ (at 1 year)	6% ⁷⁷ (at 1 year)	12.5% ⁷⁸ (at 68 weeks)	17.8% ⁷⁹ (72 weeks)
Mean placebo-subtracted weight loss (%) in participants with diabetes	3.2% ⁸⁰ (at 1 year)	6.7% ⁸¹ (at 1 year)	2.5% ⁸² (at 1 year)	4.0% ⁸³ (at 1 year)	6.2% ⁸⁴ (at 68 weeks)	11.6% ⁸⁵ (at 72 weeks)
Proportion of participants with 5% and 10% weight loss at 12 to 18 months (vs placebo) in participants without diabetes	48% and 25% (16 and 7% placebo)	67% and 47% (17 and 7% placebo)	73% and 41% (45 and 21% placebo)	63% and 33% (27 and 11% placebo)	86% and 69% (31 and 12% placebo)	91% and 84% (35 and 19% placebo)
Proportion of participants with 5% and 10% weight loss at 12 to 18 months (vs placebo) in participants with diabetes	45% and 19% (vs 19 and 6% placebo)	65% and 37% (vs 24 and 9% placebo)	33% and 10% (vs 13 and 4% placebo)	54% and 25% (vs 21 and 7% placebo)	69% and 46% (vs 28 and 8% placebo)	83% and 65% (vs 33 and 10% placebo)
Mean change from baseline in systolic blood pressure/diastolic blood pressure mm Hg (placebo)	–0.1/0.0 (vs –1.9/–0.9 placebo)	–2.9/–1.5 (vs 0.9/0.4 placebo)	–7.3/–3.6 (vs –5.2/–2.6 placebo)	–4.2/–2.6 (vs –1.5/–1.9 placebo)	–6.2/–1.1 (vs –0.4/–0.4 placebo)	–7.2/–4.8 (vs –1.0/–0.8 placebo)
Mean % change from baseline in HbA _{1c} in participants with diabetes (vs placebo)	–0.6% (–0.1% in placebo)	–1.6% (–1.2% in placebo)	–0.6% (–0.3% in placebo)	–1.3% (–0.3% in placebo)	–1.6% (–0.4% in placebo)	–2.1% (–0.5% in placebo)

HbA_{1c}=glycated haemoglobin. SBP/DBP=systolic blood pressure/diastolic blood pressure. *Adverse events present in more than 10%, based on US Food and Drug Administration approved product information leaflet (modified). All effects given for maximum doses or pooled medication group.

Table 2: Summary of obesity medications approved for long-term use, and outcomes reached after at least 12 months of use

Tirzepatide is a dual agonist of receptors for the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) and is approved for both type 2 diabetes and obesity. The SURMOUNT-1 study showed an average weight reduction of 20·9% over 72 weeks of treatment with tirzepatide 15 mg along with clinically meaningful improvements in cardiometabolic risk factors among patients without diabetes.⁷⁹ SURMOUNT-2 showed a mean weight reduction of 15% over 72 weeks of treatment among patients with type 2 diabetes. 49% of participants reached normalisation of HbA_{1c} (>5·7%) without any severe hypoglycemia.⁸¹ In SURMOUNT-3 and SURMOUNT-4, participants had a mean weight reduction of approximately 26% when either started after a low calorie diet run-in period (SURMOUNT-3) or when tirzepatide was only continued in individuals who tolerated an initial 36-week run-in period (SURMOUNT-4).^{90,91} Tirzepatide's effects on major cardiovascular outcomes and heart failure are being investigated (NCT04847557).⁹²

Two drugs are approved for genetic causes of obesity. Metreleptin, a leptin analogue, is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalised lipodystrophy (a form of abnormal adipose tissue that affects health).⁹³ A real-world study reported on the 47 patients treated with metreleptin in France over a decade.⁹⁴ After a median follow-up of 31·7 months, only individuals with general lipodystrophy syndromes had significant and sustained improvements in metabolic parameters (HbA_{1c} and triglycerides), while people with partial lipodystrophy only had small and non-sustained improvements.

Setmelanotide is a melanocortin-4 receptor agonist indicated for treatment of severe obesity in adults and children aged 6 years or older with pro-opiomelanocortin, proprotein convertase subtilisin/kexin type 1, leptin receptor deficiency, or Bardet-Biedl syndrome. A meta-analysis that included 376 people treated with setmelanotide showed an average reduction in BMI of 10·55 kg/m² among adults who were treated for at least one year.⁹⁵

With regards to new drugs under development for obesity, the pharmacotherapy pipeline is very rich. Most agents in the pipeline target the incretin system to promote weight loss (variations of single, dual, or triple agonists of GLP-1, GIP, and glucagon), while others range in mechanism from amylin agonism, to taste receptor activators, leptin sensitisers, dopamine reuptake inhibitors, and others. Agents that are currently in phase 3 development are listed:

Retatrutide is a triple agonist at GIP, GLP-1, and glucagon receptors. In a phase 2 clinical trial, 24% weight loss was reached at the end of the 48-week treatment period, with the weight loss curves suggesting that the nadir was not yet reached. Retatrutide 12 mg subcutaneously once a week also led

to improvements in cardiometabolic risk factors including systolic and diastolic blood pressure, triglycerides, total and LDL cholesterol, HbA_{1c}, and fasting glucose and insulin. Retatrutide is the first medication with which all participants in a clinical trial reached weight loss of at least 5%. The overall safety and tolerability profile of this medication is similar to GLP-1 receptor agonists.⁹⁶

CagriSema is a fixed-dose combination of semaglutide and an amylin analogue (cagrilintide). The effectiveness and safety of CagriSema (2·4 mg semaglutide and 2·4 mg cagrilintide), compared with the individual components semaglutide 2·4 mg and cagrilintide 2·4 mg (all administered once weekly), were evaluated in a phase 2 clinical trial⁹⁷ in participants with type 2 diabetes and obesity. After 32 weeks, individuals treated with CagriSema lost 15·6% of their total bodyweight and their HbA_{1c} decreased by 2·2%, compared with 5·1% weight loss and HbA_{1c} reduction of 1·8% for people treated with semaglutide alone. The combination appeared safe and well tolerated.⁹⁷

Survodutide is a subcutaneous, once-weekly GLP-1 and glucagon receptor dual agonist. Reports⁹⁸ note 18·7% weight loss after 46 weeks of treatment, with the weight loss curves suggesting the nadir was not reached. Gastrointestinal side-effects were the most frequent drug-related adverse events. Most of the treatment discontinuations due to adverse events occurred during the rapid dose-escalation phase and might be mitigated with more gradual dose escalation.⁹⁸ This study supports a potential reconsideration of how quickly doses of all these new medications are increased, with slower dose titration possibly being part of the solution to increase long term adherence.

Orforglipron is a non-peptide oral GLP-1 receptor agonist (once-daily) being evaluated for the treatment of obesity. A randomised, double-blind trial showed weight reductions of 14·7% over 36 weeks of treatment, while the weight loss curves suggested the nadir weight was not yet reached.⁹⁹ An additional phase 2 study that enrolled people with type 2 diabetes showed that after 26 weeks of treatment HbA_{1c} was reduced by an average of 2·1% and up to 96% of participants reached a HbA_{1c} of less than 7·0%. A HbA_{1c} of less than 5·7% was reached by 34% of participants.¹⁰⁰ The safety profile of orforglipron was similar to other incretin-based therapies.^{99,100}

In summary, the results of the phase 2 and 3 trials of semaglutide, tirzepatide, retatrutide, CagriSema, survodutide, and orforglipron suggest these new medications are effective and safe for the treatment of obesity. The drugs will not replace nutritional or surgical treatment options, but treatment algorithms might have to be redefined, with a shift from using nutritional therapy for weight loss to using it for health gain instead; better nutritional health should be especially important when patients consume fewer calories while using these medications.

Furthermore, expectations should be set regarding treatment chronicity. Obesity is a chronic disease, therefore in the absence of long-term therapy, relapse rates are high. For example, when treatment with weekly subcutaneous semaglutide 2.4 mg was discontinued after 68 weeks of treatment, two thirds of the weight lost was regained within a year of discontinuing treatment.¹⁰¹ Studies are exploring approaches to long-term weight maintenance after weight loss induction, but at present, chronic treatment is recommended to facilitate long-term weight loss maintenance.

Devices and endoscopic procedures

The rationale of endoscopic bariatric procedures is to provide an option other than medical and surgical treatment with intermediate efficacy and invasiveness. Endoscopic bariatric procedures in clinical use include intragastric balloons and endoscopic gastroplasty. These interventions are mainly intended to reduce food intake by restriction or occupying gastric space and might not be optimal treatments for obesity.

A range of intragastric balloons are available, with different shapes and filling systems, and all must be removed after 6–12 months.¹⁰² Considering that obesity is a chronic disease, this short-term duration of treatment might be a downside. Meta-analyses show a mean total bodyweight loss of 7–14% at 12 months after intragastric balloon use (compared with 3–8% with lifestyle intervention) and indicate significant weight regain after device removal.^{103,104} Complications are infrequent (in <1% of cases) and include gastric outlet obstruction, gastric ulceration, and gastric perforation.

Endoscopic gastroplasty is an endoscopic plication of the greater gastric curve. Only one randomised controlled trial¹⁰⁵ compared endoscopic gastroplasty with lifestyle interventions, reporting a mean total bodyweight loss of 13.6% (vs 0.8% for lifestyle intervention alone) at 52 weeks. About 1% of patients have complications, such as perigastric collections, major bleeding, and deep vein thrombosis. Given their risk–benefit balance and durability reported to date, the use of endoscopic treatments might be difficult to justify.

Bariatric (metabolic) surgery

Bariatric surgery is referred to as metabolic surgery when it is specifically performed to address the metabolic complications of obesity. Bariatric surgery comprises procedures that induce weight loss through physiological mechanisms¹⁰⁶ and is the most effective treatment for obesity and all its associated complications.¹⁰⁷ In 2022, mounting evidence of the safety and long-term effects of bariatric surgery led the International Federation for the Surgery of Obesity and Metabolic Disorders and the American Society for Metabolic and Bariatric Surgery to update the indications for surgery,¹⁰⁸ which were previously published in 1991, by the US National Institutes of Health (table 3).¹⁰⁹

	1991-NIH	2022-IFSO/ASMBS
BMI and co-morbidities	>40 kg/m ² ; or >35<40 kg/m ² for individuals with co-morbidities (ie, diabetes, sleep apnoea, hypertension, osteoarthritis, etc)	>30 kg/m ² with medically uncontrolled diabetes; >35 kg/m ² individuals without comorbidities when suboptimal response after the best available medical treatment
Age	No data available for adolescents and people older than 70 years	Age limits expanded to include people older than 70 years after evaluation of risks and benefits; and adolescents with BMI >120% of the 95th percentile for their age with related medical problems; or adolescents with BMI >140% of the 95th percentile for their age
Special situations	None	Bridge to joint replacement, correction of abdominal wall hernia, or organ transplantation
Procedures recommended	RYGB, VBG	RYGB, SG

RYGB=Roux-en-Y gastric bypass. SG=sleeve gastrectomy. VBG=vertical banded gastroplasty.

Table 3: Differences between the 1991 National Institutes of Health Guidelines (NIH)¹⁰⁹ and the 2022 joint International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) and American Society for Metabolic and Bariatric Surgery (ASMBS) guidelines for bariatric surgery¹⁰⁸

	Follow-up (years)	Primary endpoint	Proportion achieving primary endpoint
RYGB and SG ¹¹⁸	5	HbA _{1c} <6% (42.2 mmol/mol) regardless of antidiabetic agents	29% (RYGB), vs 23% (SG), vs 5% (medical treatment; p<0.03)
RYGB ¹¹⁹	5	Composite endpoint of HbA _{1c} <7.0% (53 mmol/mol), LDL <2.59 mmol/L and systolic blood pressure <130 mm Hg	23% (RYGB) vs 4% (medical treatment)
RYGB and AGB ¹²⁰	5	Partial remission: HbA _{1c} <6.5% (47.5 mmol/mol) or FPG <126 mg/dL (7 mmol/L), without glucose-lowering agents; complete remission: HbA _{1c} <5.7% (39 mmol/mol) and FPG ≤100 mg/dL (5.5 mmol/L), without glucose-lowering agents	Partial remission: 30% (RYGB) vs 19% (AGB) vs 0% (medical treatment) (p<0.001); complete remission: 5% (RYGB), vs 0% (AGB), vs 0% (medical treatment)
RYGB ¹¹⁶	5	HbA _{1c} <6.5% (47.5 mmol/mol), regardless of glucose-lowering agents	60.2% (RYGB) vs 25.4% (medical treatment)
RYGB and BPD ¹²¹	10	FPG <100 mg/dL (5.5 mmol/L) and HbA _{1c} <6.5% (47.5 mmol/mol), without glucose-lowering agents	25% (RYGB), vs 50% (BPD), vs 5.5% (medical treatment)
RYGB ¹²²	5	≥30% reduction in total number of antihypertensive medications while maintaining blood pressure <140/90 mm Hg	80.7% (RYGB) vs 13.7% (medical treatment)
RYGB ¹¹⁵	3	No OSA or less severe OSA (based on apnoea-hypopnoea index)	No OSA status: 70.8% (RYGB) vs 4.2% (medical treatment); moderate OSA: 8.3% (RYGB) vs 42.7% (medical treatment); severe OSA: 0% (RYGB) vs 20.8% (medical treatment)
RYGB ¹¹⁶	5	uACR <30 mg/g creatinine	69.7% (RYGB) vs 59.6% (medical treatment)
RYGB and SG ¹¹⁷	1	Histological resolution of MASH without worsening of fibrosis	56% (RYGB), vs 57% (SG), vs 16% (medical treatment; p<0.0001)

AGB=adjustable gastric banding. BPD=biliopancreatic diversion. FPG=fasting plasma glucose. HbA_{1c}=glycated haemoglobin. LDL=low density lipoprotein. MASH=metabolic dysfunction-associated steatohepatitis. OSA=obstructive sleep apnoea. RYGB=Roux-en-Y gastric bypass. SG=sleeve gastrectomy. uACR=urine albumin creatinine ratio.

Table 4: Randomised controlled trials of at least 3 years duration comparing bariatric surgery to best medical treatment

The two most common bariatric operations are the sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB). Both have robust evidence of long-term outcomes regarding weight loss and improvement of obesity-related diseases.¹⁰⁷ Other surgical techniques have been reported and utilised but have not gained wider implementation.

Weight loss and health benefits of bariatric surgery

Studies with long-term follow-up have consistently shown that bariatric surgery leads to superior weight loss compared with non-operative medical treatment of obesity and related diseases.^{110,111} The Swedish Obesity Subjects study showed sustained loss of more than 25% of total bodyweight over 20 years in the RYGB surgery group.¹¹² Moreover, several randomised controlled trials confirmed the health benefits of bariatric surgery (RYGB and sleeve gastrectomy) compared with best available medical treatment on glycaemic endpoints, sleep apnoea, hypertension, kidney outcomes, and liver outcomes (including liver fibrosis; table 4).^{48,110,113–117} These studies were done before the availability of medications with greater efficacy for reduction in blood glucose and bodyweight and there are no randomised controlled trials comparing bariatric surgery with the new generation of more effective obesity medications.

Several large cohort studies have investigated the long-term effects of bariatric surgery on cardiovascular events, mortality rates, and cancer incidence. A meta-analysis of 49 studies showed a beneficial effect on coronary artery disease (HR 0.68, 95% CI 0.52–0.91, $p=0.008$), myocardial infarction (HR 0.53, 95% CI 0.44–0.64, $p<0.01$), heart failure (HR 0.45, 95% CI 0.37–0.55, $p<0.01$), cerebrovascular accident (HR 0.68, 95% CI 0.59–0.78, $p<0.01$), and cardiovascular mortality (HR 0.48, 95% CI 0.40–0.57, $p<0.01$).¹²³ The effect on atrial fibrillation was not statistically significant (HR 0.81, 95% CI 0.65–1.01, $p=0.07$). Bariatric surgery was also associated with a lower risk of cancer (HR 0.67, 95% CI 0.53–0.85) in the Swedish Obesity Subjects study,¹²⁴ and in a retrospective cohort study ($n=30\,318$), which showed a lower risk of obesity-associated cancer (HR 0.68, 95% CI 0.53–0.87, $p=0.002$) and cancer-related mortality (HR 0.52, 95% CI 0.31–0.88, $p=0.01$).³⁹

Safety

Overall, bariatric surgery is safe. Perioperative mortality is very low, ranging between 0.03% and 0.2%.¹²⁵ Complications, such as venous thromboembolism, haemorrhage, staple line or anastomotic leak, reoperation, and readmission in the first 90 days after surgery range from 0.8% to 9%, depending on the severity of obesity and associated diseases.¹²⁵ In all randomised controlled trials, the incidence of complications has been comparable between RYGB and sleeve gastrectomy.^{118,126–128}

Cost-effectiveness

Although the upfront costs of the surgery might be substantial, studies^{129–134} have shown that the long-term cost savings outweigh the initial investment. In general, the cost of surgery is considered favourable compared with non-surgical obesity care due to improved resolution of obesity-related conditions and reduced medication costs over the lifetime horizon.^{129–131} Depending on the country, the incremental cost-effectiveness ratio of bariatric surgery is about US\$18 000 to \$46 000 per quality-adjusted life-years saved, which is below most willingness-to-pay thresholds worldwide.^{132–134} Economic benefits are greater in people with greater severity of disease, such as individuals with type 2 diabetes and with BMI of more than 50 kg/m².¹³⁵

Preoperative and postoperative care

Before bariatric surgery, patients should undergo a comprehensive evaluation by a multidisciplinary team to assess and optimise the balance of benefits and risks, identify and address medical, nutritional, and psychological issues, and prepare patients for what to expect postoperatively.¹³⁶

Long-term postoperative follow-up will depend on the patient's health status, needs, and the procedure type. The follow-up should include guidance and support for changes in patient's eating patterns and physical activity, long-term micronutrient supplementation, monitoring progress of bodyweight change, obesity-related diseases (including adjustment of medications as required), nutritional status, bone density, as well as short-term and long-term complications. Emergence (or re-emergence) of issues related to mood, body image, and alcohol and substance use have been associated with bariatric surgery more so than non-surgical obesity treatments.¹³⁶

Long-term obesity management

In keeping with the chronic nature of obesity, management strategies for this condition need to take a long-term approach, and treatment combinations might be needed for optimal management. Lifestyle changes aimed at optimising nutritional quality and physical activity are beneficial to health regardless of weight loss and are important in minimising the potential risks (such as loss of muscle mass and nutritional deficiencies) of large weight losses associated with medications and bariatric surgery, as well as in maintenance of the weight lost.

Individual responses to pharmacological interventions for the treatment of obesity are highly variable, hence, if treatment goals are not reached with medications, bariatric surgery should be considered. Conversely, people with a suboptimal response to bariatric surgery, recurrence of obesity-related diseases, or impairments after initial control, might benefit from addition of an obesity medication (figure 2). In the management of other chronic diseases, when the response to a single

medication is suboptimal, combinations of medications with complementary mechanisms of action are often more effective and better tolerated compared with increasing doses of monotherapy. This approach has not been evaluated in clinical trials of medications currently approved for obesity management, but is being studied for medications in development, such as the combination of semaglutide with cagrilintide and bimagrumab (NCT05616013).⁹⁷

With the first-generation obesity pharmacotherapies, a poor early response to treatment was associated with poor long-term weight loss outcomes. Therefore, these medications should be discontinued if total bodyweight loss of less than 5% is not reached after 12 weeks of treatment. The newer medications are more potent and therefore far fewer patients do not respond to treatment. These newer medications' titration schemes over several months and long half-life results in nadir weight loss to be observed at 9–18 months of treatment, therefore non-responder assessment should take into consideration these factors. Furthermore, when a medication is initiated in the setting of weight regain, its efficacy might be reflected in stabilising weight, which might still have the benefit of preventing recurrence of obesity-related diseases.

Medications for obesity only work when they are in use. Hence, if they are effective, long-term use is probably required for health benefits to be sustained, although data on long-term clinical outcomes are scarce. Additionally, long-term adherence to treatment is low (<10%) in real-world studies,¹³⁷ though this might partly reflect high out-of-pocket costs to patients, supply chain shortages for the newer medications, and patients' dissatisfaction with previous less effective treatments.

Treatment inertia, the failure to start or intensify therapy when clinically indicated, is common at all stages in the management of obesity, leading to delays in care and increasing the risk of obesity-related complications.^{138,139} This inertia might partly result from the common misconception that obesity is entirely a self-imposed condition that could be treated by simple lifestyle changes, which creates a clear discrepancy in the care provided to people with obesity compared with patients with other chronic diseases both at an individual and systemic levels. Most health-care systems do not provide the same level of access or coverage for effective treatments for obesity as for other chronic diseases.

Risks associated with weight loss

Despite the overall health benefits of sustained weight loss, there are also potential risks that should be monitored and treated proactively. Many of these risks are likely to be related to the efficacy of the intervention, being most common with bariatric surgery, and are likely to occur also with the latest generation of more effective pharmacotherapies.

Gallstones

Rapid weight loss can cause changes in the saturation of bile with cholesterol, forming cholesterol monohydrate crystals, which can then aggregate to form gallstones. The risk of developing de novo gallstones after bariatric surgery varies from 2% to 8%, regardless of the procedure.¹⁴⁰ A meta-analysis of eight trials showed a higher risk for a gallbladder and biliary disease composite for tirzepatide compared with placebo and insulin (HR 1.97, 95% CI 1.14–4.42), but similar risk compared with selective GLP-1 receptor agonists.¹⁴¹ The risk of pancreatitis with GLP-1 receptor agonist treatment, which is much talked about in the lay press, has not been seen in large controlled trials or meta-analyses.

Sarcopenia, bone mineral loss, and fractures

A meta-analysis of studies that used dual-energy X-ray absorptiometry, computed tomography, and magnetic resonance imaging to measure body composition after bariatric surgery showed that despite substantial heterogeneity across the studies, there was 21% loss of fat-free mass and 22% of lean body mass 1 year after bariatric surgery, regardless of the surgical technique used.¹⁴² Moreover, a prospective observational cohort study found the prevalence of sarcopenia based on sex-specific skeletal muscle mass index increased from 8% to 32% within 1 year post-bariatric surgery.¹⁴³ Studies of bone loss in people who underwent substantial weight loss are challenging. Dual-energy x-ray absorptiometry technology loses accuracy in people with obesity, and changes in fat mass introduces artifacts that might compromise accuracy and precision.¹⁴⁴ Other methods, including whole body imaging with computer tomography or magnetic resonance spectroscopy, can more accurately quantify fat vs fat-free mass, but are expensive and not readily available clinically.

After weight loss, proposed mechanisms of bone mass loss include skeletal unloading and increased bone turnover, abnormalities in calciotropic hormones, and changes in gut hormones that might be associated with pathophysiological changes like increased parathyroid hormone.¹⁴⁵ Whether the skeletal changes that occur after bariatric surgery are pathological and are associated with skeletal fragility remains to be seen.¹⁴⁶ Decreases in bone mineral density and fat-free mass are anticipated irrespective of the treatment used and are likely linked to the amount of weight loss rather than the means of weight loss. Exercise (especially anaerobic exercise) and adequate protein intake are encouraged to prevent sarcopenia related to aging;¹⁴⁷ however, specific recommendations for prevention of sarcopenia in individuals treated for obesity are not currently available.

Data on fractures after bariatric surgery are heterogeneous and primarily based on retrospective series. One randomised controlled trial did not observe increased risk 2 years after bariatric surgery.¹⁴⁸ However, the Swedish Obesity Subjects study,¹⁴⁹ which compared

three different surgeries with a medical control group with up to 26 years of follow-up, found an increased risk of fracture after RYGB compared with the control group (adjusted HR 2.58, 95% CI 2.02–3.31, $p < 0.001$). The gastric banding group (adjusted HR 1.99, 95% CI 1.41–2.82, $p < 0.001$) and the vertical banded gastroplasty group (adjusted HR 2.15, 95% CI 1.66–2.79, $p < 0.001$) had a risk of fractures lower than RYGB, but greater than the control group. RYGB resulted in more weight loss than the other procedures and a greater percentage of patients undergoing RYGB were postmenopausal women who are prone to bone mass loss.

Mental health

Overall, treatment of obesity is associated with beneficial effects on mood and quality of life. However, there are increased rates of some psychiatric adverse effects, particularly after bariatric surgery. Body dysmorphia is characterised by an obsessive preoccupation with perceived flaws in one's appearance. Up to 74% of people with overweight or obesity have body image distortion or dissatisfaction, however postoperative body dysmorphia is less investigated and its incidence is poorly reported.¹⁵⁰ Among other factors, body dysmorphia is associated with excessive skin looseness due to the loss of skin elasticity.¹⁵¹ In people who underwent bariatric surgery and seek consultation for plastic surgery after major weight-loss, body image dissatisfaction appears to be a common characteristic. Several studies have found that between 7% and 16% of patients seeking plastic surgery meet the diagnostic criteria for body dysmorphic disorder.¹⁵²

Short-term and medium-term improvement in depressive symptoms is common after surgery. However, a subgroup of patients experiences attrition of these improvements or new onset of depression in the longer term.^{153,154} Additionally, disordered eating behaviours can occur during or after weight loss. These might be linked to depression and include restrictive eating, binge eating, or purging behaviours. These events are not fully understood but proposed explanations include body image disturbances, increased stress, fear of regaining weight, or the pressure to meet societal expectations.¹⁵⁵

Bariatric surgery can lead to altered sensitivity to alcohol or drugs.¹⁵⁶ Individuals might find that their tolerance to these substances has changed, increasing the risk of dependence or addiction if not properly managed.

An increased risk of suicide has been reported after bariatric surgery. In the Swedish Obesity study,¹⁵⁷ during 68 528 person-years of follow-up, suicide or non-fatal self-harm events were more common in the surgery group ($n=87$) than in the control group ($n=49$, adjusted HR 1.78, 95% CI 1.23–2.57, $p=0.0021$); of these events, nine and three were suicides, respectively. This risk is not well understood but might be contributed to by alcohol and substance misuse,¹⁵⁷ disappointment due to weight regain and recurrence of obesity-related

comorbidities after initial remission,¹⁵⁸ neurohormonal changes after some surgical procedures,¹⁵⁹ and high rates of pre-existing mental illness.

The effect of newer pharmacotherapies on similar outcomes is under investigation. The GLP-1RA class of medications has been in clinical use for nearly 20 years with no earlier signal for adverse effects on mental health. In April, 2024, the European Medicines Agency completed a review of data on suicidal thoughts and self-harm in people using these agents and concluded that the available evidence did not support a causal association.¹⁶⁰ Reports of large prospective randomised⁷⁹ and real-world data¹⁶¹ reported no increase in the risk of suicidality. Based on preclinical data showing GLP-1 receptor agonists reduce consumption of alcohol and modify neural responses to addictive drugs, several clinical trials are in progress investigating their potential to treat alcohol and substance use disorders.

Nutritional deficiencies

Meal replacement in very low-energy diet programmes can improve nutritional status as they contain high-quality protein and essential vitamins and minerals. In contrast, there is a risk of nutritional deficiencies resulting from bariatric surgery and pharmacotherapy (due to smaller and likely unbalanced food portions) without appropriate attention to adequate nutrient intake.¹⁶² Common deficiencies include vitamins (such as vitamin D and B12), minerals (such as calcium, magnesium, and iron), and essential fatty acids. These deficiencies can have health implications and might require dietary adjustments or supplements.

Outstanding research questions

Despite the incredible progress in the last two decades in our understanding of obesity and the development of increasingly effective and safer treatment options, many questions remain unanswered.

Obesity is undertreated in clinical practice,¹⁶³ and it is imperative to find strategies to overcome the numerous barriers to implementation of effective obesity care in routine practice, such as a perceived insufficient time and training among health-care providers, insufficient funding models for provision of co-ordinated multidisciplinary care, and the major bias against the treatment of obesity compared with other chronic diseases, including among health-care providers.

How to manage obesity at scale over the long term in both a cost-conscious and equitable manner is a related high-priority question. The prohibitive cost of medications, and hence their unfavourable cost-effectiveness at a population level (and inaccessibility to patient payers), remain important barriers to their widespread use.^{164–166} Prioritisation of treatment of people at highest risk of complications, or those most likely to respond, might be necessary. However, at present, there are no straightforward or reliable ways to predict these

outcomes. Stringent health economic analysis might be the best way to ensure equity and value for money to the population at large.^{167,168}

How to prospectively determine optimal treatment goals and approaches for each individual remains uncertain. For example, although treatment targets are used widely in chronic disease management, it is still unclear whether for obesity the target should account for the starting point (eg, weight loss of 15%), or be fixed (as is more common in other chronic diseases, eg, a goal BMI). Either way, the fact that these are surrogate markers for the overarching goal of improving health must be acknowledged. When and how to optimally combine different treatment modalities, and to what extent the benefits of various therapies are driven by weight loss or weight-independent effects, remains to be established. For example, what lifestyle intervention would optimise the benefits of highly effective medications?⁹⁴ The traditional approach of adding medications to lifestyle interventions has been unsuccessful might need to be re-evaluated considering evidence of the benefits of obesity medications in people with a good response to lifestyle interventions.⁹¹ A similar principle might apply to the combination of medications and bariatric surgery.

The cardiovascular benefits seen in the SELECT study raises the question of whether this is an effect specific to semaglutide, a GLP-1 receptor agonist class effect, or an effect of weight loss of more than 10% bodyweight. Whether GLP-1 receptor agonists have weight-independent benefits on cardiovascular risk will be challenging to untangle. Bariatric surgery has consistently shown, in observational studies, to have cardiovascular benefit.¹¹² Comparing cardiovascular outcomes following similar weight loss induced by bariatric surgery or pharmacotherapy would be informative.

Accepting that medications have weight loss-independent benefits appears easier than accepting that bariatric surgery has weight loss-independent benefits.^{82,84,169,170} However, further studies might provide an opportunity to understand why GLP-1 receptor agonist-based medications appear equally effective after bariatric surgery and, more importantly, whether the benefits of surgery and medications are synergistic when combined.¹⁷⁰

Finally, the need to improve access to effective obesity treatment for affected individuals is not in competition with the need for population-level prevention strategies. Both approaches are fundamental in tackling this growing public health problem. Advances over the last decade in prevention of obesity with population-based strategies have been incremental and insufficient.¹⁷¹ There is a pressing need to identify effective strategies and policies and implement them at a societal level.

Conclusions

Obesity is a growing global epidemic with major health consequences. Lifestyle interventions targeting improvements in eating patterns, physical activity, stress

management, and sleep quality are the mainstay of treatment for obesity and important components of any treatment approach geared to improve long-term health outcomes. However, lifestyle interventions are seldom sufficient to reach and maintain treatment goals in the absence of additional therapeutic interventions. The pharmacological treatment of obesity has experienced substantial progress in the last decade and has a promising pipeline that is likely to further revolutionise treatment of obesity. Bariatric surgery remains a proven effective and safe obesity treatment. Although these treatments offer considerable benefits for individuals affected by obesity, it is crucial to enhance prevention efforts and explore effective interventions that are scalable irrespective of sociodemographic considerations to curtail the ongoing obesity epidemic.

Contributors

All authors contributed to the design of the review, data review, initial drafting, and subsequent edits. All authors approved the final submission. All authors contributed equally to this manuscript.

Declaration of interests

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