REVIEW

Navigating obesity: A comprehensive review of epidemiology, pathophysiology, complications and management strategies

Ning Xiao,[1,13,19] Yi Ding,[2,14,19] Bing Cui,[3,19] Rong-rong Li,[4,19] Xin-ru Qu,[5,15,16,19] Hong Zhou,[6,19] Ka-hei Au,[7,19] Xiu-de Fan,[8,19] Jin-chen Xie,[9,19] Yuan Huang,[11,19] Shu-min Zhang,[1,13] Hong-yi Du,[1,13] Yi-fan Wu,[1,13] Peng Wang,[1,13] Xiao-fei Hu,[12,*] You-fa Wang,[9,*] Jia-jun Zhao,[8,*] Wah Yang,[7,*] Ying Wang,[10,*] Xiao-lei Zhang,[5,15,16,17,18,*] Wei Chen,[4,*] Yao-hua Zhang,[3,*] Sheng-shou Hu,[1,*] Yu-fang Bi,[2,14,*] and Xue Feng[1,13,*]

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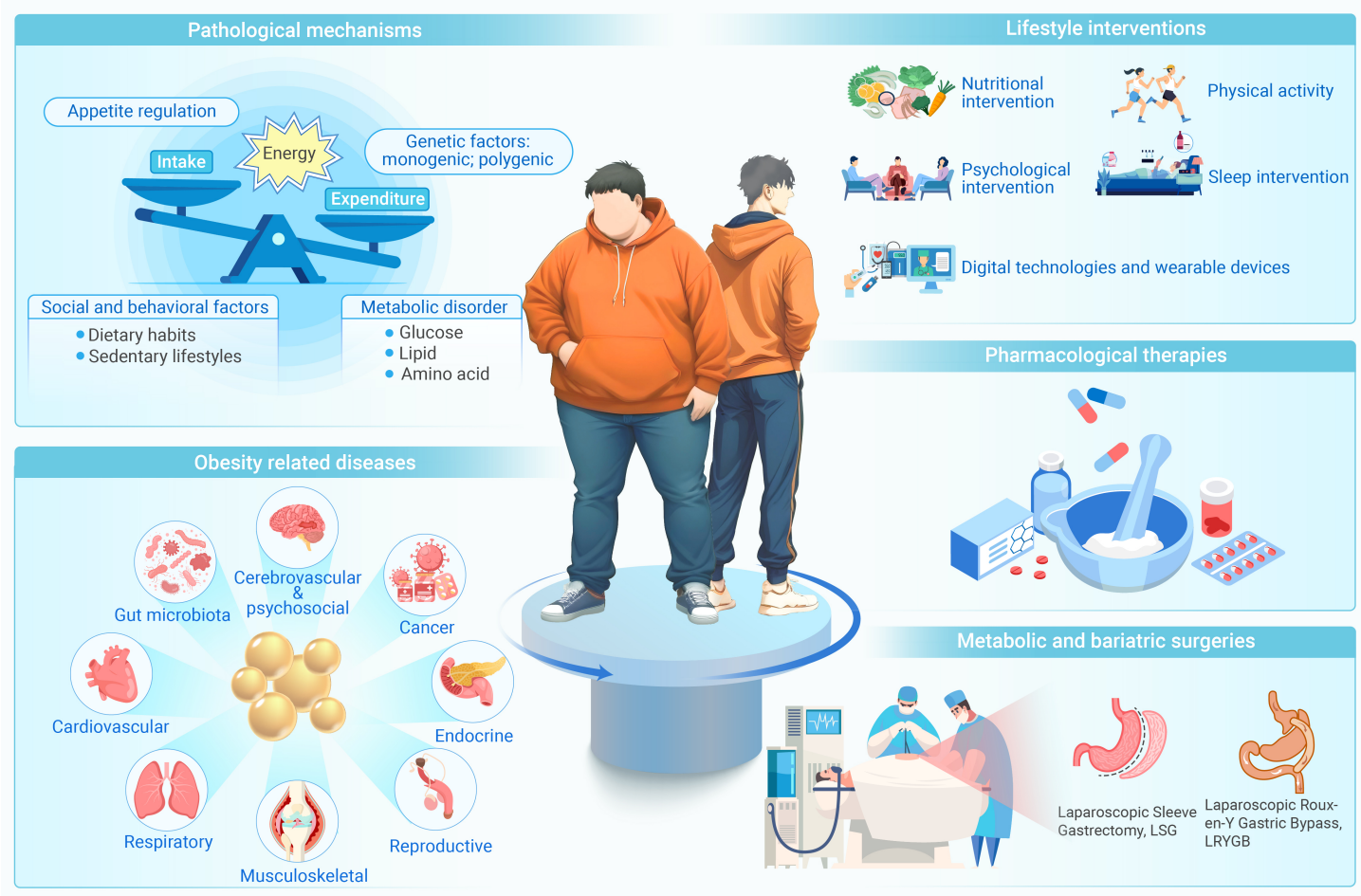
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Lifestyle interventions are the preferred method for obesity intervention and treatment.
- Advancements in digital technology and wearable devices provide a new pathway for obesity management.
- Interdisciplinary collaboration is crucial for obesity intervention.

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Obesity, a growing global health crisis, is driven by a complex interplay of genetic, biological, environmental, behavioral, socio-cultural, and economic factors. This comprehensive review encapsulates the epidemiology, pathophysiological mechanism, and the myriad of health complications it triggers, such as cardiovascular diseases (CVDs), cancer, neurological disorders, respiratory ailments, digestive diseases, mobility impairments, and psychological stress. The etiology of obesity is multifaceted, involving genetic predispositions, environmental influences, behavioral tendencies, and socio-economic elements. The pathophysiological underpinnings of obesity encompass multifaceted aspects of energy metabolism, including the regulation of appetite, glucose, lipid, and amino acid metabolism. This review also addresses the seemingly contradictory roles of obesity in various diseases, offering insights into these phenomena. The management of obesity is multi-pronged, including lifestyle modifications, pharmacological interventions, and metabolic surgeries. Lifestyle changes are foundational, but advancements in molecular techniques, digital technology, wearable devices, and artificial intelligence are opening new avenues for personalized treatment and early intervention. Pharmacological treatment and metabolic surgery are effective but should be judiciously tailored to individual patient needs. This review underscores the importance of a multifaceted approach to obesity management, aiming to curb the escalating trend and enhance future interventions and treatments. The ultimate goal is to synthesize current evidence and innovative strategies to combat obesity effectively.

INTRODUCTION

Obesity is a global health issue that impacts health and health-related outcomes. The World Health Organization (WHO) has defined obesity as "abnormal or excessive fat accumulation that represents a health risk",[1] with a body mass index (BMI) ≥ 30 kg/ m². The incidence of obesity has surged across the globe, affecting both genders. Currently, over one billion individuals are obese. Data from 2022 indicate that 43% of adults are classified as overweight.[2,3]

Obesity is recognized as a chronic metabolic disorder that is driven by interactions among genetic, biological, environmental, behavioral socio-cultural, and economic factors.[4–8] Although numerous medications are available for the treatment of obesity, we still lack a thorough understanding of the disease's pathogenesis and progression.

Obesity, with numerous complications, has raised increasing concerns regarding the deteriorating situation. Evidence shows that obesity severely affects both physical and psychological health, leading to CVDs, diabetes mellitus, cancers, neurological disease, respiratory disease, and digestive disease, but also sleep disturbance, mobility difficulties, and psychological distress.[9]

Currently, lifestyle interventions are the mainstay for obesity management among children and adults. Lifestyle change is an approach to obesity treatment that addresses priorities and concerns about health and quality of life. However, lifestyle interventions are difficult for many patients to maintain. Many obese patients have increasingly turned to pharmacological treatments and metabolic surgery, as these options are also effective and

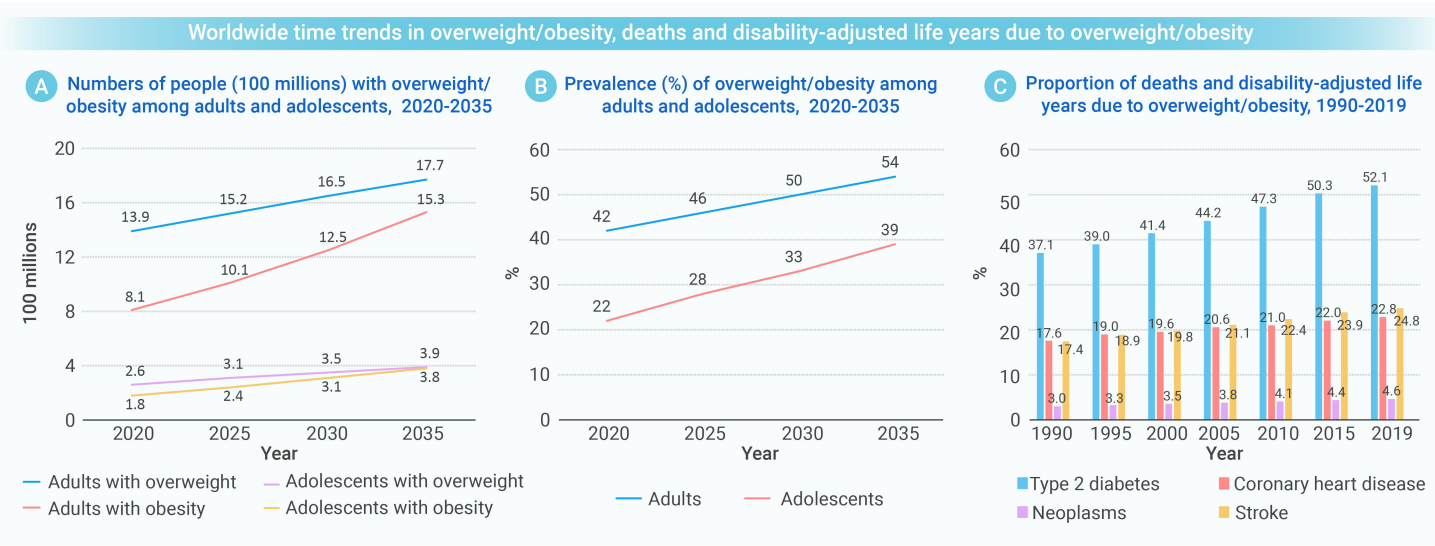

Figure 1. Worldwide trends in overweight/obesity, deaths, and disability-adjusted life years due to overweight/obesity (A) Numbers of people (100 million) with overweight/obesity among adults and adolescents, 2020-2035. (B) Prevalence (%) of overweight/obesity among adults and adolescents, 2020-2035. (C) Proportion of deaths and disability-adjusted life years due to overweight/obesity, 1990-2019. Data source: World Obesity Atlas 2024. London: World Obesity Federation. Available at: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2024.

sustainable interventions for obesity.

In this review, we synthesized a vast array of literature, providing a nuanced perspective on the complex relationship between obesity and health outcomes. We explored the epidemiology and pathophysiological mechanisms of obesity and identified the multiple health complications and associated diseases caused by obesity. We also explored the paradoxical role of obesity in various diseases, elucidating potential explanations for these phenomena. In addition, the efficacy of lifestyle interventions, wearable device interventions, current drugs, and surgical treatments for obesity have also been summarized.

EPIDEMIOLOGY AND DISEASE BURDEN

Obesity has become a major public health problem worldwide.[10] In 2020, 2.2 billion adults were overweight (BMI ≥ 24 kg/m²) or obese (BMI ≥ 28 kg/m²), representing 42.3% of the global adult population. By 2035, these numbers may rise to 3.3 billion and 54.2%, respectively.[11] The United States and China have the largest numbers of people with overweight and obese individuals. In 2023, approximately 41.9% of American adults had obesity,[10] and over 50.0% of adults in China were overweight or obese.[12]

Globally, the increase in overweight and obesity among youth is alarming. In 2020, 22.4% of 430 million adolescents and children (5-19 years old) were affected. By 2035, these numbers may increase to 39.2% and 770 million (Figure 1).[11]

Moreover, the majority of affected individuals are increasingly from low- and middle-income countries (LMICs). In 2020, over 65.1% of overweight and obese adults and more than 80.0% of affected children were from LMICs. By 2030, the proportion of adults may rise to 70.0%, and most affected children will be from LMICs.[11]

The health burden of overweight and obesity

Of the 41 million deaths from chronic diseases annually worldwide, 5 million are attributable to overweight and obesity, with nearly 4 million resulting from diabetes, stroke, coronary heart disease, and cancer.[11] In China, noncommunicable disease-related deaths increased from 80.0% in 2002 to 86.6% in 2012, and 88.5% in 2019.[13] From 1990 to 2019, the proportion of deaths and disability-adjusted life years (DALYs) due to obesity-related chronic diseases has steadily increased.

The future health consequences of obesity are likely remarkable given the rapid increase in childhood obesity, which is associated with increased risks of obesity, premature death, and disability in adulthood. Overweight children are more likely to develop many health problems such as type 2 diabetes mellitus (T2DM), hypertension, and CVDs.[14]

Economic burden attributable to obesity

In 2020, the economic burden of obesity accounted for 2.4% of the global GDP and is projected to rise to $4.3 trillion by 2035.[11] In most countries, obesity treatment is not covered by their healthcare systems, making it challenging for disadvantaged groups to afford the high expenses of obesity treatment.[15] The estimated medical cost of obesity in China was 9.3 billion US dollars in 2010 and is projected to be 61 billion US dollars in 2030.[16]

Determinants and risk factors

Obesity is a result of the complex interplay of numerous factors, including biological, genetic, behavioral, social, and environmental factors. The increasing obesity trend worldwide is attributed to many socioeconomic factors and individual-level factors. These factors include economic development, rapid urbanization, urban planning, food systems, sociocultural norms, and national policies that have shaped individual-level risk factors for obesity.[17]

In many countries, over the past three decades, substantial changes in dietary patterns, including increased consumption of animal-source foods, fried food, refined grains, sugar-sweetened beverages, and highly processed, high-sugar, and high-fat foods and reduced intake of traditional diets that are rich in vegetables, have occurred.[17] According to the United Nations Food and Agriculture Organization, the global average caloric intake has increased from approximately 2,360 kcal per person per day in the early 1960s to approximately 2,960 calories in 2023.[18]

Moreover, physical activity levels have decreased with increasing sedentary behaviors, as a result of changes in occupation structure and living environments, including transportation systems.[17] More than a quarter of the global adult population is insufficiently active, and over 80% of adolescents have not met the recommended physical activity levels since the beginning of the 21st century.[19]

In general, there is a positive association between socioeconomic status and overweight and obesity in LMICs worldwide but an inverse association in high-income countries. However, this association seems to have changed in recent years, especially among females and in urban areas of LMICs.[20] Some countries show a positive association between socioeconomic status and overweight and obesity in males but an inverse association in females. This trend differs from the patterns observed in the United States and Europe.[20]

Obesity is a global health crisis, escalating rapidly in LMICs. Targeted interventions are essential, with extra support for disadvantaged groups.

PATHOGENESIS OF OBESITY

Obesity is influenced by both intrinsic and environmental factors, with genetics playing a key role. Studies indicate that obesity is heritable, with esti-

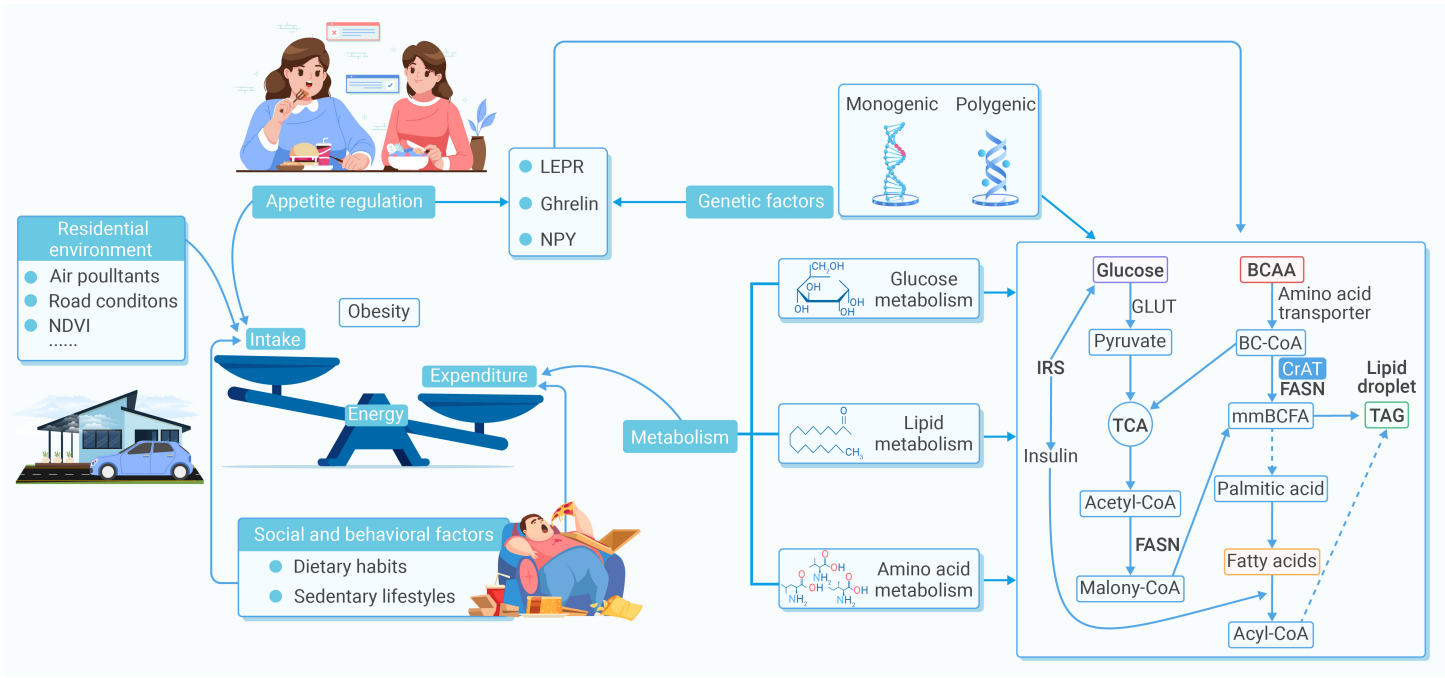

Figure 2. The pathogenesis of obesity Obesity is a multifactorial condition influenced by genetic and environmental factors. Heritability in obesity can be due to single-gene mutations or multiple genetic variations. Genetic regulation of appetite significantly impacts energy intake, and genetic anomalies can disrupt metabolic pathways, thereby affecting glucose, lipid, and amino acid metabolism. The residential environment and sedentary lifestyles contribute to increasing obesity rates, as energy intake exceeds energy expenditure. BCAA: branched-chain amino acid; *CrAT*: carnitine acyl transferase; mmBCFA: monomethyl branched-chain fatty acid; *GLUT*: glucose transporter; NDVI: normalized difference vegetation index.

mates ranging from 40% to 70%.[21] Obesity is influenced by both monogenic and polygenic genetic factors. Monogenic obesity, which is rare, is caused by mutations in single genes, such as leptin (*LEP*), leptin receptor (*LEPR*), and melanocortin 4 receptor (*MC4R*), which primarily affect the leptin-melanocortin signaling pathway, leading to severe early-onset obesity.[22] Polygenic obesity results from multiple genetic variations that increase obesity risk. Key genes include fat mass and obesity-associated protein (*FTO*), transmembrane protein 18 (*TMEM18*), and glucosamine-6-phosphate deaminase 2 (*GNPDA2*), which influence BMI and body weight regulation.[23] Khera et al. developed a polygenic risk score using millions of genetic variants and demonstrated a strong link between polygenic scores and obesity risk.[24] Obesity-related gene variants in genes involved in adipokine and fat distribution have been linked to inflammation and insulin resistance (IR). The upregulation of G-protein-signaling modulator 1 (*GPSM1*) and CXC motif chemokine ligand 10 (*CXCL10*) and its receptor CXC chemokine receptor 3 (*CXCR3*) signaling activates nuclear factor kappa-B (*NF-κB*), increasing pro-inflammatory cytokines tumor necrosis factor-alpha (*TNF-α*) and interleukin-6 (*IL-6*). Besides genetic factors, epigenetic modifications such as DNA methylation, histone changes, and non-coding RNAs also contribute to obesity and its related health issues.[25]

The primary etiology of obesity stems from a disparity between energy intake and expenditure, resulting in weight gain as the predominant outcome. Genetic and epigenetic alterations can disrupt metabolic processes, specifically glucose, lipid, and amino acid metabolism. These alterations significantly disrupt the energy balance and are intricately associated with the development of obesity. The regulation of appetite and energy metabolism are critical components in the pathogenesis of obesity.

Key genes involved in appetite regulation include *LEPR*, ghrelin (*GHRL*), neuropeptide Y (*NPY*), insulin receptor substrate (*IRS*), and glucose transporter 4 (*GLUT4*).[26] Hormonal signaling, particularly involving insulin and leptin, influences appetite regulation by modulating key signaling pathways like the AMP-activated protein kinase (*AMPK*) and mammalian target of rapamycin (*mTOR*) pathways.[27] These pathways regulate energy expenditure and satiety. Insulin and leptin resistance, linked to genetic predisposition and poor dietary choices, interfere with the body's regulatory processes, resulting in heightened appetite, energy consumption, and ultimately, the development of obesity.[28] This intricate interplay between appetite regulation and metabolic pathways underscores the complexity of obesity etiology. Energy metabolism in obesity involves a complex network of factors, including disruptions in glucose, lipid, and amino acid metabolism; genetic predisposition; and epigenetic changes. These factors collectively regulate body weight.[29,30]

Glucose serves as a primary energy source for the human body. Disrupted gene signaling in glucose metabolism significantly contributes to obesity. Variations in *IRS1* and *IRS2* genes impair insulin signaling, causing IR and altering glucose metabolism, which promotes fat storage. Additionally, abnormal expression of the glycogen synthase gene (*GYS*) worsens fat accumulation by affecting glycogen synthesis and blood glucose levels.[31,32]

Genetic anomalies that disrupt lipid metabolism pathways also drive the development of obesity. Aberrant expression of genes such as *ACACA* and *FASN*, which are involved in fatty acid synthesis, promotes excessive fat accumulation when aberrantly expressed. Concurrently, dysregulated expression of genes such as *PPARα* and *PPARGC1α* disrupts fatty acid oxidation, compromising energy production and exacerbating obesity.[33]

In the amino acid metabolism pathway, dysregulated gene signaling pathways can affect the levels of branched-chain amino acids (BCAAs) and glutamine, consequently influencing energy metabolism and fat deposition. Variations in genes such as *BCAT1* and *BCAT2* alter BCAA levels, whereas metabolism and fat deposition. Moreover, abnormal expression of the glutaminase gene (*GLS*) affects glutamine metabolism, thereby influencing fatty acid synthesis and energy metabolism.[34,35]

Besides intrinsic factors, social-environmental elements and behaviors also predispose individuals to obesity. Societal influences like dietary habits and sedentary lifestyles play a major role in the obesity epidemic.[36] The increasing prevalence of high-caloric diets and reduced levels of physical activity exacerbate this phenomenon.[37,38] Children and adolescents are especially prone to obesity because of their rapid growth, and their living environment plays a crucial role. A study of more than 214,000 Chinese youth revealed that air pollution, poor road conditions, and high built density increased obesity risk, whereas a greater normalized difference vegetation index (NDVI), forests, and specific weather conditions reduced risk.[39] A study of 20,677 US children found that living in high-opportunity, low-vulnerability neighborhoods, especially from birth, was associated with a lower risk of obesity from childhood to adolescence (Figure 2).[40]

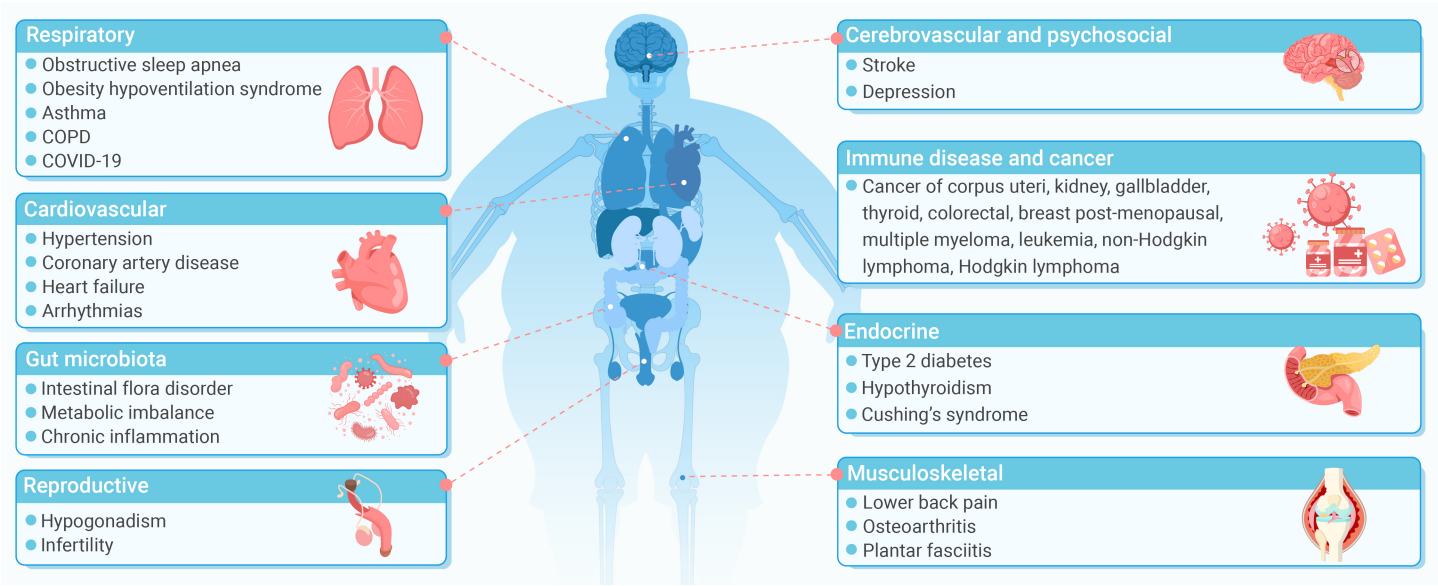

Figure 3. Obesity-related diseases affect multiple systems in the human body.

OBESITY-RELATED DISEASE FOR MULTIPLE SYSTEMS

Obesity has extensive adverse effects on health. Here, we delineate the multiple health complications and associated diseases engendered by obesity, including CVDs, cancer, neurological disorders, respiratory ailments, digestive diseases, mobility impairments, and psychological stress (Figure 3).

Obesity and CVDs

Obesity is a firmly established risk factor for the development of CVD, presenting distinctive challenges in the maintenance of cardiovascular health. Obesity directly fosters the onset of various cardiovascular risk factors, such as dyslipidemia, T2DM, hypertension, and sleep disorders.[41] Although studies have used various indicators, such as waist circumference,[42] body fat percentage,[43] visceral fat,[44] BMI, and waist-to-hip ratio,[45] all the findings indicate that obesity increases the risk of CVDs. Notably, obesity correlates with an increased occurrence of hypertension, coronary artery disease, heart failure, and arrhythmia.

Obesity and hypertension. Excess adiposity leads to higher blood pressure (BP) through activation of the renin-angiotensin-aldosterone and sympathetic nervous systems.[46] A meta-analysis of 57 prospective cohort studies, pooling 2.3 million individuals, reported a 1-2-fold increase in the risk of developing hypertension with increasing various obesity indices, such as BMI, waist circumference, and waist-to-height ratio.[47] All major hypertension guidelines recommend weight loss for the management of BP in individuals with overweight or obesity.[48]

Obesity and coronary artery disease. Compared with individuals with normal weight, patients with obesity experience chronic coronary disease (CCD) events at an earlier age, live with CCD for a greater proportion of their lifetime, and have a shorter average life span.[41] The APPROACH registry revealed that patients with class 3 obesity and high-risk coronary anatomy experienced higher 5- and 10-year mortality rates after percutaneous coronary intervention (PCI) than did those with a normal BMI (odds ratio of 1.78 at 5 years and 1.57 at 10 years).[49] Excessive adiposity not only accelerates atherosclerosis but also induces detrimental changes in cardiac function by affecting the myocardium. Studies have linked obesity with an increase in circulating inflammatory mediators, accompanied by alterations in fibrinolysis and coagulation, which can contribute to endothelial dysfunction and atherosclerosis.[50-53] Moreover, inflammation triggered by obesity heightens the probability of low-density lipoprotein oxidation.[54,55] The AHA included recommendations for CCD management in 2023 guidelines,[56] which suggest that patients with CCD and overweight or obesity should receive counseling on diet, lifestyle, and weight loss goals.

Obesity and heart failure (HF). Excess adiposity promotes changes in cardiac function.[57] Obesity also directly affects the myocardium through myocardial fat accumulation and subsequent fibrosis, which can lead to the development of left ventricular diastolic dysfunction (LVDD) and HF with preserved ejection fraction (HFpEF). A study of 5,881 participants from the Framingham Heart Study demonstrated that the incidence of HF rose by 5% in men and 7% in women for every one-unit increase in BMI, even after adjusting for other risk factors. Moreover, the risk of HF trended to increase across the entire BMI range. Several large, prospective epidemiological studies have confirmed these results.[58]

Obesity and arrhythmias. Obesity significantly increases the risk of developing various cardiac arrhythmias, including atrial fibrillation (AF) and sudden cardiac death (SCD). Research has demonstrated a 16% increase in SCD risk with every 5-unit increase in BMI, highlighting obesity as a major nonischemic contributor to SCD.[59] Additionally, obesity, particularly abdominal adiposity, has been identified as a notable risk factor for SCD.[60]

Obesity poses a significant risk for CVDs, contributing to hypertension, coronary artery disease, heart failure, and arrhythmias. While the obesity paradox suggests better outcomes in some patients, excess adiposity accelerates atherosclerosis and adversely affects cardiac function. Weight loss remains crucial for managing cardiovascular health, emphasizing the importance of lifestyle interventions in combating obesity-related cardiovascular risks.

Obesity and cerebrovascular and psychosocial diseases

Obesity is a substantial risk factor for a range of neurological disorders, including stroke, cognitive decline, neurodegenerative diseases, and mental health conditions. The intricate relationship between obesity and brain pathology is mediated through hormonal, inflammatory, and vascular mechanisms, which collectively contribute to neuronal dysfunction and the progression of brain disease.

Excess adiposity significantly raises the risk of cerebrovascular diseases, especially stroke. A study suggests a J-shaped dose-response relationship, with the lowest risk observed at a BMI of 23-24 kg/m² and a substantial increase in risk at BMI values exceeding 25 kg/m².[61] A large study of 26,185 people over an 11.8-year found 1,507 new stroke cases, showing higher stroke risk with increasing BMI.[62]

The brain, specifically the hypothalamus, regulates body weight by controlling appetite, food intake, and energy use. The brain maintains energy balance by integrating signals like leptin and insulin with neural inputs to manage hunger and fullness.[63]

The melanocortin system is a crucial part of the brain's response to obesity. Leptin stimulates the hypothalamus to release appetite-suppressing peptides, reducing food intake and boosting energy expenditure. However, obesity can cause leptin resistance, diminishing the brain's response to leptin

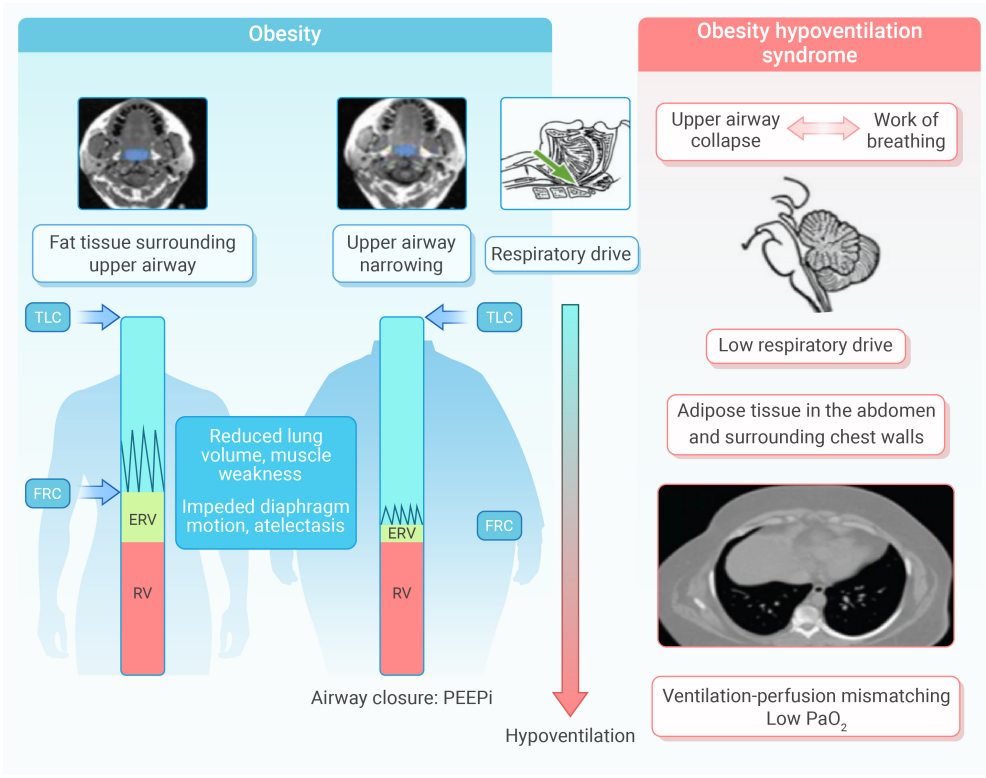

Figure 4. Effect of obesity on respiratory physiology An increased BMI can contribute to a reduction in pulmonary volume. Fat tissue surrounding the upper airway can result in upper airway narrowing and collapse. Tissue in the abdomen and surrounding chest walls can lead to ventilation-perfusion mismatching and hypoxia. Ventilation drive in obese patients compensates for respiratory work and low respiratory efficiency. In patients with OHS, the failure of this mechanism and a decline in central drive will lead to hypercapnia and hypoxemia.

satiety signals and potentially leading to further weight gain.[64] Additionally, lower leptin levels have been implicated in reduced hippocampal volume and impaired memory performance.[65]

Obesity leads to chronic low-grade inflammation that can compromise the blood-brain barrier and cause neuro-inflammation. Pro-inflammatory cytokines such as *IL-6* and *TNF-α* from adipose tissue can cross into the brain, impacting function and potentially leading to cognitive decline and neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.[66,67]

Psychological factors also play a significant role in obesity. Psychological conditions, including stress, anxiety, and depression, have the potential to modify neural function, resulting in dysregulated eating behaviors and eating in response to negative emotions (EE). Stress can activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels, which may contribute to weight gain, especially in the abdominal region.[68] People with obesity commonly face a pervasive, resilient form of social stigma. While EE is a mediator between depression and obesity, obesity unequivocally influences and potentially exacerbates depressive symptoms.[69,70] The brain's role in obesity is complex, requiring more research to understand its mechanisms and develop effective treatments.

Obesity and endocrine disease

The prevalence of endocrine disorders in obese patients is considerable but heterogeneous across different diseases.[71] The bidirectional relationship between obesity and endocrine diseases is complex. Common endocrine disorders associated with obesity are summarized below (Table S1).

Insulin – T2DM, insulinoma. Obesity is considered a vital risk factor and driver of the worldwide increase in T2DM and other metabolic diseases.[72,73] Conversely, early muscle IR in T2DM patients causes excessive fat accumulation.[74] As recommended by ACE/AACE, individuals with obesity and experiencing progressive weight gain should be screened for prediabetes, T2DM, and metabolic syndrome.[5,75]

Insulinoma is the most common functioning endocrine neoplasm of the pancreas, but tumors are rare, with an incidence of 0.7-4 cases per million annually.[76] Characterized by hypoglycemia and hunger, insulinoma can be linked to hyperphagia, which sometimes induces weight gain and overt obesity.[8,77]

Thyroid hormone - hypothyroidism. Hypothyroidism, a thyroid hormone deficiency, ranks among the most prevalent endocrine diseases.[78] Hypothyroidism is closely linked to obesity due to the influence of thyroid hormones on metabolism through the regulation of basal metabolic rate and promotion of lipolysis, glycogenolysis, and glyconeogenesis.[79] Hypothyroidism-associated weight gain may arise from body fat accumulation, water retention, and increased deposition of glycoaminoglycans.[12-14] However, the causal relationship between lower thyroid function and weight gain, or whether weight gain stimulates the pituitary-thyroid axis, leading to increased serum TSH levels, remains uncertain.[80] Given the high prevalence of hypothyroidism and its associated comorbidities accompanied by obesity, both ESE[81] and ACE/AACE recommend routine assessment of thyroid function in individuals with obesity.

Glucocorticoids – Cushing's syndrome (CS), pseudo- Cushing's syndrome. CS results from chronic exposure to excess glucocorticoids from either exogenous pharmacological agents or an endogenous source of cortisol.[82] Glucocorticoids play crucial roles in metabolic regulation, and a combination of increased fat storage, heterotopic fat distribution, IR, and fluid retention contribute to the characteristic weight gain and central obesity in CS. The estimated incidence of CS ranges from 2-8 per million people annually.[83] Among obese patients, the pooled prevalence of hypercortisolism was 0.9% (95% CI: 0.3–1.6).[71] Weight gain is among the most common nonspecific features of CS, as was observed in 57–100% of patients.[84] In particular, CS-related obesity manifests as abdominal rather than generalized weight gain.[84] Considering the epidemic of obesity and the relatively low proportion of CS in obese patients, routine screening for CS is not recommended unless specific features of hypercortisolism are found.[81,83] For diagnosis, exogenous exposure to glucocorticoids should be excluded first. First-line tests including urine cortisol, salivary cortisol, and serum cortisol, should be performed.[85,86]

Syndromic and monogenic obesity. In patients with early-onset severe obesity, the most common forms of syndromic obesity include Prader-Willi syndrome (PWS) and Bardet-Biedl syndrome (BBS).[87] In children with non-syndromic early-onset severe obesity, an estimated 7% of cases may be attributed to monogenic obesity,[88] including those most commonly related to a single genetic variant in the leptin-melanocortin signaling pathway.[89,37] Additionally, some genetic variations related to energy homeostasis also exert a pronounced influence on early-onset obesity.[38-41]

Other abnormalities. Other hormone abnormalities, although rare, are also associated with obesity.[90,91] Secondary endocrine hypertension is also associated with obesity, with primary aldosteronism (PA) being the most common manifestation.[92-94] Besides, pregnancy and aging are related to specific alterations in hormones; therefore, obesity-associated endocrine disorders during these stages require special considerations.[81]

Obesity and respiratory disease

Effect of obesity on respiratory physiology. Obesity can affect respiratory function in numerous ways. Multiple studies indicate that higher BMI reduces pulmonary volume.[95,96] Specifically, functional residual capacity (FRC) decreases by about 3% and expiratory reserve volume (ERV) decreases by 5% for each unit increase in BMI from 20 to 30 kg/m². Additionally, total lung capacity (TLC), vital capacity (VC), and residual volume (RV) each decrease

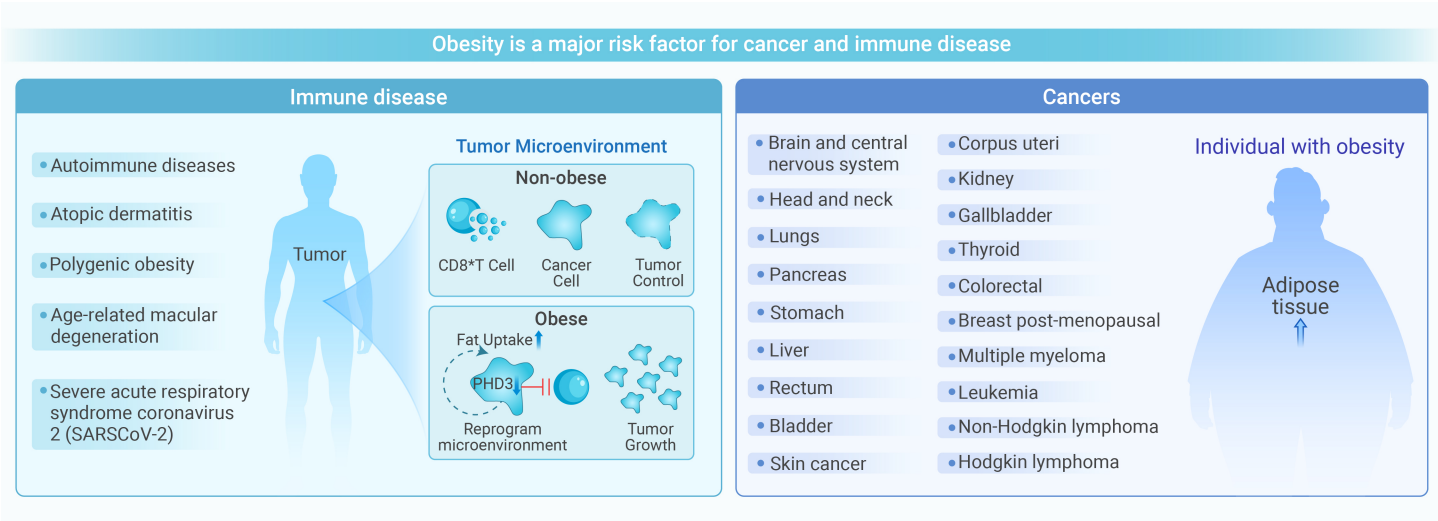

Figure 5. Obesity is a major risk factor for cancer and immune disease Obesity affects the number and function of $CD8^+$ T cells in the tumor microenvironment and promotes immune disease and cancer growth.

by approximately 5% per unit increase in BMI.[97-99] Total respiratory compliance in obese patients has also been shown to decrease by as much as two-thirds compared with normal values.[100] Reduced lung compliance lowers total lung volume and raises intrinsic positive end-expiratory pressure due to airway closure. Abdominal and chest wall tissue can cause ventilation-perfusion mismatch and hypoxia. Additionally, increased tongue and pharyngeal wall volume are independent risk factors for upper airway collapse in obese patients with sleep-disordered breathing (Figure 4).[101,102] Furthermore, the pro-inflammatory state caused by obesity is also a potential factor in airway hyperresponsiveness in obese individuals.[103,104]

Obesity-related respiratory diseases. *Obesity and sleep-disordered breathing.* Obesity is the main risk factor for obstructive sleep apnea (OSA). OSA is characterized by repeated episodes of complete or partial collapse of the upper airway during sleep. Approximately 50% of OSA patients are obese, while the prevalence of OSA among obese individuals is approximately 40%.[105] Obesity hypoventilation syndrome (OHS) is another sleep-related hypopnea disorder that can be caused by severe obesity and mainly exhibits chronic hypercapnia and hypoxemia.[106,107] In obese patients, ventilation compensates for respiratory effort and inefficiency. However, in patients with OHS, the failure of this mechanism and reduced central drive can cause hypercapnia and hypoxemia, leading to respiratory failure, pulmonary hypertension, and other serious conditions.[108,109]

Obesity and asthma. Obesity may improve the prevalence, incidence, and severity of asthma[110]. Compared with slim asthma patients, overweight asthma patients are more likely to be hospitalized and have a lower quality of life.[110,111] Obesity often contributes to asthma by reducing lung volume and chest wall compliance. In addition, a unique "extra obese asthma phenotype," marked by fewer eosinophils and more neutrophils in sputum, has been distinguished. This phenotype exhibits more severe symptoms like panting, airway obstruction, and airway remodeling, and shows less responsiveness to glucocorticoid therapy.[112,113] While some studies indicate that weight loss may benefit certain asthma patients, there is insufficient evidence to determine its effects across different asthma phenotypes.[114]

Obesity and chronic obstructive pulmonary disorder (COPD). Obesity may be a risk factor for COPD or vice versa.[115] In a study from the Netherlands, obesity was more prevalent in early COPD stages GOLD I-II and less prevalent in patients with COPD GOLD IV.[116,117] The mechanisms underlying the associations between obesity and COPD are unclear. It's possible that obesity and COPD mutually amplify their effects on pulmonary mechanics and ventilatory demand. An obesity paradox phenomenon was reported in patients with COPD, with increased BMI potentially being a protective factor in some patients. Data suggests that there is a tendency towards increased mortality in patients with COPD who are underweight.[118] However, it must be noted that this paradox is influenced by the heterogeneous phenotypes of COPD. In mild COPD patients, obesity appears to increase the risk of cardiovascular morbidity.[119]

Obesity and COVID-19. Multiple reports have demonstrated that obesity can increase the incidence of COVID-19 pneumonitis and the risk of hospitalization and death.[120,121] Several mechanisms explain the relationship between obesity and COVID-19. For example, *IL-16*, which can be secreted by adipose tissue, is a risk factor affecting the severity of COVID-19, and obesity can improve the impact of *IL-16* on COVID-19 severity.[122,123] Besides, adipocytes act as reservoirs and replication sites for SARS-CoV-2,[124] which can be beneficial for virus reproduction. Furthermore, obese individuals are more likely to suffer from chronic diseases such as hypertension, CVDs, and T2DM, which can also contribute to increased morbidity and mortality in patients with COVID-19.[125]

Obesity and reproductive disease

Obesity significantly impacts reproductive health and sexual function through a complex interplay of hormonal, metabolic, and inflammatory mechanisms, affecting both men and women.[126] In women, obesity can cause hormonal imbalances like IR and high insulin levels, disrupting the menstrual cycle and ovulation. Excess fat tissue converts androgens to estrogens, possibly leading to estrogen dominance, which can harm fertility and raise the risk of endometrial hyperplasia and gynecological cancers due to prolonged high estrogen exposure.[127] In men, obesity is associated with reduced sperm quality and quantity due to increased scrotal temperature and hormonal disruptions, such as decreased testosterone levels, which are pivotal for spermatogenesis and sexual function.[128] Moreover, obesity can lead to a decrease in libido and erectile dysfunction, further affecting sexual performance and satisfaction.[129]

The adipose tissue's role as an active endocrine organ is central to obesity-related reproductive and sexual dysfunction. Adipose tissue secretes adipokines like leptin and adiponectin, which can modulate reproductive hormone levels and functions. Leptin resistance, prevalent in obesity, disrupts hormonal pathways, whereas the effects of adiponectin on androgen levels may influence fertility.[130] Obesity-induced inflammation activates cytokines such as *TNF-α* and *IL-6*, contributing to oxidative stress and potentially impairing ovarian follicle development, endometrial function in women, and testicular function in men.[131] Beyond direct impacts on gamete quality, obesity can lead to comorbidities that indirectly affect fertility and sexual health. The increased risk of T2DM in obese individuals can impair fertility by affecting insulin signaling and blood flow to reproductive organs. Additionally, obesity is linked to a higher prevalence of polycystic ovary syndrome (PCOS), which is characterized by hormonal imbalances and ovarian cyst formation, leading to irregular menstruation and infertility in women.[4]

Understanding these mechanisms is vital for developing targeted interventions to improve reproductive health and sexual function in obese individuals. Lifestyle modifications, including a healthy diet and regular exercise, are

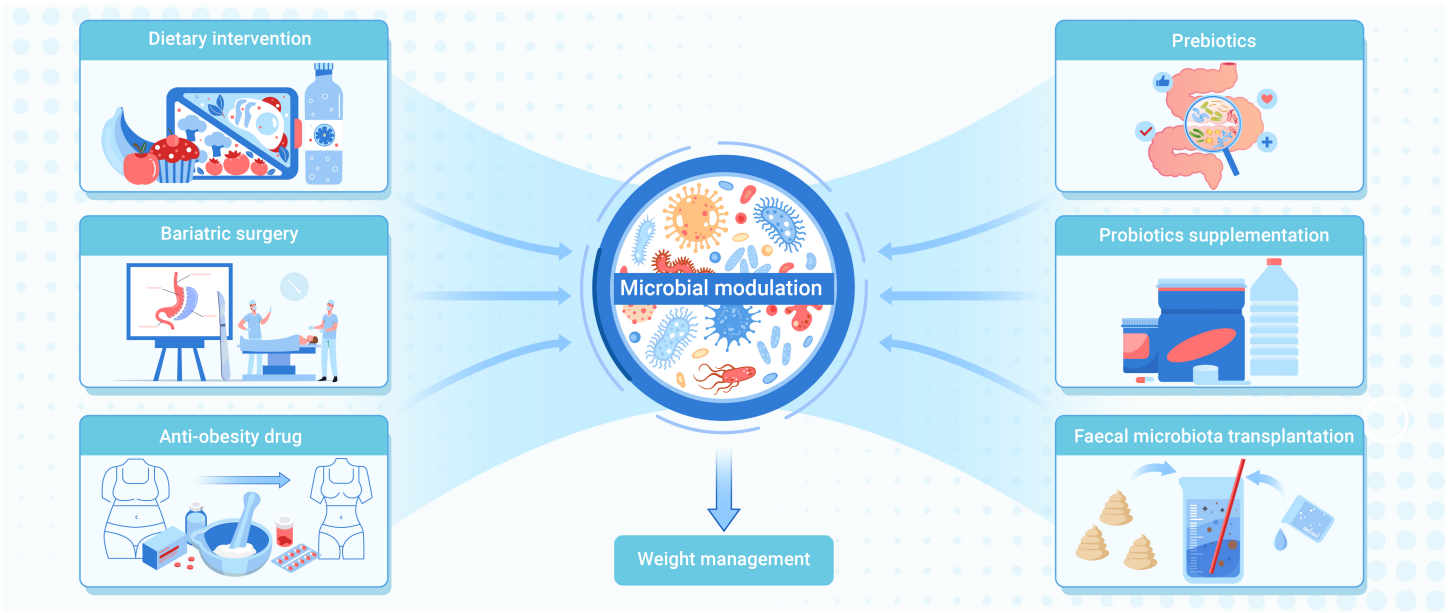

Figure 6. Microbial modulation and obesity In the context of obesity treatment, dietary intervention, prebiotics, probiotic supplementation, fecal microbiota transplantation, anti-obesity drugs and bariatric surgery all exert varying degrees of microbial modulation, ultimately contributing to weight management.

crucial for weight loss and can improve fertility by reducing IR, restoring hormonal balance, and enhancing the reproductive system's overall function.[132] Furthermore, addressing the chronic inflammation and oxidative stress associated with obesity may improve both reproductive health and sexual function. In conclusion, obesity's impact on reproductive health and sexual function is extensive and complex. Obesity has direct effects on gamete quality and sexual performance, as well as indirect effects through comorbidities. Addressing obesity is essential for improving fertility, reproductive health, and sexual well-being. Future research should focus on the specific roles of adipokines and inflammatory cytokines in reproductive function and disease, identifying potential therapeutic targets to mitigate the negative effects of obesity on fertility and sexual health.

Obesity and musculoskeletal disease

Excessive accumulation of fat in adipose tissue is the core characteristic of obesity. The musculoskeletal system must compensate for extensive fat deposition around the waist, inner thigh, and hips to maintain balance, which increases mechanical stress on bones and joints. Since morbid obesity is not physiologically or biomechanically sustainable. To compensate for the biomechanical balance, postural and skeletal derangements exhibited alteration. Obesity has serious effects on the hip, knee, and ankle joints.[133] The protrusion of the abdomen in obese individuals displaces the center of gravity forward, resulting in lumbar lordosis, and anterior pelvic tilt, and increases lumbar lordosis and sacrum slant angle. The anatomical alterations may be one reason for low back pain in obese individuals.[134]

Although there is evidence that risk factors associated with the initiation of degenerative joint disease may differ from those associated with pain and progression, obesity has been consistently identified as a risk factor for both the development and progression of osteoarthritis of weight-bearing joints; principally of the knee and, to a lesser extent, the hip.[135-138] Vismara et al. investigated correlations between chronic low back pain and loss of mobility among obese individuals. Their result showed that in obese patient static and dynamic adaptations in the kinematics of the spine: under static conditions, obesity was correlated with an increased anterior pelvic tilt; under dynamic conditions, to impaired mobility of the thoracic spine.[139]

In addition to bone and joint diseases, emerging evidence shows that obesity also has a far-reaching effect on soft-tissue structures, such as tendons, fascia, and cartilage.[140-142]

Obesity is a risk factor for developing plantar fasciitis.[143] Plantar heel pain is believed to stem from mechanical issues, often linked to prolonged weight bearing and obesity. Riddle et al. found that obese individuals (BMI > 30) are five times more likely to experience heel pain compared to those with a BMI under 25.[144]

Excessive weight is associated with musculoskeletal disorders in the back, hip, knee, ankle, and foot. Although the exact mechanisms are unclear, it is known that extra weight stresses bones, joints, and tissues, increasing injury risk. Obesity is a significant and adjustable risk factor for developing and worsening these conditions.

Obesity, immune diseases, and cancer

Obesity is a major risk factor for cancer. Obesity can negatively affect the number and function of $CD8^+$ T cells in the tumor microenvironment and promote tumor growth.[145] A higher BMI was positively associated with risk of 9 cancers (corpus uteri, kidney, gallbladder, thyroid, colorectal, postmenopausal breast, multiple myeloma, leukemia, non-Hodgkin lymphoma) and was positively associated with 3 additional cancers among never smokers (head and neck, brain and central nervous system and Hodgkin lymphoma).[146] Other studies[147,148] have shown that longer duration, greater degree, and younger age of onset of overweight and obesity during early adulthood are positively associated with the risk of 18 cancers, including leukemia, non-Hodgkin lymphoma, and head and neck, and bladder cancers which are not yet considered as obesity-related cancers in the literature among never-smokers. In the meta-analysis of both cohorts,[149] compared to participants with normal weight (BMI < 25 kg/m^2) and without CVD, participants with both exposures (BMI ≥ 25 kg/m^2 and CVD) had a 3.4 times higher risk of obesity-related cancer. Respective HR for participants with normal weight but with a CVD, and for participants with overweight/obesity without CVD were 2.68 and 1.23. Irrespective of cardio-metabolic disease (CMD) status, a higher BMI increases the risk of obesity-related cancer among European adults.

There were linear protective associations between cardiorespiratory fitness (CRF) and mortality after any cancer diagnosis, malignant skin cancer, non-Hodgkin lymphoma, and cancer in the lungs, head and neck, pancreas, stomach, liver, rectum, and bladder. Obesity was associated with increased mortality after any cancer (HR for obesity vs. normal weight 1.89), malignant skin cancer (HR 2.03), Hodgkin lymphoma (HR 2.86), and cancer in the head and neck (HR 1.38), thyroid (HR 3.04), rectum (HR 1.53), kidney (HR 1.90), bladder (HR 2.10), and prostate (HR 2.44).[150] The damage to hematopoietic stem cells caused by obesity is a long-term damage, once it occurs, it cannot be easily changed through weight loss or transplantation, which is related to blood diseases, especially leukemia. Obesity gene *FTO* plays an oncogenic role in acute myeloid leukemia and drug resistance as an N (6)-Methyladenosine RNA Demethylase, secifically.[151] A study also revealed that adipocyte-mediated upregulation of galectin-9 on B-ALL cells can be targeted with anti-

Table 1. Exercise prescriptions for overweight or obese adults

	Aerobic exercise	Resistance exercise	Flexibility exercises
Frequency	more than 5 days/week	2-3 days/week	more than 2-3 days/week
Intensity	Start with moderate intensity (e.g., 40%-50% VO2R or HRR, and gradually increase to higher intensity (≥60% VO2R or HRR) for more health gains	60%-70%1RM, which can be gradually increased to increase muscle strength and muscle mass	Stretch until you feel nervous or mildly uncomfortable
Duration	30 min/day, or 150 min/week; gradually increase to 60 min/day, or not less than 250-300 min/week	8-12 repetitions in at least 2-4 sets of different upper and lower body exercises	Static stretching for 10-30 sec, repeat each movement 2-4 times
Type	such as walking, cycling, swimming	free weights or weight machines	static stretching, dynamic stretching, and/or PNF stretching

VO2R = Reserve oxygen consumption; HR = heart rate; HRR = heart rate reserve; RM = repetition maximum; PNF=Proprioceptive neuromuscular facilitation

body-based therapies to overcome obesity-induced chemoresistance.[152]

Obesity was once considered a metabolic issue related to sugar, fat, and energy surplus. However, it is fundamentally an immune problem. Adipose tissue acts as an immunologically active organ, producing adipocytokines that influence systemic immune responses. Conversely, immune cells impact adipocyte homeostasis and metabolism through pro-inflammatory and anti-inflammatory cytokines.[153] Compelling epidemiological evidence[154] reveals a strong association between being overweight or obese and the risk of developing autoimmune diseases, that is metabolic overload caused by obesity can affect immune metabolism, thus changing the susceptibility to autoimmune diseases.

Recent evidence indicates that obesity can also influence the immune system[145] by converting the classical type 2 T helper (TH2)-predominant disease associated with atopic dermatitis to a more severe disease with prominent TH17 inflammation. This change not only causes obese mice to exhibit more severe inflammatory responses but also causes effective treatment drugs to become "poisons" that aggravate the disease.[155] The scientists[156] showed that modifications in the so-called immune checkpoint proteins of mice on a Western "high fat" diet were linked to dramatic reductions in the development of obesity and diabetes. A history of obesity triggers persistent epigenetic changes that affect innate immunity and exacerbate neuroinflammation.[157] Age-related macular degeneration is a prevalent neuroinflammatory condition and a major cause of blindness driven by genetic and environmental factors such as obesity. Polygenic obesity (predisposition to obesity caused by multiple genetic variants and environmental factors) has also been proposed to be an autoimmune-like disease.[158] Indeed, severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection is associated with the production of autoantibodies and is more severe in obese individuals (Figure 5).[159]

Obesity and the gut microbiota

The human gut microbiota, comprising approximately 10^14 bacterial cells from 400 to 500 species per gram of colonic content, varies across different sections of the gastrointestinal tract and forms a symbiotic relationship with the host.[160] Dysbiosis, characterized by alterations in gut microbiota composition, is closely linked to the development of obesity and related metabolic diseases. In obese populations, Bacteroidales genera, such as *Lactobacillus spp.*, *Bifidobacterium spp.*, *Bacteroides spp.*, and *Enterococcus spp.*, as well as the ratio of Firmicutes to Bacteriodetes and the Enterobacteriaceae species, are upregulated, while Clostridia, including *Clostridium leptum, Akkermansia muciniphila,* and *Enterobacter spp.*, are downregulated.[160-165] The gut microbiota patterns associated with obesity may differ depending on race/ethnicity.[166] The association between lower alpha diversity (microbial richness) and higher BMI seemed to be most consistent in studies among non-Hispanic white populations and/or those with high socioeconomic status. This relationship between a greater relative abundance of Prevotella and a higher BMI appeared to be stronger in black and Hispanic populations than in non-Hispanic whites. Population heterogeneity caused by genetic and environmental differences and dietary and socioeconomic factors could influence the microbiota–obesity association.

The gut microbiota influences nutrient metabolism, including energy storage via short-chain fatty acids (SCFAs). Germ-free (GF) or antibiotic-treated mice show reduced digestive absorption and higher fecal calories. The microbiome also impacts lipid absorption and metabolism, affecting fat storage by regulating factors like Fiaf and producing bile acids and SCFAs.[167] Gut microbiota may hinder β-oxidation in conventional mice, contributing to weight gain, as seen in GF mice showing increased β-oxidation. Additionally, the carbohydrate transport system can be influenced by the microbiome. In obese individuals, gut microbiota exhibits higher levels of the phosphotransferase system (PTS), enhancing carbohydrate utilization. Moreover, the obesity-related gut microbiota shows reduced activity in the citrate cycle, impacting cellular energy metabolism. These microbiotas also possess an increased ability to metabolize aromatic and branched-chain amino acids, leading to elevated serum levels of these amino acids.[167,168]

Different weight loss methods, including very-low-calorie diets, intermittent fasting, ketogenic diets, the Mediterranean diet, and fiber-rich diets, can alter gut microbiota to aid in weight loss and improve health.[169,170] Specific changes include increased levels of bacteria like *Akkermansia muciniphila* and SCFA producers.[171,172] Prebiotics (fiber supplements) that selectively stimulate the growth of certain beneficial gut bacteria have shown the potential to aid weight loss. Studies demonstrate effects on the gut microbiota, gut hormone secretion, appetite regulation, and metabolism.[173] Probiotic supplements, like Bacteroides strains, have been studied and may improve metabolic markers and glycaemic control in obesity.[174] Fecal microbiota transplantation from lean donors has demonstrated effects on gut microbial engraftment and some metabolic outcomes in patients with obesity.[168,175,176] Bariatric surgery profoundly alters the gut microbiota in ways thought to contribute to weight loss and metabolic improvements, such as increased SCFA producers and B. thetaiotaomicron.[167,177-179] Anti-obesity drugs like orlistat and GLP-1 receptor agonists directly influence the gut microbiota in animal and human studies, which may partly explain the metabolic effects (Figure 6).[180]

In short, the gut microbiota impacts nutrient metabolism and obesity. Adjusting the gut microbiota through diet, probiotics, and bariatric surgery can improve metabolic health and support weight management.

The obesity paradox

Obesity has been proven to be a risk factor for many diseases as mentioned above through numerous pathogenetic mechanisms. Unexpectedly, some studies suggest that subjects with overweight/obesity have better clinical outcomes than their normal-weight peers. This phenomenon is known as the "obesity paradox". The obesity paradox has been documented in various medical conditions, including cardiovascular and cerebrovascular diseases, diabetes, aging, fractures, cancer, and chronic obstructive pulmonary disease, among others.

Traditionally, obesity is considered a major risk factor for CVD, but studies indicate that obese patients might have better survival rates and outcomes after a cardiovascular event.[144] Clinical evidence supports this "obesity paradox" in post-coronary artery disease PCI and heart failure cases. Research indicates that, compared with normal-weight individuals, BMI >25 kg/m² is a significant independent predictor of higher survival rates within 5 years after PCI, unaffected by clinical presentations such as unstable angina, non-ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction.[181] Additionally, the study recorded the mortality of 30,258

Figure 7. Illustrations of obesity intervention and treatment *Specific medication selection should be based on clinical practice.

patients undergoing PCI, finding that within six months, the mortality rate was lower in patients categorized as overweight or obese compared to those with normal BMI, further confirming the obesity paradox.[182] In addition, clinical studies in heart failure have found that the clinical outcomes of overweight or class 1 obese patients are better than those of normal-weight patients, particularly evident in HFrEF patients, but less pronounced in HFpEF.[183,184]

The obesity paradox is also observed in stroke patients. Compared with their normal-weight counterparts, overweight or obese individuals with chronic diseases, including stroke, may exhibit lower mortality rates, whereas underweight patients have the poorest prognosis.[185-187]

In patients with diabetes, similar findings have been reported[188]. A recent large cohort study observed a U-shaped association between BMI and mortality, with the lowest mortality observed among obese individuals with a BMI of 26.4-29.4 kg/m².[189] A cohort study involving patients with T2DM without known CVD at baseline found that overweight patients had a lower mortality risk, while obese patients had a mortality risk similar to that of normal-weight individuals.[190]

There also have been reports of obesity paradox in certain lung diseases, including pneumonia, acute lung injury /acute respiratory distress syndrome (ARDS), COPD, and lung cancer.[191] A higher BMI has been linked to better outcomes, possibly due to the protective effect of increased fat-free mass and a reduced risk of skeletal muscle wasting.

Regarding cancer, the relationship is complex and varies by cancer type and treatment modalities. Cancer patients with low to normal BMI or those with weight loss have worse outcomes than obese patients.[192] Obesity promotes tumor initiation and progression but can also augment responses to immunotherapy, contributing to the observed paradox.[193]

In summary, while obesity is a well-established risk factor for numerous chronic diseases, the obesity paradox suggests that in the context of these diseases, obesity may be associated with better outcomes. The mechanisms behind this phenomenon are not fully understood. Perhaps due to limitations in the study of the obesity paradox, such as observational study design, lack of weight measurement, selection bias, and survival bias. Another explanation for this paradox involves the body's metabolic adaptations. Some overweight and obese individuals may exhibit better insulin sensitivity and lipid profiles despite a higher BMI, a condition termed "metabolically healthy obesity," which could explain the observed paradox.[194] The obesity paradox presents a fascinating challenge to our understanding of obesity and its relationship with health outcomes. It may not always be a risk factor for poor outcomes. This paradox invites further research into the complex relationships between body weight, metabolism, and disease to clarify its mechanisms and clinical significance.

INTERVENTION AND TREATMENT

Lifestyle intervention

Nutritional intervention. As the cornerstone of lifestyle medicine, nutritional intervention is the most fundamental weight-loss treatment measure. According to the current nutrition guidelines for the treatment of obesity, the overall principle of nutritional intervention for weight loss is to maintain a negative energy balance, which can be achieved by reducing dietary energy intake.[195,196] An energy deficit of 500 to 750 kcal per day, or a 30% reduction compared with the recommended energy intake, is the most common intervention goal. The specific daily caloric intake is often adjusted for an individual's weight and physical activity level. The recommended macronutrient composition of a calorie-balanced diet is approximately 55%~60% of daily calories from carbohydrates, 20%~35% from fat, and the remainder from protein as noted in the dietary guidelines worldwide.[195,197]

In addition to an energy deficit, macronutrient components and dietary patterns are also important factors for weight loss, long-term maintenance, and cardiovascular health. Although there is limited evidence that macronutrient composition itself causes significant differences in weight loss when diets are calorie-restricted, a variety of evidence-based dietary approaches might facilitate the achievement of weight loss goals and the improvement of cardio-metabolic risk factors. A high-protein diet (i.e., usually more than 20% but less than 30% of total energy as protein) could improve adiposity and cardiometabolic risk factors, including glucose homeostasis and lipid metabolism.[198-200] However, long-term using a high-protein diet to lose weight should be offered under medical supervision and nutrition consultation. Other healthy dietary patterns such as DASH (Dietary Approaches to Stop Hypertension) or a Mediterranean diet can also be considered. Many studies have shown that these dietary patterns have beneficial effects on weight compared with a typical diet.[201-204] It should be noted that although there might be differences in weight loss between various diet approaches, long-term effects are generally comparable.[205] Additionally, as long as the diet is maintained, most calorie-reducing diets could result in clinically significant weight loss. Therefore, the ideal diet is tailored to incorporate a person's preferences, nutritional needs, and adherence.

Physical activity. Physical activity is recognized as a key factor in the management of overweight or obese, Clinical guidelines recommend that all

patients participate in 150 to 300 min/week of moderate or 75 to 150 min/week of vigorous physical activity, as well as resistance training 2 to 3 times a week,[206] which can help patients lose fat while maintaining lean body mass. However, exercise is not typically used as a stand-alone weight loss intervention program,[207] and the impact of different exercise prescriptions on overweight or obese also varies. In fact, any type of exercise can increase maximal oxygen uptake (VO_{2max}) in overweight or obese people compared with untrained people, with high-intensity interval exercise (HIIT) and aerobic exercise shown to better improve CRF, while resistance exercise interventions (alone or in combination with aerobic exercise) can improve muscle strength, and in particular, can reduce lean mass loss during weight loss.[208] The results of the current meta-analysis suggest that high-load resistance exercise interventions combining high-intensity aerobic exercise are superior to any other exercise type at reducing abdominal adiposity, improving lean body mass, and increasing CRF.[209] Exercise is often combined with dietary interventions, and performing aerobic exercise alone or combined with resistance exercise during dietary restriction leads to an additional weight loss (approximately 1.5 kg on average) and visceral fat loss in overweight or obese compared with diet-only controls,[210] and there was a dose-response effect of exercise for visceral fat loss.[211] Therefore, exercise intervention can help to change the metabolic abnormalities of overweight or obese, although exercise did not have a significant effect on weight maintenance. However, for people with obesity complications (such as metabolic fatty liver disease, pre-diabetes, dyslipidemia, hypertension, and CVD, etc.), a detailed assessment should be carried out, and cardiopulmonary exercise tests should be performed to evaluate cardiopulmonary function to ensure the effectiveness and safety of exercise. Activity tracking via wearable devices can better encourage these people to complete exercise prescriptions and increase physical activity.[212]

It is recommended that inactive overweight or obese adults gradually increase their level of exercise by adjusting the duration, frequency, and intensity of exercise, as outlined in Table 1.

Psychological and sleep interventions. Psychological and sleep interventions are integral components of weight management.[213] The incidence of psychological disorders among obese individuals ranges from 20% to 60%.[214] There is a bidirectional relationship between mental health and obesity. The risk of depression increases by 55% in obese individuals, while the risk of obesity increases by 58% in individuals with depression.[215] Therefore, incorporating mental health professionals into the weight management teams can facilitate the identification, intervention, and referral of psychological disorders. Additionally, mental health professionals in the team can promote lifestyle changes through psychological interventions. Motivational Interviewing[216] is a method that increases motivation and determination for change. It involves working with patients to enhance their autonomy and adherence to weight management programs and is especially useful when clients are uncertain. Cognitive behavioral therapy (CBT)[217] helps people change negative thoughts about diet, weight, and body image, such as self-criticism and fatalism. CBT involves identifying extreme thoughts and replacing them with neutral or positive thoughts, focusing on facts, and changing automatic thoughts. Sleep duration, quality, and timing are all related to weight gain, so the evaluation and guidance of sleep should also be an important part of weight management.[218]

Digital technology and wearable devices. Digital technology, including telemedicine, wearable devices, and artificial intelligence (AI), offers attractive and viable solutions for obesity management and intervention through innovative solutions that offer real-time monitoring, personalized feedback, and motivational strategies.

Several studies have evaluated telemedicine's effectiveness. One found that a 3-year telehealth lifestyle intervention helped pregnant women with overweight or obesity reduce excess gestational weight gain.[219] Another revealed that participants using activity trackers lost more weight over 24 months compared to those who didn't.[220]

Virtual reality (VR) and gamification are effective tools for assessing and treating eating disorders and obesity. Simulating healthy eating environments with VR can enhance the eating habits of obese patients.[221] Using social incentives and gamification to track behavior with a partner led to significant weight loss through 36 weeks.[222]

Drug treatment

For obese adults with weight-related issues or poor response to lifestyle changes, antiobesity drugs should be added to lifestyle therapy.[75,223] In children and adolescents, medications should be used cautiously, considering all risks and benefits.[224-226] Chronic use is recommended due to limited short-term benefits and the risk of regaining weight.[207,223] After initiation, long-term monitoring of weight loss and adverse events is necessary, and switching to or adding another agent may be considered if 3-5% weight loss is not achieved or if the first agent is intolerable.[227]

The array of antiobesity medications (AOMs) available for clinical prescription varies worldwide.[227] AOMs are classified into intra-gastrointestinal, centrally acting, and nutrient-stimulated hormone (NuSH)-based medications, depending on their action targets.[228] The FDA-approved and phase 2 trial-assessed AOMs were summarized in Table S2. Besides, several medications (mostly anti-diabetic drugs) are used off-label for the management of obesity.[207]

Orlistat, a commonly used and affordable AOM, is now less recommended due to its limited weight-loss effectiveness and significant gastrointestinal side effects.[223,229] Centrally acting AOMs curb appetite via various mechanisms. Phentermine-topiramate emerged as a top weight-loss agent in the largest network meta-analysis, but both phentermine-topiramate and naltrexone-bupropion had the highest rates of adverse events.[230] Novel NuSH-based AOMs, which mimic entero pancreatic hormones like GLP-1, GIP, and GCG, demonstrated significant weight-loss potential, nearly matching that of metabolic surgeries.[228,231] These treatments provide cardiovascular, metabolic, and renal benefits but may cause lean body mass loss and gastrointestinal issues. The AGA guideline was the first to provide recommendations on medication selection in order of priority, where semaglutide 2.4 mg is prioritized considering the magnitude of net benefit.[223] However, current evidence requires frequent updates given the rapid emergence of novel highly-effective medications. In conclusion, the selection and application of antiobesity pharmacotherapy should not only rely on the weight-loss effects but also be highly individualized according to patient comorbidities, preferences, heterogeneity, affordability and access, etc.[223,227]

Metabolic and bariatric surgeries

Metabolic and bariatric surgery (MBS) is an effective and sustainable intervention for obesity.[232-235] MBS can result in rapid and sustained weight loss and improvement in obesity complications.[236-238] The benefits of MBS in patients with T2DM and other metabolic disorders have also been confirmed.[239-241] Compared with nonsurgical treatment, MBS is associated with lower all-cause mortality compared with nonsurgical treatment.[242-246] Laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB) are the two most commonly performed procedures worldwide.[247-249] Studies have shown that patients undergoing LSG may have fewer postoperative complications and reoperation rates than those in LRYGB.[250,251] MBS deserves more active consideration in the treatment of severe obesity,[252] and also for young patients with obesity and T2DM.[253]

According to the Chinese Surgical Guidelines for Obesity and T2DM (2019) by the Chinese Society for Metabolic and Bariatric Surgery (CSMBS), patients with a BMI over 27.5 with poor weight loss by medications or lifestyle modification, and with at least 2 components of metabolic syndrome or with comorbidities, can be considered for MBS.[254] MBS candidates should be given a conversation about the risks and benefits of surgery compared with conventional medical treatments.[255] Multidisciplinary management should also be considered.[256] Long-term follow-up is important to enhance the postoperative outcomes. Combined use of medication like GLP-1 receptor agonists in weight loss and bariatric surgery is an option in future obesity management.[257] AI like chatGPT and other large language models should not be neglected in MBS in the clinical practice (Figure 7).[258-260]

Six steps in quality intervention development （6SQuID）

According to 6SQuID,[261] obesity is a public health issue influenced by complex factors at multiple levels, beyond just individual behavior. These factors include obesogenic environments and broader systemic forces, impacting individuals and populations differently.[16,262] Interpersonal dynamics, particularly through social networks and peer influence, are pivotal in rein-

forcing social norms and facilitating behavioral imitation, leading to weight gain.[263] Community-level factors, such as the accessibility of food outlets, sports facilities, and green spaces, are critical in modulating the energy balance equation, thereby influencing OW/OB risks.[264] Additionally, environmental exposures like the built environment, pollutants, and chemical exposures, have been increasingly recognized as disruptors of metabolic homeostasis, and affecting obesity.[265] National policies on trade, urban planning, agriculture, health, and fiscal matters, including food pricing regulations and subsidies for food, appliances, and cars, collectively influence food production, diets, nutrition, and lifestyle patterns (Figure 7).[16]

CONCLUSION AND FUTURE PERSPECTIVE

Obesity has become a global, preventable health crisis affecting multiple organ systems and is linked to various diseases. This health crisis requires a concerted, multidisciplinary effort to address its causes and consequences effectively. The successful prevention and treatment of obesity depend on the collaborative efforts of medical professionals, nutritionists, biologists, psychologists, policymakers, and the community at large.

The advancement of molecular techniques and multi-omics methods has brought greater insights into the pathophysiological mechanisms of obesity.[266] Research on obesity must continue to evolve, with a focus on personalized treatment strategies. Genetic and genomic research may offer insights into individual susceptibility to obesity and guide the development of targeted pharmacological interventions. Lifestyle interventions are the first option for weight management, given the low cost and minimal effort.[267] Furthermore, pharmacotherapy and bariatric surgery are also thoroughly evaluated for both efficacy and safety, as already mentioned above.

Advances in mobile technology and the pervasive use of wearable devices, these emerging tools can provide real-time feedback on dietary intake and physical activity, facilitate behavior change, and support long-term weight maintenance.[268,269] The advent of digital technology and wearable devices presents an exciting frontier in obesity management, facilitating more informed decision-making and personalized feedback. The integration of AI and machine learning algorithms could further refine these approaches, providing predictive analytics and early warning signs of weight gain or related health complications.

Moreover, the role of public health policy in obesity management cannot be overstated. Policymakers should foster healthy choices by regulating the food industry, promoting exercise, and educating on nutrition. This involves effective food labeling, limiting unhealthy food marketing to kids, and supporting community initiatives for fresh produce and safe exercise spaces. In 2022, the UK government mandated calorie labels on menus in restaurants, cafes, and takeaways to help reduce calorie intake.[270] Similarly, Singapore launched the nutri-grade labeling system for beverages to reduce high-sugar drink consumption by categorizing them according to sugar and saturated fat content.[271]

In conclusion, the future of obesity research and treatment is promising yet challenging. A multidisciplinary approach is essential for addressing obesity, as it brings together diverse expertise to develop comprehensive treatment strategies. By embracing innovative technologies and fostering a culture of collaboration, we can work towards a future where obesity is effectively managed and its burden on society is significantly reduced.

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AUTHOR CONTRIBUTIONS

S.H., Y.B., and X.F. designed the manuscript and supervised this project. N.X., Y.D., B.C., R.L., X.Q., H.Z., K.A., X.F., J.X., and Y.H. prepared and wrote the first draft. X.H., Y.W., J.Z., W.Y., Y.W., X.Z., W.C., and Y.Z. supervised the project. S.Z., H.D., Y.W., and P.W. reviewed and revised the manuscript. All authors approved the submitted version of this manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Not applicable.

SUPPLEMENTAL INFORMATION

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