IJAGing International Journal of Aging

Int J Agin, 2024, 2, e19
10.34172/ija.2024.e19
http://ijage.com

Review Article

Obesity: Global Epidemiology, Trends, Risk Factors, and Clinical Aspects

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Article History:
Received: October 13, 2024
Accepted: October 24, 2024
ePublished: December 1, 2024

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Abstract

Objectives: To review the current literature on obesity risk factors, epidemiology, and trends, providing insights for effective prevention and intervention strategies.

Design: Review article.

Setting(s): Global.

Outcome Measures: A systematic search was performed using MEDLINE (via PubMed), Scopus, Web of Science, and Google Scholar up to January 2024. Studies on obesity's history, epidemiology, risk factors, health impacts, and preventive or therapeutic approaches were included. Both primary and secondary studies were considered, excluding those in languages other than English, in vitro studies, and animal studies. No restrictions were applied regarding publication date or article type.

Results: The overweight- and obesity-attributable burden of diseases has significantly increased, particularly among adults aged 60 and older, with the most severe effects observed in women aged ≥ 75, highlighting a growing public health challenge and a markedly greater rate of increase in older adults compared to those under 60. The causes of obesity were found to be multifaceted, predominantly influenced by behavioral and environmental factors, with an imbalance between calorie intake and expenditure being the primary issue. The adverse health consequences of obesity have been well documented, with associations noted in various non-communicable diseases, including diabetes, cardiovascular diseases (CVDs), and musculoskeletal disorders.

Conclusions: Understanding obesity-comorbidity links is vital to identifying high-risk individuals and prioritizing interventions. Limited access to effective weight management treatments remains a key barrier to improving health outcomes for those affected by obesity.

Keywords: Obesity, Overweight, Epidemiology, Risk factor, Worldwide, Disability

Please cite this article as follows: Safiri S, Daei Sorkhabi A, Aletaha R, Hamidi S, Motlagh Asghari K, Sarkesh A, et al. Obesity: global epidemiology, trends, risk factors, and clinical aspects. Int J Aging. 2024;2: e19. doi: 10.34172/ija.2024.e19

Introduction

Obesity is a significant global public health concern.[1] The World Health Organization (WHO) defines obesity as an abnormal or excessive accumulation of fat that poses a health risk, categorizing it as a body mass index (BMI) exceeding 30.[2] In recent decades, the worldwide prevalence of obesity has escalated to pandemic levels.[3-6] As reported by the WHO, the prevalence of obesity has more than

tripled since 1975, with over 1 billion individuals classified as obese globally in 2020.[2]

Obesity is a multifaceted disease influenced by various factors and is regarded as a chronic, progressive condition rather than merely a risk factor for other ailments.[7-9] The primary cause of this disease is a sustained energy imbalance between calorie intake and expenditure.[10,11] Excess energy is converted into triglycerides and stored in adipose tissue depots, which enlarge, increasing body fat and weight gain.[8] Several factors contribute to the onset of obesity, including genetic predisposition, neuroendocrine influences, environmental factors, sociocultural aspects, and lifestyle choices.[12-17]

Obesity poses a considerable health challenge, as it heightens the risk of metabolic disorders, including type 2 diabetes mellitus (T2DM) and fatty liver disease, as well as cardiovascular diseases (CVDs) such as myocardial infarction,[18] hypertension (HTN), and stroke.[19, 20] Obesity is also linked to osteoarthritis, Alzheimer's disease (AD), obstructive sleep apnea (OSA), depression, and some types of cancer.[11,21-22] Furthermore, obesity and its associated comorbidities not only significantly impact the quality of life and overall well-being,[23] but also place a staggering burden on healthcare systems.[24]

The above-mentioned findings, which highlight the rising prevalence of obesity and its association with various health conditions, underscore the strong need for a comprehensive understanding of obesity epidemiology to address this growing public health crisis. The present article aims to explore the diverse range of factors contributing to the development and progression of obesity. Genetic predisposition, environmental influences, lifestyle behaviors, and socio-cultural determinants all play significant roles in this complex issue. Understanding the risk factors associated with obesity is of paramount importance for designing effective prevention and intervention strategies. Additionally, this article provides a comprehensive overview of obesity, including its epidemiology, trends, and risk factors. Examining these aspects can provide us with deeper insights into the magnitude of the obesity problem, enabling the identification of high-risk populations and the subsequent development of more effective evidence-based interventions and policies.

Methods

The MEDLINE (via PubMed), Scopus, and Web of Science databases, along with Google Scholar, were systematically searched up to January 2024 to identify eligible studies using a combination of keywords pertaining to obesity, encompassing its history, epidemiology, risk factors, health consequences, and preventive and therapeutic approaches. No search filters, such as publication date or article type, were applied in this regard. The review incorporated both primary and secondary studies that examined the relationship between biological or psychological factors and obesity. Additionally, our analysis included research presenting data on the epidemiological attributes or burden of obesity at global, regional, and national levels, as well as studies assessing the relationship between various disorders and obesity in humans. Studies conducted in languages other than English, along with in vitro and animal studies, were excluded from the review.

A Brief History of Obesity

Humanity has grappled with obesity since ancient times, as evidenced by excavations from the Paleolithic era.[25] One of the oldest surviving depictions of a person with excessive body weight dates back to over 2000-3000 years old.[25] The Venus of Willendorf, a famous statue portraying a woman with prominently delineated breasts, abdomen, and thighs, was unearthed in 1908.[26] The historical imagery or metaphor of excess body fat is intriguing, considering the prevalent food shortages, the constant need to hunt animals, and the struggle for survival.[25] The stone tombs of several high-ranking officials from ancient Egypt suggest that obesity was not uncommon among them.[25] Additionally, large human figurines have been discovered during archaeological excavations in ancient Mesopotamia, Aztec, and Inka cultures.[25]

As society and science progressed, overweight became recognized as a medical concern.[27,28] The writings of Hippocrates contain the earliest explicit mention of obesity as a significant clinical issue.[27] According to Hippocrates, obesity was attributed to an overall surplus of the four humors (fluids) that constitute a healthy human, including blood, black bile, yellow bile, and phlegm.[27] Hippocrates was the first medical professional to assert that obesity increases the risk of early death, CVDs, menstrual problems in women, and infertility. He also advocated for dietary restrictions and exercise as effective means to reduce excess body weight.[27,28] Soranus of Ephesus, another Greek physician, asserted that exercising, following a diet with extremely few calories, and intensifying diuresis could all aid in weight loss. Two Roman physicians, Galen and Areteus, also espoused similar views in this regard.[29] Galen described a condition he named "polysarkia" (poly = numerous and sark = flesh), which is now recognized as morbid obesity.[30,31] He observed that individuals with this condition faced difficulties in cleaning themselves, breathing easily, giving birth, or walking without perspiration.[30,31]

The "dark ages" in Europe witnessed few notable medical advances until the Renaissance.[32] Meanwhile, medical research and other scientific fields were thriving in the Middle East.[32] Influenced by historical figures such as Hippocrates and Galen, Muhammad ibn Zakariya Al-Razi discussed obesity in his book Al-Hawi Fit-Tibb (an encyclopedia of medicine).[33,34] Other Persian doctors, such as Ibn Sina (Avicenna), Ibn Hubal Al–Baghdad, and Ibn Al–Nafis, focused their research on the pathophysiology of obesity and its associated complications.[34] They explored the connection between obesity and respiratory, endocrine, and cardiovascular conditions, as well as

reduced fertility.[34]

In the Baroque era, being overweight began to symbolize health and happiness again, largely due to the resurgence of plagues, poverty, and starvation.[35] This sentiment is reflected in the works of writers, paintings, and even the descriptions of fictional characters such as Sir John Falstaff, who appeared in three plays by William Shakespeare.[35,36] English physician Thomas Short produced the first monograph on obesity in 1727.[37] Short advocated for a successful weight-loss strategy involving the elimination of factors that contribute to obesity, such as a sedentary lifestyle and unrestrained overeating, in order to restore the body's natural equilibrium.[37,38] Adolphe Quetelet's cross-sectional research in 1835 concluded that measuring weight adjusted for height would be the most effective means to identify obesity.[39,40] Ancel Keys coined the term "body mass index (BMI)" in 1972, originally known as the "Quetelet index", which is still used in clinical settings today.[39,40]

Hassall provided the first descriptions of adipocyte growth and evolution in 1849,[41] and proposed that certain kinds of obesity, now known as hyperplastic obesity, are caused by an increase in fat cells.[41] In 1967, Stewart first used behavioral therapy to treat obesity.[42] Despite advances in dietetics, the increasing popularity of physical exercise, and attempts at pharmaceutical therapies, efforts to combat the obesity epidemic have been ineffective.[42] Currently, surgery is the most common approach for treating morbid obesity.[42] Initially, procedures that removed a portion of the small intestine to reduce the absorption area were dominant, but they had several drawbacks.[42] Methods to reduce stomach capacity have been employed since the 1970s.[42] Mason and Ito implemented the first such procedure, the Roux-en-Y gastric bypass (RYGB).[42] Better surgical procedures were gradually developed, leading to the introduction of gastric banding in the 1980s.[43] The introduction of the less invasive laparoscopic technique in the last decade of the 20th century greatly increased the popularity of bariatric surgery.[43,44] In 1986, an international association was founded for the study of obesity.[25]

The perception of obesity as a symbol of affluence and wealth has changed significantly over time, and obesity has now emerged as one of the most significant health challenges facing society in the twenty-first century.[45] Despite the remarkable progress made in identifying the underlying causes, triggers, and effects of obesity over the last 25–30 years, combating a clinical issue that has existed for thousands of years remains one of the most serious problems of modern medicine.[45]

Global Epidemiology

In 2019, the summary exposure value of high BMI ranged from 56.5 (43.4–66.2) in Qatar to 4.52 (2.27–8.08) in the Democratic People's Republic of Korea per 100,000 population. The United Arab Emirates had the second highest exposure value, with 53.6 (41.7–61.8), while Somalia had the second lowest value of 4.5 (2.5–7.4), the details of which are shown in Figure 1.[46]

Fiji and the Cook Islands had the highest percentage of disability-adjusted life years (DALYs) due to high BMI in all ages, with 24.5 (18.5–29.5) and 24.2 (17.9–29.60), respectively. Conversely, Somalia, Chad, and Niger had the lowest percentage of disability with 0.6 (0.2–1.2), 0.8 (0.4–1.3), and 0.8 (0.5–1.3), respectively, in 2019 per 100 000 population (Figure 2).[46] In 2019, the age-standardized DALY rates due to high BMI varied from 10000.5 (6266.5–

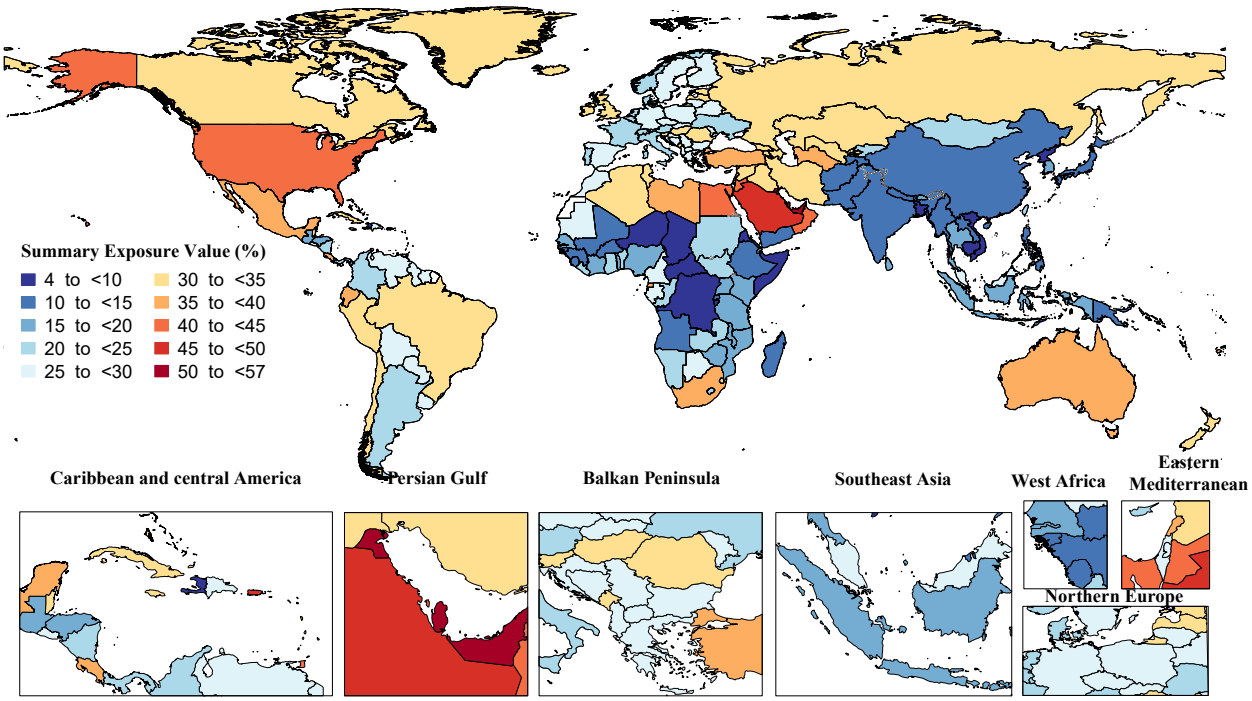

Figure 1. Summary Exposure Value of the Diseases Attributable to High Body Mass Index in 2019 by Country. *Note*. DALY: Disability-adjusted life years. *Source*. Generated from data available on http://ghdx.healthdata.org/gbd-results-tool

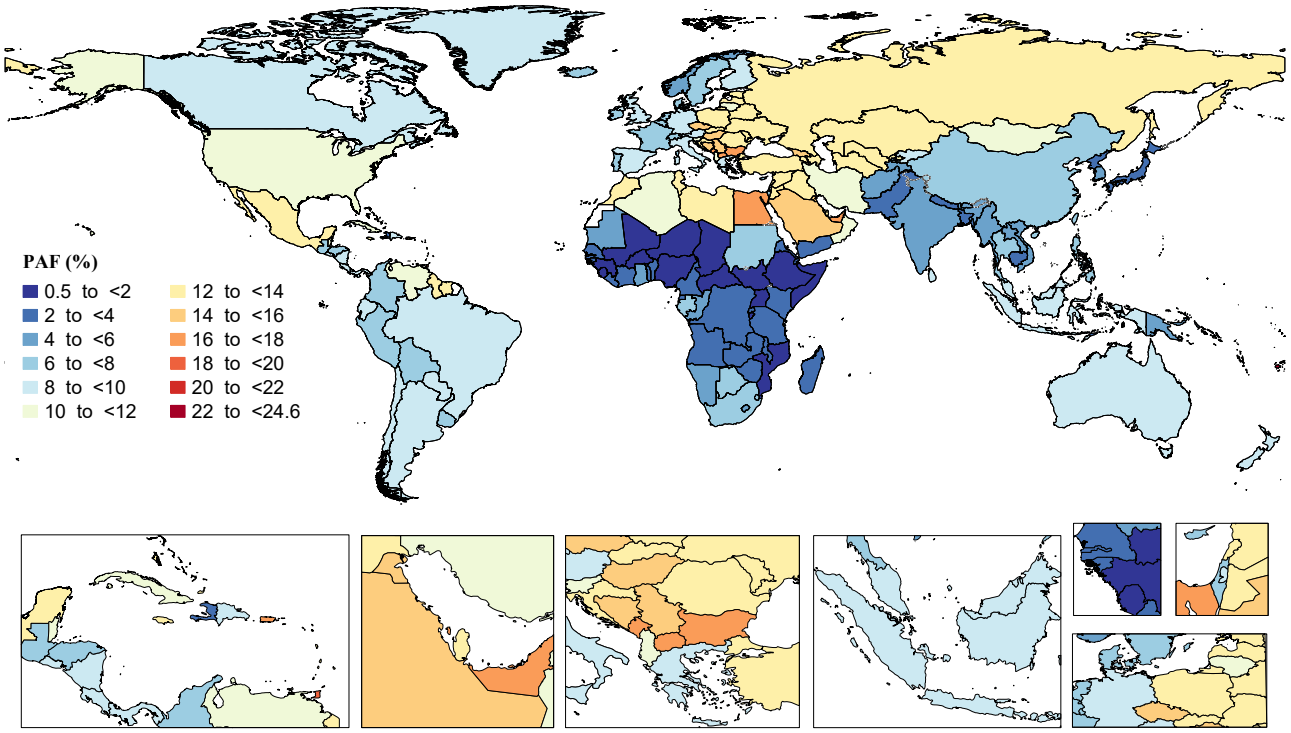

Figure 2. Population Attributable Fraction of the DALYs From Diseases Attributable to High Body Mass Index in 2019 by Country. *Note*. DALY: Disability-adjusted life years. *Source*. Generated from data available on http://ghdx.healthdata.org/gbd-results-tool

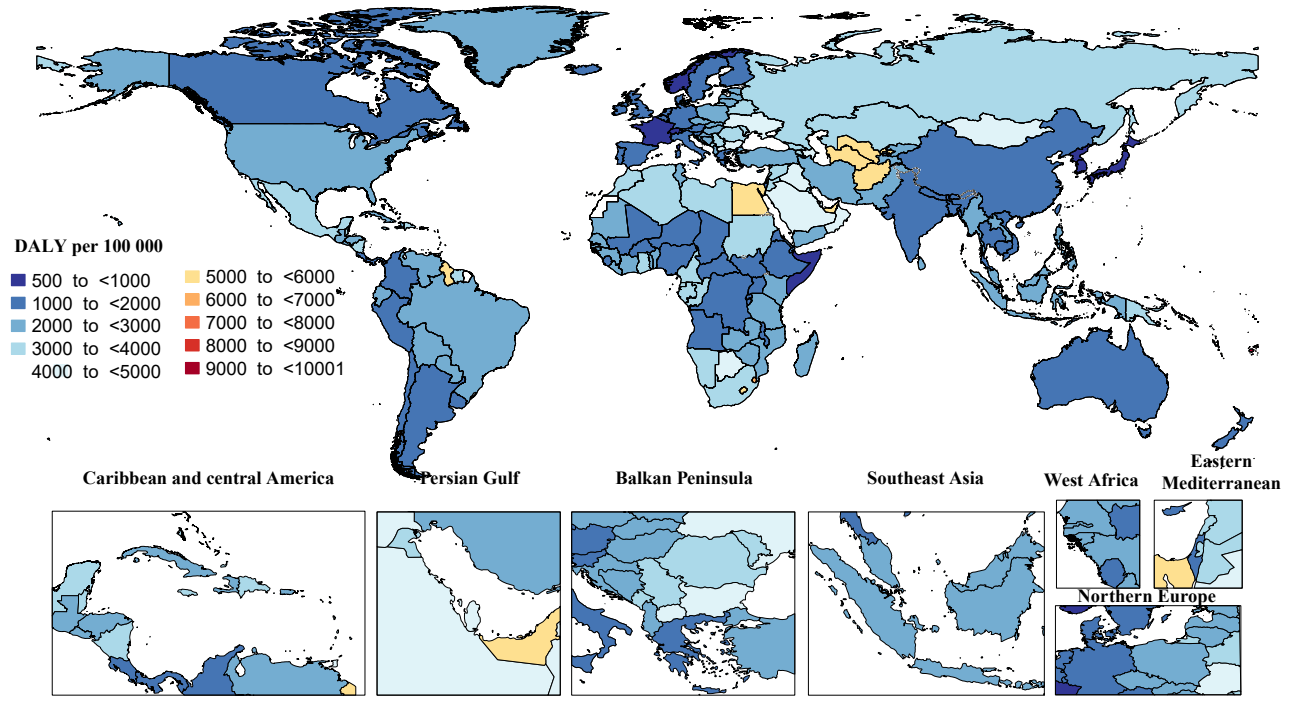

Figure 3. Age-standardized Rates of the DALYs From Diseases Attributable to High Body Mass Index in 2019 by Country. *Note*. DALY: Disability-adjusted life years. *Source*. Generated from data available from http://ghdx.healthdata.org/gbd-results-tool

14159.1) in Kiribati to 503.2 (199.9–888.7) in Japan per 100 000 population (Figure 3).[46]

The death percentage of high BMI in all ages ranged from 1.1 to 31.7. In 2019, Fiji had the highest percentage, with 31.7 (23.3–39), whereas Somalia had the lowest percentage, with 1.1 (0.3–2.4) per 100,000 population (Figure 4).[46] In addition, Fiji and Nauru had the highest age-standardized death rate due to increased BMI, with 319.07 (213.7–444.9) and 302.6 (192.9–428.9) per 100 000 population. Contrarily, Japan and the Republic of Korea had the lowest age-standardized rate of death, with 12.6 (4.7–23.6) and 22.8 (10.3–37.6) per 100 000 population (Figure 5).[46]

Based on the Global Burden of Disease 2017 report, in adults aged ≥ 60 years, the burden of overweight and obesity on mortality and DALYs became increasingly

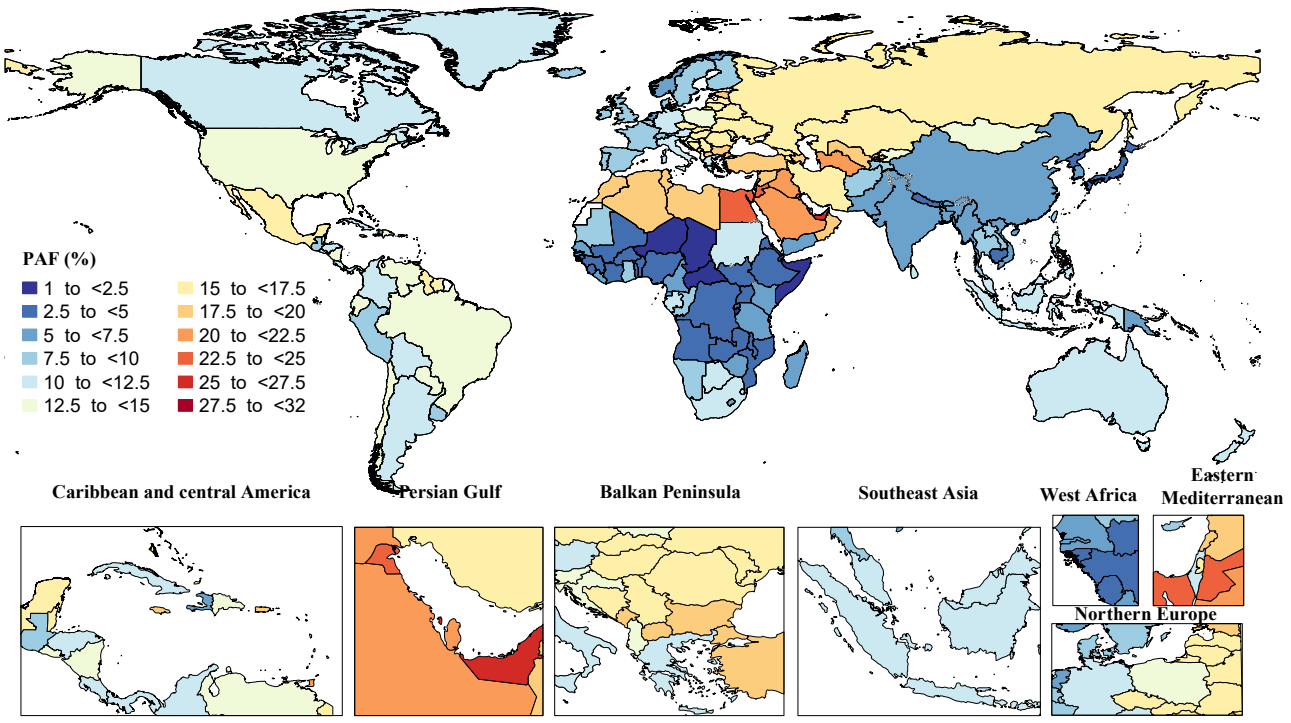

Figure 4. Population Attributable Fraction of Deaths Attributable to High Body Mass Index in 2019 by Country. *Source*. Generated from data available from http://ghdx.healthdata.org/gbd-results-tool

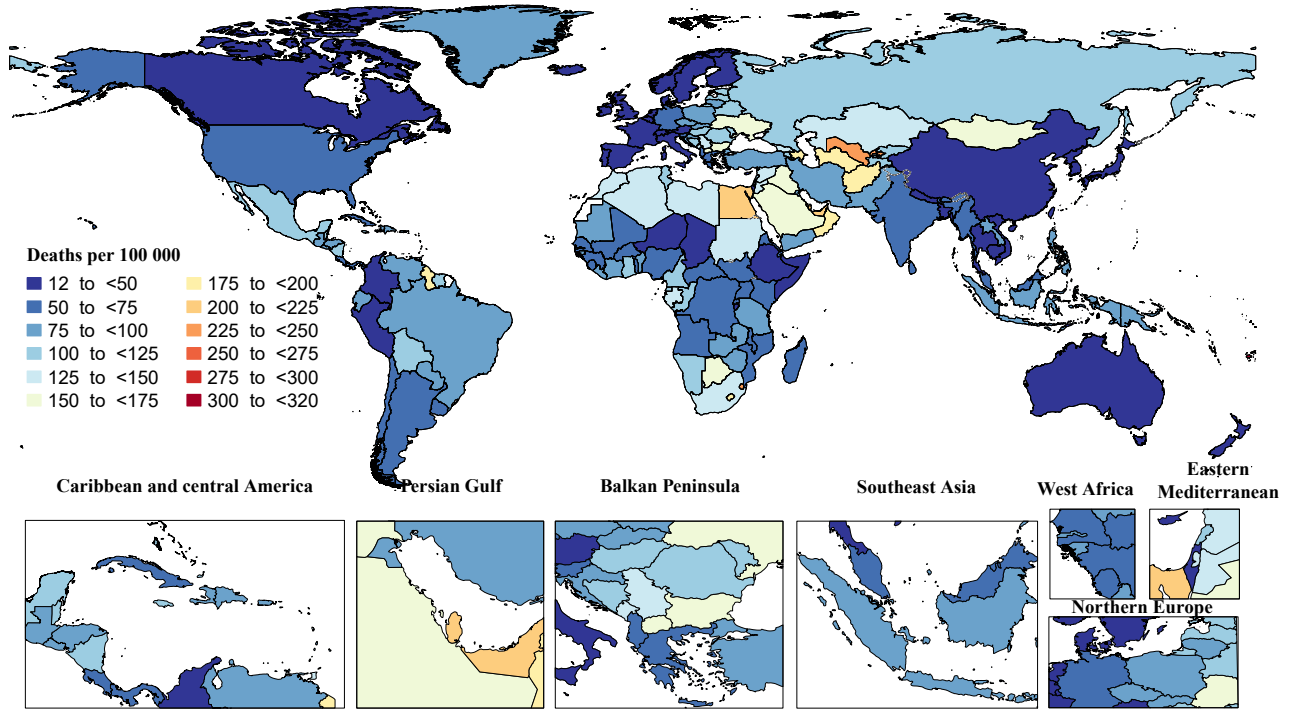

Figure 5. Age-standardized Rates of Deaths Attributable to High Body Mass Index in 2019 by Country. *Note*. Generated from data available from http://ghdx.healthdata.org/gbd-results-tool

significant. Overweight and obesity-related deaths and DALYs show substantial increases with advancing age, with notable differences between genders.

Among older females, the number of deaths attributable to overweight and obesity peaks in the 75–79 age group, while in males, this peak occurs earlier, in the 65–69 age group, suggesting that males experience the highest mortality burden from overweight and obesity at a younger age compared to females. However, in individuals aged 70 years and older, females surpass males in the number of deaths attributable to overweight and obesity, reversing the trend observed in younger age groups where males have higher death rates. This shift indicates that older women are more susceptible to the cumulative effects of overweight and obesity in later life.

In terms of DALYs, the burden peaks in the 60–64 age

group for both genders. However, among those aged 75 years and older, females experience higher DALY rates than males, underscoring the heavier disease burden borne by older women. Notably, a decline in DALYs is observed in the 75–84 age group, which deviates from the upward trend observed in the 60–74 age range. This reduction may be influenced by survivorship bias, where individuals with overweight and obesity may not survive into the oldest age groups, or by the presence of competing health risks.

Despite the considerable increase in absolute numbers of deaths and DALYs among adults aged 60 years and older, age-standardized rates provide a nuanced view. The age-standardized rate of overweight and obesity-related deaths remained stable for females while increasing by 14.5% for males. Meanwhile, the age-standardized DALY rate rose by 12.7% and 26.8% for females and males, respectively, highlighting a more pronounced rise in the disease burden for older men. These findings demonstrate the profound and growing impact of overweight and obesity in older adults, particularly women aged ≥ 75 years. As life expectancy increases in many regions, the long-term health consequences of overweight and obesity in this age group present a significant public health challenge, necessitating targeted interventions to address this growing issue.[47,48] The burden of overweight and obesity on mortality and DALYs has significantly increased, particularly in adults aged ≥ 60, with the most severe impact observed in women aged ≥ 75, highlighting a growing public health challenge and a notably greater rate of increase in older adults compared to those ≤ 60.[47]

The WHO reports that the number of overweight individuals has been rising gradually over the last few decades, and this trend is expected to continue.[49] Several different factors influence the prevalence of obesity,[50] among which socioeconomic changes, increased access to high-calorie meals, more diverse leisure activities, and changes in work patterns are of importance, leading to a more sedentary lifestyle.[50] The development of technology and expanded access to cars, computers, and other devices also contribute to reduced physical activity.[51] It is important to note that increased psychological disorders such as anxiety,[52] depression, and stress [53] in recent years have contributed to heightened obesity rates through emotional eating, such as bulimia nervosa, and diminished motivation for physical activity.[54] The prevalence of psychological disorders has significantly increased in recent decades and is projected to continue rising over the upcoming years. Furthermore, weight gain could be a side effect of certain medications, such as corticosteroids[55] and antidepressants.[56] Moreover, environmental factors widely influence obesity through the availability of nutritious food alternatives and safe exercise areas, which low-income countries may lack. Further, cultures play a role in influencing people's food consumption and levels of physical activity.[57]

Despite the large number of parameters contributing to the increased prevalence of obesity in recent years, as mentioned above, there are preventive measures that can be taken to halt this trend.[58] Public health interventions, such as raising public awareness through education campaigns to alter cultural perceptions about obesity and health, are critical in this respect.[58] Additionally, policy interventions should be implemented, such as restricting the availability of unhealthy foods and investing in infrastructure such as bike lanes.[14] Personalized medicine, tailoring diets to individuals' cultural customs and genetic predispositions to obesity, offers another powerful tool in obesity management.[59] In addition, technology can have a significant role in controlling obesity through smartphone applications and wearable devices. With these tools, monitoring physical activity and providing beneficial advice remotely become feasible.[60]

Overall, various underlying factors will likely contribute to the future of obesity, exerting both aggravating and preventive effects depending on how their implementation is effective. While anticipating the exact course of events remains challenging, it is evident that without efficient prevention and treatments, the incidence of obesity will likely continue to rise.

Risk Factors of Obesity

Genetic and Epigenetic Factors

Building on traditional methods, current genetic technologies such as genome-wide association studies (GWAS), candidate gene analysis, and next-generation sequencing have identified susceptibility genes implicated in obesity development.[61] Research indicates that genetic factors contribute to 40%–80% of obesity,[62] with heritability varying according to weight ranges of 30%–35% and 60%–80% in normal-weight individuals and obese and severely obese individuals, respectively. Similarly, heritability estimates across populations are in the range of 40%–80%, 30%–60% for waist-to-hip ratio, and 35–85% for other obesity-related characteristics.[63-66] While genetics explains 15% of metabolic syndrome (MetS) according to GWAS analysis, the remaining 85% is attributable to environmental factors.[67] Therefore, genetic predisposition is not solely responsible for obesity; its interaction with environmental factors (G × E) plays a significant role.[68]

Although there is a continuum of clinical characteristics present in genetic forms of obesity, they have historically been categorized into syndromic, non-syndromic monogenic, and non-syndromic polygenic subtypes.[69] Monogenic variants of obesity, which are autosomal or X-linked and are inherited according to the Mendelian principle, are characterized by chromosomal abnormalities and uncommon pathogenic mutations in genes that encode critical proteins for the regulation of energy balance.[70]

Studies demonstrate that childhood obesity, both syndromic and non-syndromic subtypes, occurs on a spectrum. GWAS has uncovered single-nucleotide

polymorphisms (SNPs) in or adjacent to syndromic obesity genes such as *BDNF*, *NTRK2*, *SIM1*, *BBS2*, *BBS4*, *SH2B1*, and *SDCCAG8*.[71] Numerous loci associated with non-syndromic genetic childhood obesity, including proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), and the melanocortin-4 receptor (MC4R), have also been linked to polygenic childhood obesity.[72] Recent multi-level genetic analyses, including single-marker, tag-SNP, and gene-based approaches, discovered that 17 out of 54 candidate genes for syndromic childhood obesity overlapped with genes and pathways implicated in polygenic obesity, suggesting common mechanisms between these seemingly distinct forms of obesity.[73]

Syndromic obesity occurs alongside additional clinical symptoms such as developmental delays, skeletal abnormalities, or endocrine problems and accounts for up to 10% of severe obesity cases worldwide. Prader–Willi, Bardet–Biedl, and Alström syndrome are among the common examples of syndromic obesity.[74]

Monogenic obesity, on the other hand, can be characterized by a single gene mutation that regulates body weight. Given the wide variability of factors contributing to obesity, rare genetic mutations typically cause early-onset severe obesity (< 10 years old).[61] The majority of genes linked to this kind of pediatric obesity are involved in the leptin-melanocortin signaling pathway. *AgRP* (Agouti-related peptide), *PYY* (Peptide YY), and *MC4R* (the melanocortin-4 receptor), among other genes associated with monogenic obesity, interact with hormones that regulate ghrelin, leptin, and insulin, which are sensed by receptors in the hypothalamic arcuate nucleus.[75] Consanguinity in populations has enhanced the chance of discovering mutations owing to a higher number of deleterious mutations, as monogenic obesity frequently exhibits a recessive inheritance pattern.[76] According to an investigation, mutations in the *leptin*, *LEPR* (leptin receptor), and *MC4R* genes account for 30% of cases of extreme obesity in a consanguineous Pakistani group,[77] whereas single-gene abnormalities account for almost 50% of cases.[78] Farooqi et al demonstrated that homozygous obesity leptin gene deletion of G133 caused a frame-shift mutation, resulting in a non-secreted truncated protein and severe early-onset obesity, whereas other homozygous mutations result in lower amounts of leptin in circulation.[79,80] Similarly, leptin receptor deficiency, an autosomal recessive condition, can occasionally result from a LEPR-splicing mutation that prevents the formation of the transmembrane region.[81] It was shown that although obese people had high amounts of leptin, there was also a decline in the number of soluble leptin receptors, which were crucial for leptin activity. Hyperinsulinemia and extreme hyperphagia, together with aggressive behavior when deprived of food, are symptoms of LEP and LEPR deficiencies.[75] Among various genetic obesity forms, MC4R mutations are thought to be the most common monogenic cause of severe, early-onset dominance-inherited obesity.[82] Pathogenic MC4R mutant carriers have severe early-onset obesity, hyperinsulinemia with euglycemia, a higher frequency of MetS (up to 68%), a higher usage of antihypertensive medications, and frequent binge eating disorder.[83] Children with MC4R mutations have a more severe phenotype than adults, as observed by increased hunger, poor satiety, and severe hyperinsulinemia, with the severity of these symptoms decreasing with age.[84] Furthermore, POMC mutations and hypermethylation result in a deficiency of the alpha-melanocyte-stimulating hormone, which lowers calorie intake by interacting with MC4R in the hypothalamus.[85] Although some studies have linked POMC mutations to glucose metabolism changes, Potoczna et al identified POMC mutations in 48% of individuals with obesity seeking gastric band surgery (13 different variants). However, these mutations did not appear to directly cause obesity or metabolic issues.[86,87] Additionally, PCSK1 encodes proprotein convertase 1, a neuroendocrine enzyme that degrades POMC. The absence of this enzyme impairs the normal functioning of other prohormones and neuropeptides, including POMC, leading to early-onset obesity, moderate hyperphagia, and postprandial hypoglycemia.[69]

Polygenic obesity, also known as common obesity, results from the combined influence of hundreds of small-effect genetic variations and environmental factors. Fat mass and obesity-associated gene (*FTO*) mutations are the most common causes of polygenic obesity, accounting for 1% of BMI variations in the general population. In addition, recent research has revealed that specific genes are involved in obesity and related health conditions,[88] including *BDNF*, *MC4R*, and *NEGR*, which regulate appetite and satiety. Other genes, such as *TCF7L2* and *IRS1*, affect insulin secretion and action, while *FTO*, *RPTOR*, and *MAP2K5* influence energy and lipid metabolism.[88] Gene ontology investigations have also identified shared pathways among obesity-related disorders such as diabetes, HTN, and coronary artery diseases.[89] Interestingly, not only do rare genetic variants cause non-syndromic monogenic obesity, but there are also common genetic variations that contribute to polygenic obesity in a variety of ethnic groups. Specifically, several polymorphisms in PCSK1, MC4R, and POMC have been strongly linked to polygenic obesity.[90,91]

Through the process of epigenetics, which modifies gene expression without changing the DNA sequence, environmental variables such as diet and lifestyle may influence the tendency to become obese. DNA methylation, histone modifications, and non-coding RNAs are the most prevalent epigenetic alterations that have been widely examined in the context of obesity.[92] DNA methylation is a well-studied epigenetic process that involves the addition/removal of methyl groups from the cytosine base 5-carbon position, which occurs primarily at CG positions (CpG loci) that are unevenly scattered around the genome, although it less frequently occurs in

the non-CG context.[93] Several studies have suggested that DNA methylation of genes involved in obesity plays an essential role in obesity development. In this way, DNA methylation of leptin and adiponectin has been shown to be associated with BMI, waist circumference, and low-density lipoprotein cholesterol (LDL-C) levels.[94-97] Similarly, it was found that DNA methylation of genes related to eating behavior had a positive association with BMI for POMC[98] but a negative association for NPY[99] and MCHR1.[100,101] Similar findings have also been obtained for the methylation of genes implicated in lipid metabolism (e.g., *LPL*, *PPARG*, *SREBF1*, and *CD36*),[102-104] glucose metabolism (*IRS1* and *GF2/H19*),[105,106] circadian rhythm (*BMAL1*, *PER2*, *PER3*, and *CLOCK*),[107,108] hypoxia (*HIF3A*),[109] and inflammation (*LY86* and *TNFA*).[110,111]

Histone protein tail modifications affect chromatin structure via altering enhancer and promoter activity, which serve critical functions in modulating metabolic genes in response to environmental stimuli in metabolic organs. Histones can undergo a range of chemical modifications after they have been translated from their genetic code, including acetylation, methylation, phosphorylation, adenosine diphosphate ribosylation, O-GlcNAcylation, and lactylation.[112] For example, previous research reported that obese individuals had lower levels of H3 lysine 4 trimethylation (H3K4me3) in their adipose tissue compared to lean individuals. This reduction was more prominent near genes involved in the metabolism of fats and inflammation.[113] Another case-control investigation involving women with normal weight and women with obesity revealed a variation in histone deacetylase (HDAC) 2/4/5/6 expression that might be correlated with obesity and the inflammatory processes related to obesity.[114]

Another epigenetic process implicated in obesity development is related to the function of non-coding RNAs, which are the post-transcriptional regulators of numerous biological and pathological pathways. Differential expression patterns of several non-coding RNAs, including microRNAs, long non-coding RNAs, and circular RNAs, among obese and non-obese subjects in different tissues have been well identified and attributed to the dysregulation of several pathways, including those linked with adipocytokines, calcium signaling, MAPK, FOXO, PI3k/Akt, Wnt-β-catenin, and PPAR signaling pathway.[115]

Building upon our understanding of genetics and epigenetics in obesity, it is now possible to unlock the potential for more personalized and targeted therapeutic approaches.

Diet

Extensive research has focused on the relationship between dietary patterns and chronic non-communicable diseases.[116-118] Even though there are many other causes of obesity, poor diet is a major risk factor. One study identified unhealthy dietary patterns as the primary cause of mortality worldwide, surpassing all other risk factors.[119] Unhealthy diets are typically those that are high in sodium, trans-fatty acids, sugar-sweetened beverages (SSBs), and red or processed meat and low in fibers, calcium, vegetables, fruits, whole grains, legumes, nuts and seeds, seafood, healthy fats (polyunsaturated and omega-3 fatty acids), and milk.[119]

Research on environmental changes to the food system and obesity suggests an association between increased food energy availability and higher energy intake with the global rise in obesity rates. A study conducted by Bleich et al[120] investigated alterations in energy availability within the food supply of the members of the Organization for Economic Cooperation and Development from 1961 to 2002. The findings revealed that the escalation in the supply of calories was a significant contributing factor to the rise in obesity rates in most countries. According to the results of the study by Kant and Graubard,[121] analyzing data from the National Health and Nutrition Examination Survey (NHANES), there was a rise in both the amount and energy density of food consumed in the United States from 1976 to 1980 (NHANES II) and 1999 to 2002 (NHANES III). Additionally, estimates adjusted from the US food supply indicated that per capita calorie intake among the population increased by over 300 kilocalories from 1985 to 2002.[122] People's dietary preferences are influenced by a variety of cultural, environmental, behavioral, and socioeconomic factors.[123] The affordability of added sugars, fats, and refined grains has resulted in an increase in diets that are high in energy-dense, nutrient-poor foods, as opposed to those that consist of whole foods such as lean meats, vegetables, and fruits.[124]

The United States' out-of-home consumption of food has also increased since the 1970s.[125-127] Similar shifts in eating habits have also been observed in Australia, where fast food and eating out are becoming more popular.[128] Due in part to the larger serving sizes, high-energy-density foods, increased variety, and preferred flavor of the foods, eating out may raise the risk of obesity.[129-131] Fast food consumption in particular has been associated with poor diet quality and detrimental dietary variables related to obesity, including greater intakes of calories, saturated fat, and SSBs.[132,133] The consumption of fast food has been linked to an elevated BMI, increased weight gain, and reduced efficacy in maintaining weight loss.[132,134-136]

The timing of food consumption is another modifiable behavior that may affect how the body regulates its energy and the likelihood of becoming obese. Despite the fact that morning energy intake was irresponsible for obesity, Wang et al[137] found that people who consumed ≥ 33% of their daily energy in the evening had a two-fold higher risk of being obese than those who ate in the morning.[137] The study findings suggest that a decreased likelihood of being overweight or obese is associated with a higher proportion of daily energy consumption during the midday meal. The combination of an individual's choices and behaviors, which have an impact on their balance of energy intake,

and their genetic and metabolic factors collectively determine their body weight and composition.[138]

Physical Activity

Physical activity is a crucial modifiable risk factor for obesity.[139-141] It refers to any bodily movement produced by skeletal muscles that requires energy expenditure[142] and encompasses a wide range of activities, including exercise, sports, and recreational pursuits. Various international health organizations provide guidelines for physical activity to promote health and prevent obesity. For instance, the WHO recommends at least 150–300 minutes of moderate aerobic activity per week (or equivalent vigorous activity) for all adults and an average of 60 minutes of moderate aerobic physical activity per day for children and adolescents.[143] Nonetheless, according to the WHO, more than 80% of adolescents and 27% of adults do not meet these recommended levels of physical activity.[143] This affects individuals over their life course and places a financial burden on health services and society.[143,144] The WHO's Global Action Plan on Physical Activity 2018-2030 provided recommendations to help countries increase levels of physical activity within their populations. Regular physical activity promotes mental and physical health in people of all ages. It is proven to help prevent and treat non-communicable diseases such as heart disease, stroke, diabetes, and breast and colon cancer.[143,144] It also helps prevent HTN, overweight, and obesity and can improve mental health, quality of life, and well-being.[143,144]

Higher physical activity levels are associated with a lower risk of obesity or weight gain over time.[141,145,146] Engaging in regular physical activity has been consistently associated with a reduced risk of obesity and its related health complications.[145,147-155] Conversely, insufficient physical activity or a sedentary lifestyle is related to an increased risk of obesity[156-158] and weight-related health problems, including metabolic disorders[159-161] and CVDs.[162-164] Despite the well-established benefits of physical activity, the global prevalence of physical inactivity remains a significant concern.[165,166] Sedentary behaviors, such as prolonged sitting and excessive screen time, have become increasingly prevalent due to modern lifestyles and technological advancements.[167,168] These sedentary behaviors contribute to reduced physical activity levels and an increased risk of obesity.[158]

This link can be understood through the concept of energy balance, which is determined by the equilibrium between calories consumed (energy intake) and calories expended (energy expenditure).[169] The mechanisms underlying the relationship between physical activity and obesity involve complex physiological processes related to energy expenditure, appetite regulation, and fat distribution.[169,170] Regular physical activity increases total energy expenditure through both exercise-induced energy expenditure and non-exercise activity thermogenesis.[171,172] Non-exercise activity thermogenesis refers to the energy expended during daily activities such as walking, standing, and fidgeting, which can significantly contribute to overall energy balance.[173] Physical activity plays a role in energy expenditure by increasing energy demand, implying that as individuals engage in physical activity, their muscles require additional energy to perform the work.[174,175] This energy is derived from the metabolism of stored body fat and glycogen.[176-178] Consequently, regular physical activity helps increase total energy expenditure and create a negative energy balance, favoring weight loss or weight maintenance.[179] Furthermore, physical activity influences body composition by reducing fat and preserving or increasing lean mass.[180,181] Further, it stimulates fat oxidation, promoting the use of stored fat as a source of energy, and enhances post-exercise lipid metabolism, which contributes to weight loss.[177-179] Moreover, physical activity helps maintain muscle mass,[182] which is more metabolically active than fat tissue and contributes to a higher resting metabolic rate.[183,184]

Physical activity also affects appetite regulation and hormonal responses. Intense physical activity has been shown to influence various appetite-regulating hormones, such as ghrelin and peptide YY, leading to decreased appetite and improved satiety.[185-187] In other words, engaging in physical activity can reduce cravings and emotional eating, helping individuals to maintain a balanced and healthy diet. Physical activity also influences the psychological and behavioral factors related to obesity.[188] Regular exercise has been shown to improve mood, reduce stress levels, and enhance overall mental well-being.[189,190] It can also be a positive coping mechanism for emotional and stress-related eating, reducing the risk of overeating and weight gain. Furthermore, engaging in physical activity can improve self-esteem and body image, promoting a healthier relationship with one's body and reducing the risk of disordered eating patterns.[191,192] Additionally, physical activity is crucial for long-term weight maintenance. While diet plays a significant role in initial weight loss, sustaining weight loss over time often requires regular physical activity.[193]

Behavioral and Psychological Factors

Obesity is a complex condition that is influenced by a number of different causes, including psychological and behavioral factors.[194] These factors play an essential role in the development and progression of obesity, alongside genetic, environmental, and physiological elements.[194,195] It is crucial to understand the psychological and behavioral risk factors associated with obesity to effectively prevent and manage the condition.[195]

Behavioral treatment has been shown to cause modest weight loss of around 5%–10% of initial body weight.[196,197] Psychological factors such as having unrealistic weight goals, poor coping or problem-solving skills, and low self-efficacy can hinder weight maintenance and increase the risk of relapse into obesity.[198]

Depression and anxiety, two of the most common psychiatric disorders, are strongly associated with obesity.[199] Previous research has linked obesity with

depression and anxiety,[199-202] although some studies suggest that body fat distribution and sleep behavior might play an even greater role in this association.[203-205] A systematic review by Luppino et al revealed that people with obesity had a 33% increased risk of developing anxiety over time and that anxious people had an 84% increased risk of developing obesity over time.[200] According to another study, people with obesity were 32% more likely than people with a normal BMI to have depression.[206]

Depression is characterized by persistent feelings of sadness, loss of interest, and a range of emotional and physical symptoms.[207] While not all individuals with depression experience changes in appetite or sleep patterns, these symptoms are relatively common.[208-210] Depression can lead to increased appetite, particularly for high-calorie comfort foods.[211, 212] Hormonal and neurochemical changes, such as dysregulated cortisol levels (the stress hormone), can contribute to an increased preference for fat, sugar, and carbohydrate-rich foods.[210-212] Depression can also disrupt the functioning of other appetite-regulating hormones such as leptin and ghrelin, leading to overeating and weight gain.[213-215]

Furthermore, depression often coexists with sleep disturbances such as insomnia or hypersomnia, both of which can influence appetite regulation and energy balance.[216] Sleep disturbances can disrupt the normal production and release of hormones that regulate appetite.[208,216] Reduced sleep duration or quality can affect leptin and ghrelin levels,[208] resulting in increased hunger and cravings for high-calorie foods, thereby contributing to weight gain.[217,218] Conversely, excessive sleepiness or hypersomnia can disrupt regular meal schedules, leading to irregular eating patterns and a higher likelihood of consuming larger meals or frequent snacking.[209] Excessive sleepiness can also reduce motivation for physical activity, promoting a sedentary lifestyle and weight gain.[219]

Depression, appetite dysregulation, and sleep disturbances are interconnected, forming a complex interplay that exacerbates the risk of obesity.[220] Changes in eating behaviors and disrupted sleep patterns create a cycle that contributes to weight gain. Managing/preventing obesity in individuals with depression requires addressing the psychological symptoms, as well as the associated appetite and sleep changes.

The relationship between anxiety and obesity is complex and involves various psychological, behavioral, and physiological factors.[221] While anxiety itself may not directly cause weight gain, the behaviors and physiological responses associated with anxiety can contribute to weight gain and the development of obesity.[222,223]

Emotional or stress eating is common among individuals experiencing anxiety, as they may turn to food to cope with emotional distress.[224] This can lead to excessive calorie intake and weight gain over time. Anxiety can also disrupt normal eating patterns, with some individuals experiencing loss of appetite during heightened anxiety and others resorting to binge eating as a response to anxiety.[224] These irregular eating patterns negatively affect metabolism and contribute to weight gain.[225]

Anxiety triggers the release of stress hormones, such as cortisol, which can affect weight regulation.[212,226] Elevated cortisol levels increase appetite, especially for calorie-dense foods, and promote fat storage, particularly in the abdominal area.[212,226] This hormonal response contributes to weight gain, particularly in individuals experiencing chronic or prolonged anxiety.[212,226] Additionally, anxiety can lead to a sedentary lifestyle and reduced physical activity, as individuals may avoid anxiety-inducing activities or situations, including exercise and social interactions.[227] The lack of physical activity decreases energy expenditure and further contributes to weight gain.

Moreover, some individuals with anxiety or depressive disorders may be prescribed medications, such as certain types of antidepressants, which can have weight gain as a side effect.[228,229] Not all anxiety medications have this effect, but some antidepressants, such as tricyclic antidepressants,[230] and monoamine oxidase inhibitors,[231] are more likely to cause weight gain due to their effects on appetite, metabolism, and insulin sensitivity. It is noteworthy that individual responses to antidepressants can vary, and not everyone will experience weight gain or obesity-related effects.

Socioeconomic Factors

Socioeconomic factors significantly influence the prevalence and persistence of obesity.[232-234] Income and socio-economic status, food environment and neighborhood characteristics, education, health literacy, and social and cultural factors are all intertwined and play important roles in shaping an individual's risk of obesity.[232-236]

Income and socioeconomic status (SES) are among the most critical socio-economic factors influencing obesity.[235,236] Several studies have found a strong association between low income and higher obesity rates, particularly in low-income countries.[235,236] In countries with a low human development index or low-income countries, there is also a positive correlation between SES and obesity for both men and women, implying that more affluent individuals in low-income countries are more likely to be obese.[236] In terms of obesity in children, it seems to be predominantly a problem of the wealthy in low- and middle-income countries.[236] Nevertheless, some studies have reported that neighborhood SES had a more robust and more consistent relationship with obesity for women than for men and for higher-income women than for lower-income women.[237] Due to their higher costs, individuals with limited financial resources often face challenges accessing healthy food options, such as fresh fruits, vegetables, and lean proteins.[238-242] As a result, they are more likely to rely on cheaper, energy-dense processed foods that are high in calories and low in nutritional value.[238-240] Additionally, individuals with a lower SES may have limited access to recreational facilities and

opportunities for physical activity, further exacerbating the risk of obesity.[243]

The food environment and neighborhood characteristics also significantly influence obesity rates.[244,245] Specific communities, often those with lower SES, may lack access to grocery stores or farmers' markets offering fresh, affordable, and nutritious foods.[246] These areas are described as "food deserts", where the predominant food options are convenience stores and fast-food outlets, which tend to offer energy-dense, low-quality foods.[246] The absence of safe, walkable neighborhoods with parks and recreational spaces limits opportunities for physical activity, reinforcing sedentary behaviors and contributing to obesity.[243,247]

Education and health literacy are critical socio-economic factors influencing obesity.[248] Low levels of education and health literacy can impede individuals' understanding of nutrition and health-related information, making it challenging to adopt and maintain healthy behaviors.[239] Limited health literacy can affect an individual's ability to navigate food labels, comprehend dietary guidelines, and make informed decisions about their diet and lifestyle.[239] Moreover, individuals with lower education levels may face economic constraints that limit their ability to access healthcare services, including preventive measures and weight management programs.[249]

Social and cultural factors also contribute to obesity rates.[250] Peer influence, social norms, and cultural practices can shape individuals' attitudes toward food and physical activity.[250,251] For instance, certain cultural celebrations and traditions may center on large, indulgent meals, leading to excessive calorie consumption.[252] Furthermore, social networks and social support play a crucial role in influencing individuals' eating habits and physical activity levels.[253-255] Lack of supportive social networks or living in an environment where unhealthy behaviors are the norm can contribute to developing and maintaining obesity.[254,255]

Recognizing and addressing these socio-economic determinants of obesity are crucial for developing effective interventions and policies aimed at preventing and managing obesity at the population level, as well as promoting health equity and improving overall well-being.

Health Consequences and Burden of Diseases Attributable to Obesity

Cardiovascular Diseases

Obesity and high BMI have numerous negative impacts on an individual's health, specifically in relation to the prevalence and severity of CVD and its risk factors, which is the primary cause of death in the United States for the majority of racial and ethnic groups.[19,20] This significant comorbidity is regarded as a negative prognostic factor with respect to overall life expectancy, heightened mortality, and morbidity.[256] For instance, early childhood obesity (by the ages of 11–12) is positively associated with the emergence of cardiovascular problems.[257] It is noteworthy that obesity, independent of other factors, has been found to significantly elevate the risk of nearly all CVD risk factors, such as HTN, glucose abnormalities, including T2DM, MetS, and dyslipidemia, as well as levels of inflammation. Moreover, the condition of obesity has the potential to generate a range of metabolic, neurohormonal, and hemodynamic modifications that could have negative effects on the morphology of the heart and the functioning of its ventricles.[258-261] As a result, obesity is strongly associated with an elevated risk of CVDs, particularly heart failure,[262] atrial fibrillation, coronary heart disease, HTN, and numerous other forms of CVD.[19,262,263]

The discovery of leptin and adiponectin in the 1990s sparked a revolution in our understanding of adipose tissue, transforming it from a mere energy bank into a dynamic and multifaceted endocrine organ. This groundbreaking discovery reignited research into the crucial role adipose tissue plays in interorgan communication, opening a new chapter in our exploration of its far-reaching influence on health and disease.[264,265]

Leptin has contradictory and counterintuitive effects on cardiovascular health. Frequently, hyperleptinemia is strongly associated with adverse outcomes in CVDs.[266,267] Leptin, however, can occasionally have cardioprotective effects by lowering cardiomyocyte apoptosis and hypertrophy.[268]

There is no denying the strong correlation between low levels of adiponectin and the increased prevalence of obesity-related cardiovascular illnesses, such as peripheral artery disease and ischemic heart diseases. Higher values of circulating adiponectin, however, make the issue more complicated. Elevated levels of adiponectin have been found in some circumstances to be correlated with a favorable prognosis for cardiovascular events. Conversely, in some circumstances, increased levels of adiponectin have no positive effect or even unfavorable effects, such as an increase in mortality rate. This phenomenon is known as the "adiponectin paradox".[269,270]

The escalating worldwide prevalence of obesity has been accompanied by a corresponding increase in the incidence of sleep disorders that are associated with respiratory difficulties, specifically those that manifest as repeated pharyngeal airway collapses during sleep.[271] While obesity may be a contributing factor to the development or exacerbation of sleep apnea, it is important to note that this condition can also have negative impacts on cardiovascular health. OSA is considered the most prominent sleep disorder due to its association with diverse CVDs and metabolic comorbidities.[272,273] Sleep disorders have been thought to play a causal role in the pathogenesis of weight gain, while obesity is widely recognized as the most influential demographic risk factor for the onset and advancement of OSA.[271,272]

Several researchers have concluded that the risk of all-cause mortality increases with prolonged obesity duration, regardless of various potential confounding factors and even independent of current BMI. This

correlation demonstrates a particularly strong association with cardiovascular disease mortality.[274,275] Conversely, other researchers have found evidence that current BMI is a stronger predictor than the duration of obesity.[276,277]

Neoplasms

Obesity has been identified as an independent risk factor for a variety of neoplasms, with endometrial, postmenopausal breast, and colorectal cancers accounting for more than 60% of obesity-related malignancies.[278] Based on the population-attributable fraction estimation of cancer incidence for 12 cancer types in 175 countries and 9 global regions, it was determined that in 2012, there were approximately 544 300 cancer cases—or 3.9% of all cancer cases worldwide—that could be linked to excess body weight in 2002.[279] Another study involving prospective data from 3,850 subjects concluded that weight gain of more than one pound per year was correlated with a 38% increase in overall cancer risk, with women having the highest risk.[280]

Specifically, obesity has been associated with an increased risk of estrogen receptor-positive and triple-negative phenotypes of postmenopausal breast cancer.[281,282] However, in the premenopausal period, the relationship between obesity and cancer incidence was found to be less linear and even negatively correlated with the risk of breast cancer. Individuals with a BMI of more than 35 kg/m^2 had a 76% lower risk of premenopausal breast cancer than those with a BMI of less than 17 kg/m^2.[278,283] Similarly, recent meta-analyses have indicated that obese women with breast cancer face a 30% higher risk of recurrence or mortality than normal-weight women.[284,285]

According to studies on the burden of colorectal cancer in obese individuals, higher weight circumference was a stronger risk factor than BMI and was linked to a higher risk of colorectal cancer, with each 10 cm increase in weight circumference leading to a 4% increase in colorectal cancer risk.[286] Furthermore, it has been established that this risk was greater in males than in females and that it was greater in elderly women above the age of 70 than in younger women.[287] Evidence from the past several decades has revealed a strong correlation between the increasing incidence of early-onset colorectal cancers and the childhood and adolescent obesity epidemic.[4] In a study involving a cohort primarily consisting of white women in the United States, individuals with a BMI of 23, compared to those with a BMI of 18.5–20.9 at the same age, had an almost 60% higher risk of developing early-onset colorectal cancer.[288]

Endometrial cancer has been found to be four times more common in obese women than in non-obese women. Survivors with a BMI greater than 30 had a 2.28 relative risk of mortality compared to those with a BMI less than 22.5.[289,290] Similarly, another retrospective study on endometrial cancer indicated a positive correlation between obesity and the grade and stage of the disease.[291] In addition, for esophageal adenocarcinoma, gallbladder, kidney, liver, multiple myeloma, ovary, pancreas, stomach cardia, and thyroid cancers, each 5-unit increase in BMI was associated with a 48%, 25%, 30%, 30%, 12%, 6%, 10%, 27%, and 13% increased risk of cancer development, respectively.[292]

Diabetes and Kidney Diseases

The correlation between obesity and the onset of T2DM is widely acknowledged due to the heightened insulin resistance associated with obesity. Insulin resistance serves as a predisposing factor for T2DM.[293] Early research[294] revealed that the most significant environmental factor affecting the prevalence of diabetes in a population was the level of obesity. Excess weight is responsible for 90% of T2DM cases.[295] According to several studies, individuals with BMIs of 30–35 kg/m^2 had a greater than 20-fold increased risk of developing diabetes in women and a 10-fold increased risk in men.[296,297] In addition, it is noteworthy that the presence of adipose tissue in the upper body or its central distribution constitutes a significant risk factor for the development of T2DM, independent of the individual's overall obesity level.[298-301]

The occurrence of T2DM is attributed to the pancreas' inability to compensate for the decline in insulin sensitivity.[302] This phenomenon is particularly prevalent in individuals with obesity, who exhibit higher levels of non-esterified fatty acids, glycerol, and pro-inflammatory cytokines originating from adipose tissue.[303] Hormones such as resistin, leptin, and adiponectin, among others, also play crucial roles in insulin resistance and the development of T2DM in individuals with obesity.[304,305]

Obesity significantly contributes to the pathogenesis of T2DM through various pathways. Obesity exacerbates the mortality rate and increases the risk of microvascular complications in diabetic patients.[306,307] Furthermore, obesity worsens the prognosis of T2DM.[308] Particularly concerning is the observation that obese individuals with diabetes face a poorer prognosis in terms of long-term disease outcomes compared to their non-obese counterparts. This trend is alarming, considering the global escalation in the prevalence of obesity and T2DM.[309-311]

Obesity in type 1 diabetes (T1DM), which was formerly uncommon, is now a growing problem.[312-314] There is mounting evidence that people with T1DM are also affected by obesity-related comorbidities, which were previously thought to be more common in people with T2DM. Overweight and obesity can contribute to insulin resistance in those with T1DM.[315] The prevalence and effects of obesity in T1DM are becoming increasingly obvious due to mounting evidence, which demonstrates how poorly recognized and undervalued this comorbidity is.[316]

In addition to T1DM and T2DM, obesity significantly raises the risk of developing gestational DM (GDM). Research indicates a positive correlation between BMI increase and the likelihood of developing GDM.[317] Both

GDM and obesity are associated with alterations in adipokine levels, which affect normal lipid and glucose metabolism. Insulin resistance-induced changes in glucose metabolism lead to elevated levels of free fatty acids in the blood, resulting in lipotoxicity.[318] Common features of GDM and obesity include lipotoxicity, glucotoxicity, and hyperinsulinemia, collectively contributing to increased oxidative stress. Maternal and fetal circulatory antioxidant mechanisms help mitigate these modifications.[318]

The development and progression of chronic kidney disease (CKD) have been shown to be correlated with several obesity-related variables in numerous population-based studies. In those without renal disease, a higher BMI has been linked to the development and presence of proteinuria.[319-323] Moreover, several extensive population-based studies have indicated a correlation between elevated BMI and the existence and progression of a low estimated glomerular filtration rate,[319-321,324-325] a faster decline in the estimated glomerular filtration rate over time,[326] and the occurrence of end-stage renal disease.[327-330] In individuals with pre-existing CKD, elevated BMI levels and class II obesity and above have been associated with a faster rate of CKD progression.[331]

Obesity-related kidney disorders are histologically categorized into glomerular and renal tubular injuries.[332] Among these, obesity-related glomerulopathy (ORG) stands out as a condition uniquely affecting individuals with obesity, representing one of the most prominent chronic renal consequences of obesity. ORG is defined as a renal disease characterized by proteinuria in individuals with a BMI of 30 kg/m^2 or higher, occurring in the absence of clinical and histopathological findings of other renal diseases.[333]

Between 1986 and 2015, the prevalence of obesity-associated glomerulopathy grew more than tenfold, coinciding with a higher average BMI among ORG patients compared to the general population.[334] Early studies revealed that patients with obesity-induced proteinuria exhibit focal segmental glomerulosclerosis lesions and glomerular hypertrophy upon renal biopsy.[335] Animal experiments have consistently demonstrated that obesity induces renal tubular damage, characterized by tubular hypertrophy, fibrosis, tubulo-interstitial inflammation, and the formation of lipid cytoplasmic inclusions.[336,337] Furthermore, obesity-related hyperfiltration appears to significantly contribute to the development of tubular injury, akin to its role in diabetic nephropathy.[338]

Neurological Disorders

Extensive research has explored the relationship between obesity and its effects on brain structure and cognitive abilities. Obesity has been strongly correlated with mild cognitive impairment and an increased risk of AD. Studies indicate that obesity may influence cognitive functions, leading to changes in memory, learning, and other cognitive processes.[339]

Numerous experimental studies employing animal models of high-fat diet (HFD)-induced obesity have revealed significant findings. Specifically, the hippocampus, a crucial brain region for memory and learning, has been shown to undergo structural and functional changes in response to obesity. Obesity-associated cognitive deficits have been linked to hippocampal alterations. Additionally, individuals with obesity exhibit cortical atrophy, particularly in the context of AD.[340] Moreover, several experimental studies have investigated markers of AD-related pathology in rodents fed HFDs. The HFD-fed mice demonstrated increased expression of amyloid precursor protein and amyloid precursor protein-processing enzyme, alongside abnormalities in learning and memory as well as reduced executive function, consistent with clinical observations. Notably, long-term potentiation, a key mechanism supporting learning and memory, was compromised in mouse models fed an HFD. Additionally, consumption of an HFD has been reported to decrease the brain-derived neurotrophic factor and other markers associated with neurogenesis, synaptic plasticity, and neuronal development. Intriguingly, numerous studies using animal models have produced compelling evidence, suggesting that hypothalamic inflammation precedes a vicious cycle of central nervous system dysfunction, ultimately leading to cognitive decline.[341] Furthermore, vascular dementia, which is often caused by cerebrovascular disease, can be exacerbated by obesity. These effects include the promotion of atherosclerosis in large cerebral arteries and alterations in the cerebral microcirculation.[342] T2DM has also been linked to accelerated cognitive decline and an increased risk of dementia. Shared metabolic, oxidative, and inflammatory processes are thought to contribute to neurodegeneration in both obesity and T2DM-related conditions.[343]

The concept of the "obesity paradox" arises from observations that obesity is associated with improved survival rates in certain conditions, such as heart failure and stroke. However, the underlying mechanisms behind this phenomenon remain incompletely understood. Further research is warranted to elucidate the specific factors contributing to these outcomes.[344] In conclusion, obesity profoundly affects cognitive function, brain structure, and various neurological disorders. It correlates with cognitive impairment, changes in the hippocampus and cortex, disruptions in the autonomic nervous system, and heightened risk of central disorders. Further research is needed to fully understand the underlying mechanisms and identify potential therapeutic targets linked to these relationships.

Chronic Respiratory Diseases

Obesity can influence respiratory conditions such as asthma, exertional dyspnea, OSA, obesity hypoventilation syndrome, and chronic obstructive pulmonary disease (COPD), serving as both a preventable risk factor and a disease modifier.[345-348] Furthermore, obesity adversely

impacts outcomes for acute respiratory distress syndrome and COPD, as well as increasing vulnerability to respiratory infections. Hospitalization rates are also elevated in obese patients with respiratory diseases in comparison to those with a healthy weight.[347] Both adults and children can experience wheezing, dyspnea, airway hyperresponsiveness, and orthopnea due to obesity, which can affect the prevalence and severity of the lung diseases mentioned earlier.[347,349,350]

Obesity exerts diverse effects on the respiratory system, including alterations in lung capacity and disruptions in cytokines and adipokines. Adipose tissue generates over fifty different adipokines, which can foster inflammation in conditions such as asthma and COPD. Normally, adipokines help maintain lung health through balancing pro- and anti-inflammatory actions.[351-353] However, obesity disrupts this equilibrium, leading to the onset and progression of lung disorders.[354] Additionally, surplus fat on the chest wall can reduce the compliance and endurance of respiratory muscles, resulting in increased breathing efforts and airway resistance.[355]

Weight gain and an increasing BMI can lead to reduced lung volumes, resulting in a more restrictive ventilation pattern on spirometry. An elevated BMI is associated with decreases in forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), functional residual capacity, and expiratory reserve volume (ERV) in both cross-sectional and longitudinal studies. Individuals with morbid obesity (BMI > 40 kg/m^2) may experience a slight reduction in residual volume (RV) and total lung capacity, while functional residual capacity may approach RV at this level of obesity.[345,356-361] The relationship between BMI and FEV1 is intricate; FEV1 declines at a slower rate compared to FVC or ERV. Additionally, the correlation between an increase in BMI and a decrease in FVC is more pronounced than that with FEV1.

Obesity is commonly linked to a restrictive lung ventilatory defect rather than an obstructive one, characterized by a low FVC and a high FEV1/FVC ratio (> 70).[358,361-362] Patients with COPD exhibit a higher prevalence of obesity compared to those without the condition, underscoring the association between obesity and certain chronic respiratory diseases.[363] The obesity paradox is frequently observed in individuals with COPD.[364] While being overweight is typically associated with increased mortality risk, a significant percentage of overweight or obese individuals have been shown to have a higher chance of survival compared to those with lower body weight, a phenomenon referred to as the obesity paradox.[365-367]

The relationship between obesity and asthma is well-established, with a meta-analysis of over 300 000 adults finding that increasing BMI was associated with an increased risk of asthma.[368] Obesity is a significant risk factor for the development of asthma and is often linked with more severe forms of the condition.[369] Research indicates that obese individuals with asthma experience higher rates of asthma exacerbations.[370] They further tend to have more severe disease manifestations, exhibit reduced responsiveness to standard therapies, and may demonstrate cellular glucocorticoid resistance.[355,370,371] Consequently, obesity can contribute to the development of more severe asthma phenotypes and associated comorbidities.[372,373]

Sleep apnea is a prevalent respiratory disorder that affects a significant portion of the population.[374] Obesity is the most significant risk factor associated with sleep apnea, and the relationship between the two is particularly concerning given the global obesity epidemic. The economic costs of sleep apnea are substantial for both the individual and society as a whole. Specifically, sleep apnea contributes to significant economic burdens related to motor vehicle collisions. Moreover, individuals with sleep apnea often experience daytime sleepiness, reduced quality of life, and impaired cognitive function, including deficits in learning skills, episodic memory, executive function, attention, and visuospatial cognitive functions. Left untreated, sleep apnea can lead to a range of medical complications, including CVDs, which can further increase healthcare utilization.[374]

A higher BMI greatly increases the likelihood of developing OSA.[375] Increased fat deposition around the soft tissues of the neck and tongue, often caused by obesity, can significantly contribute to upper airway obstruction. This can lead to an increase in extra-luminal pressures in the pharynx, which can elevate critical closing pressure and ultimately increase the likelihood of airway collapse.[376] In addition, it has been demonstrated that higher levels of obesity can exacerbate nocturnal hypoxemia in individuals with OSA.[377] To sum up, obesity has complex impacts on respiratory health and conditions, including worsening preexisting lung issues, increasing the chances of developing respiratory problems, and changing the way our bodies react to treatments.

Digestive Diseases

The interaction between the gastrointestinal (GI) tract and fat tissue occurs under both healthy and pathological circumstances. This interaction pathway presents an opportunity to discover novel therapeutic methods for obesity or GI diseases, which is consistent with previous evidence, suggesting the significance of peripheral signals in controlling GI motor responses and regulating food intake. Numerous pathways, including mechanical, pro-tumoral, pro-cancerogenic, and nutritional factors, may link obesity with GI diseases.[378] The quantitative and qualitative changes in gut microbiota observed in obese patients are associated with several pathophysiological pathways, potentially explaining the connection between GI diseases and obesity. Numerous investigations have demonstrated a relationship between intestinal dysbiosis and obesity.[379]

Obese individuals typically exhibit less diversified microbiomes and a different ratio of the two main gut

phyla, Bacteroidetes and Firmicutes. This imbalance results in a microbiota with an enhanced capacity for dietary energy harvesting, characterized by an increase in Firmicutes and a decrease in Bacteroidetes. Another consequence of obesity-associated dysbiosis is the reduced production of anti-inflammatory short-chain fatty acids, particularly butyrate, which also possesses anti-tumor properties through the regulation of different G-protein-coupled receptors and the suppression of histone deacetylases. These changes in microbiome diversity and metabolites can lead to increased leaking of intestinal antigens, such as lipopolysaccharides from Gram-negative bacteria, resulting in metabolic endotoxemia. This condition contributes to the generation of procarcinogenic toxic metabolites and increased extraction of energy and nutrient availability, leading to metabolic dysregulation that promotes tumor growth.[380] Therefore, the gut microbiota may serve as a key link between obesity and cancer. The prognosis for GI cancer is poorer in obese individuals, with numerous factors contributing to the correlations with neoplasia. Barrett's esophagus and gallstones, two well-established cancer-related diseases, have a higher prevalence in overweight individuals.

Obesity and MetS are also associated with preneoplastic lesions, including pancreatic intraepithelial neoplasia, colorectal adenoma, and serrated lesions of the colon. Adipocytes can release cancer-causing substances such as adipokines, insulin-like growth factors, and vascular endothelial growth factors at the cellular level. Another potential source of carcinogens is inflammatory cells, which are more prevalent in adipose tissue and systemically circulate in obese people. Animal research has provided further insights.[381,382] For example, intestinal adenomas were larger and more common in mice fed an HFD with a genetic predisposition to colorectal cancer compared to the control mice, and higher levels of mucosal oncogenic markers may be present. While weak-to-moderate correlations have been found between GI illnesses and obesity, and the underlying mechanisms are not fully understood, it is evident that obesity and multiple sclerosis have a significant, often overlooked, and potentially preventable impact on the prevalence of GI disease.[383]

Additionally, emerging mediators of the link between obesity and GI cancer include intestinal hormones. For instance, the fundic glands of the stomach produce the peptide hormone ghrelin, which possesses several metabolic and inflammatory properties, including appetite regulation, fat storage promotion, and inhibition of pro-inflammatory cytokine development. Individuals with obesity have been observed to have lower levels of circulating ghrelin than those with normal BMIs. According to a case-control study involving patients with esophageal adenocarcinoma and patients with non-cardia stomach cancer, the lowest quartile of ghrelin levels was associated with an approximately fivefold higher risk of developing both types of cancer when compared to the highest ghrelin level category.[384]

Musculoskeletal Disorders

The musculoskeletal system is crucial for facilitating daily activities and leisure pursuits. However, deviations from its standard structure or arrangement can impede functionality, leading to discomfort, pain, and sometimes physical incapacity in certain instances.[385]

Obesity has been associated with various chronic musculoskeletal conditions, including fibromyalgia,[386] osteoarthritis,[387] osteoporosis,[388] inflammatory arthritis,[388] gout,[389] chronic low back pain, carpal tunnel syndrome,[390] lumbar spine and soft tissue conditions,[388] and pelvic pain. [391,392] Numerous studies have highlighted the adverse effects of obesity on the morphology and physiology of the musculoskeletal system, particularly in the lower extremities and feet. For example, research indicates that individuals with obesity, irrespective of age, tend to have wider, thicker, and flatter feet than those without obesity.[393-397] Additionally, obese individuals exhibit noticeably higher plantar pressures while standing and walking[398-403] and undergo biomechanics changes in their feet and lower limbs while walking[404-406] compared to people without obesity. The development of musculoskeletal pain and discomfort in the foot has been linked to the continuous burden of carrying excess body mass among overweight and obese individuals.[407-409] Furthermore, being overweight or obese increases the likelihood of developing foot and ankle tendinitis, plantar fasciitis, chronic pain in one or more lower extremity regions, decreased mobility, and persistent plantar heel discomfort.[410-412] Overweight and obese individuals are also more prone than healthy or underweight individuals to experience chronic pain.[413] Further, obese individuals have a four-time higher prevalence of knee osteoarthritis than non-obese individuals.[414] Additionally, a retrospective case-control study [415] revealed an association between BMI and Meralgia paresthetica, a sensory mononeuropathy affecting the lateral femoral cutaneous nerve. Observational studies suggest a positive correlation between high BMI and the presence of degenerative disc disease of the lumbar spine, as detected through MRI.[416] Steele et al found that obesity compromises kyphosis and thoracic spine loading in the upper body of women. Their study indicated a positive correlation between elevated obesity rates and heightened occurrences of musculoskeletal pain in the upper torso region.[417]

Sense Organ Diseases

Obesity is associated with an imbalance between the sympathetic and parasympathetic divisions of the autonomic nervous system.[418] Increased sympathetic outflow to neuro-adipose junctions stimulates lipolysis via stimulatory G-protein-coupled β-adrenoceptors. This triggers a downstream signaling pathway that ends with the activation of adipose triglyceride lipase, resulting in triglyceride hydrolysis. Thus, sympathetic hyperactivation,

as observed in obesity, can promote a feed-forward mechanism leading to an increased pool of circulating long-chain fatty acids.[419] Several investigations have highlighted obesity as a standalone risk factor for polyneuropathy. Recent evidence has shown an increased risk of polyneuropathy with the number of MetS components, independent of glycemic management.[420] Abnormal lipid profiles, frequently observed in early T2DM, are associated with the onset of polyneuropathy. Increased triglyceride levels, in particular, have been linked to the development of polyneuropathy in diabetes. Additionally, individuals with prediabetes, who are typically obese, and patients with idiopathic polyneuropathy have noticeably higher triglyceride levels. These findings suggest that obesity and dyslipidemia may contribute to the pathogenesis of polyneuropathy.[421] Moreover, weight and chronic pain have been found to be significantly correlated with higher rates of pain complaints and diagnoses detected in individuals with higher BMIs. Furthermore, a higher body fat percentage and the presence of MetS indicators have been related to clinical pain situations. Studies on spinal cord injury have indicated that individuals who are overweight or underweight experience more severe pain than those of normal weight. However, further study is required to examine the connection between obesity and chronic pain in people with spinal cord injury, particularly based on the recently adopted definition of obesity for this population.[422]

Psychological Issues

Although early studies did not identify variations in the overall psychological state between individuals with obesity and those without,[423] more recent investigations have revealed that obesity is associated with multiple psychological problems. According to several studies, between 20% and 60% of individuals with obesity, particularly those who are severely obese, experience psychological disorders. Rates of mental disorders tend to be higher among those with obesity than they are in the general population.[424-428]

Depression

Individuals with severe obesity are approximately five times more likely to have experienced a significant depressive episode in the previous year than those who have an average weight.[429] The association between depression and obesity appears higher in women than in men.[430] A study revealed a higher prevalence of depressive symptoms among obese adolescents compared to the normal weight group.[431] Similarly, in another study, clinically obese adolescents exhibited higher depression ratings than non-clinically obese and normal-weight adolescents.[432] Obese children and adolescents often face difficulties in forming friendships as their peers perceive them as physically unattractive, less social, and more aggressive.[433] Additionally, bullying from peers and family members contributes to the increased incidence of depression in overweight children.[434-435]

It has been demonstrated that females who perceive themselves as overweight,[436] individuals aged ≥ 15 with obesity,[437] children with obesity,[438-439] and Class I and III obese females [440] have higher rates of suicidal ideations and attempts, which are potential consequences of depression. Nearly one-third of participants undergoing bariatric surgery exhibit clinically severe depressive symptoms at the time of surgery, with about half reporting a lifetime history of depression.[441-442] Stigma and discrimination play significant roles in these findings. Negative weight-based assumptions, such as laziness, lack of willpower, low intelligence, and poor self-discipline, contribute to discrimination, prejudice, and stigma against individuals with obesity across different spheres of life.[443-445]

The relationship between obesity and depression is controversial and complex. While some articles concluded that there is no significant relationship between obesity and depression,[446] Friedman suggested that the uncertainty in the results reflects the diverse experiences individuals have with obesity's impacts. Some may face severe psychosocial issues, while others may experience minor problems, and some may be unaffected by it.[423]

Anxiety

Anxiety problems are prevalent among patients undergoing bariatric surgery, although their frequency is less clear in individuals receiving nonsurgical care. Social anxiety disorder, which affects around 9% of patients, is the most common anxiety issue among those seeking bariatric surgery.[424] Individuals with severe obesity often report increased anxiety in social situations, which is unsurprising given Western society's emphasis on leanness as a sign of physical attractiveness.[447]

Eating Disorders

Binge eating disorder is the most prevalent eating problem among obese people.[448] A person with binge-eating disorder suffers a lack of control by eating too much food in a short period of time (less than two hours).[448] Consequently, even when not hungry, the person eats considerably more quickly than usual and often eats alone. After eating, the person often expresses distaste.[448] Studies have shown that obese adolescents,[449] females,[450] and youngsters[451-452] are more predisposed to eating disorders. In addition, obesity in childhood seems to be associated with the development of eating problems in adulthood.[453] Studies in the 1990s indicated that up to 50% of individuals presenting for bariatric surgery and a significant proportion of obese people seeking weight reduction therapy had binge-eating disorder.[454-457] More recent research suggests that 5%–15% of applicants for bariatric surgery may have the disease.[458] Night-eating syndrome is the second most prevalent eating disorder, affecting approximately 5% of individuals with obesity.[459] Night-eating syndrome is characterized by disruptions in the circadian rhythm of food intake, leading individuals to wake during the night to eat.[459,460]

Bipolar Disorder

A recent study,[461] which involved reviewing the four available studies in this field,[462-465] has reported that people with obesity are more susceptible to developing bipolar disorder (pooled adjusted odds ratio: 1.32, 95% confidence interval: 1.01–1.62). Several studies have confirmed that bipolar disorder is a risk factor for obesity, but few studies have explored the impact of obesity on the development of bipolar disorder.

Prevention and Management of Obesity

Lifestyle Interventions

Due to the absence of specific pharmaceutical therapies for treating obesity, "lifestyle modification" continues to be the most common form of treatment.[466] It is advised that individuals with obesity lose at least 10% of their body weight through lifestyle modifications (e.g., changes in diet, physical activity, and behavioral therapy).[467] Implementing a portion-controlled diet can also result in significant short-term weight loss.[468] A variety of nutritional approaches and strategies are available that can be tailored to meet the needs of individual patients.

Recent trends indicate a rise in the popularity of very low-calorie, Mediterranean, low-glycemic index, and low-carbohydrate diets.[469] Effective weight management can be achieved through regular physical activity, with aerobic exercise being recommended for all patients with obesity. It is recommended that patients engage in either 75 minutes of vigorous-intensity aerobic activity per week or 150 minutes of moderate-intensity exercise per week.[470] Exercise has been shown to improve metabolic endpoints, reduce weight, and prevent weight gain.[470] Additionally, anaerobic exercise, also known as resistance or strength training, is often more effective in reducing body fat percentage while increasing muscle mass.[471] Leisure time and occupational activities can also contribute to a patient's physical activity regimen.[472,473] For patients with obesity, behavioral changes should be tailored to their individual needs. It is crucial to conduct a thorough evaluation of the patient's current and routine behaviors before offering personalized recommendations aimed at addressing those behaviors or barriers.[474] In many cases, the adoption of lifestyle modifications yields a substantial decrease in body mass.[474] Furthermore, previous research suggests that effective holistic approaches that consider cultural norms, environmental practices, home activities, and supportive educators and parents are required for managing and preventing obesity in children.[475,476]

Given that individuals' food choices are largely influenced by their environment, it is crucial for governments to enhance their policies and environment to reduce the prevalence of unhealthy food options and increase the accessibility of healthy alternatives.[477] Restrictions should be placed on the availability of obesogenic foods marketed to children, and policies should be tailored to incentivize the production of foods containing lower levels of salt, sugar, and fat.[478] A small tax has been imposed on unhealthy foods in several regions of the US and Canada to limit consumption.[479] It is imperative to raise awareness among policymakers and practitioners regarding the potential influence of food advertising on human health and behavior. Further, it is recommended that food manufacturers be incentivized to create and distribute weight-friendly food products. Nutrition educators should teach the correct way to implement food advertising.[480] Several European nations, including Denmark, Norway, Sweden, and Austria, have restrictions on television advertising to young children.[481] Interventions aimed at encouraging behavioral modifications (e.g., social marketing, nutrition education, health promotion, and incentives for healthy living), alongside measures that address the causes of obesity (e.g., policy changes, laws, and regulations), are expected to yield significant results in reducing the growing problem of obesity.[482]

Pharmacotherapy

Over the past six decades, the treatment of obesity through medication has advanced considerably. Currently, the Federal Drug Administration (FDA) has approved seven anti-obesity medications for long-term use.[483] These drugs are recommended in conjunction with lifestyle changes, similar to treatments for other chronic diseases. Current guidelines recommend weight loss medications for individuals with a BMI of ≥ 30 kg/m^2 or those with a BMI of ≥ 27 kg/m^2 who also have an obesity-related health issue, especially if they have already tried lifestyle improvements without success.[484] Currently, setmelanotide is prescribed for specific rare obesity syndromes, including Bardet-Biedl syndrome.[483,485] In addition, six other drugs (orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, semaglutide, and tirzepatide) have been approved for treating general obesity.[483] Most of these drugs function centrally to reduce appetite, increase fullness, and act on the digestive system to slow stomach emptying.[486]

Orlistat

Orlistat, as a semisynthetic derivative of lipstatin, is a potent inhibitor of GI lipase, leading to reduced fat absorption.[487] It is indicated for individuals with a BMI of 30 kg/m^2 or more, or 28 kg/m^2 if other obesity-related health issues are present.[488] Clinical studies demonstrate that when combined with a modified lifestyle and low-fat diet, orlistat effectively aids weight loss and alleviates obesity-related conditions more effectively than diet alone. However, over 20% of users experienced side effects related to fat malabsorption in the first year, such as oily stools and abdominal pain. While these side effects decreased in frequency during the second year, the long-term efficacy and side effect profile of the drug remain unknown beyond two years.[489]

Phentermine/Topiramate

In 2012, the U.S. Food and Drug Administration approved

the combined use of phentermine and topiramate to treat obesity.[490] Aronne et al conducted a clinical trial to compare the combined use of phentermine and extended-release topiramate with individual doses of each drug and a placebo in adults with obesity. The combination treatment proved more effective in promoting weight loss and resulted in greater weight loss compared to both the placebo and individual drug treatments. Specifically, the combined doses of 7.5/46 mg and 15/92 mg led to weight losses of 8.5% and 9.2%, respectively, and a higher proportion of subjects on the combination treatment achieved a weight loss of 5% or more when compared with those on placebo or the monotherapies.[491]

Smith et al, performing a systematic review to assess the pharmacology, efficacy, and safety of the phentermine/topiramate combination for managing obesity, concluded that PHEN/TPM showed statistically significant weight loss compared to the placebo, with the most notable reduction being 10.6% after 56 weeks with the 15/92 mg dose. This weight loss persisted over two years, with a significant proportion of patients achieving weight reductions of over 5%, 10%, or 15%. The drug also reduced waist circumference, fasting triglycerides, and fasting glucose. The common side effects included paresthesia, dizziness, insomnia, and dry mouth. In conclusion, while PHEN/TPM is effective for weight loss and has received approval as an adjunct treatment, long-term safety data are still necessary.[492]

Another meta-analysis by Lei et al revealed that phentermine/topiramate therapy led to a significant average weight loss of 7.73 kg compared to a placebo, with the extent of weight loss being dose-dependent. Different doses resulted in varied levels of weight loss, with the 15/92 mg dose being the most effective. Participants taking phentermine/topiramate achieved weight reductions based on their individual baseline weights. However, this therapy was also associated with several side effects, mainly related to the nervous system, such as dysgeusia, paresthesia, and dry mouth. In addition to weight loss, the drug also positively affected waist circumference, blood pressure, blood sugar, and lipid levels.[493]

Naltrexone/Bupropion

Naltrexone and bupropion are both individually FDA-approved for different purposes. Bupropion, a dopamine/norepinephrine reuptake inhibitor, is approved for treating depression and aiding smoking cessation. Conversely, naltrexone, an opioid receptor antagonist, is approved for managing alcohol and opioid addiction.[484] However, in September 2014, FDA approval was received for the use of these drugs in combination to treat obesity.[484] The recommended dosage of the combination typically starts low and increases weekly until two tablets taken twice daily, providing 360 mg of bupropion and 32 mg of naltrexone. Four large studies (Contrave obesity research trials) involving over 4500 participants (4536 patients) demonstrated significant weight loss benefits with the combination therapy when compared to a placebo. In one trial (COR-I), the average weight loss with the drugs was 6.1% compared to 1.3% with the placebo. The studies also noted improvements in cardiovascular risk factors, such as waist circumference, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels. Additionally, diabetic participants in a COR-diabetes trial experienced a 0.6% reduction in hemoglobin A1c. However, similar to any medication, this treatment has been found to have a number of potential side effects, including nausea, dizziness, and dry mouth. It is also important to note that there may be risks when it is used with other medications or in individuals with specific medical conditions.[495-497]

Liraglutide

Liraglutide, a long-acting human glucagon-like peptide-1 (GLP-1) analog, offers therapeutic benefits for individuals with metabolic conditions such as T2DM and obesity.[498] This GLP-1 analog helps decrease food consumption, facilitate weight loss, and enhance metabolic functions. Its primary impact on appetite, metabolism, and weight reduction stems from its influence on both peripheral and central pathways, specifically activating the hindbrain and hypothalamus.[499]

A 56-week randomized controlled trial (RCT) involving 3,731 non-diabetic patients with obesity or overweight and associated health issues investigated the potential of liraglutide's weight management potential. Administered as a daily 3.0 mg subcutaneous injection, liraglutide demonstrated significant weight loss compared to a placebo. Patients treated with liraglutide experienced an average weight loss of 8.4 kg, which was significantly higher than the 2.8 kg lost by the placebo group. In addition, 63.2% of the participants on liraglutide lost at least 5% of their body weight, with 33.1% losing over 10%, compared to 27.1% and 10.6%, respectively, in the placebo group. The common side effects included mild nausea and diarrhea. The study, published in the *New England Journal of Medicine*, concluded that liraglutide, combined with diet and exercise, aids in weight reduction and metabolic control.[500] Furthermore, a meta-analysis of seven RCTs involving 6028 adults with obesity or overweight for at least one year indicated that liraglutide 3.0 mg significantly reduced weight compared to a placebo. However, it also revealed a higher incidence of adverse events among liraglutide users, resulting in more treatment discontinuations. Notably, liraglutide had a more pronounced effect on weight reduction in participants without DM.[501]

Setmelanotide

Setmelanotide is a drug that targets the MC4R and is used to treat extreme obesity due to genetic conditions, such as POMC, PCSK1, or LEPR deficiencies.[502,503]The FDA approved setmelanotide on November 25, 2020, for chronic weight management in individuals aged ≥ 6 with deficiencies in POMC, PCSK1, or LEPR.[504]

Setmelanotide represents a personalized approach to obesity treatment. Semaglutide 2.4 mg provides twice the weight loss compared to older drugs used to treat obesity and overweight conditions with comorbidities. This medication has already been used for diabetes as a GLP-1 receptor analog.[505]

In a multicenter phase 3 trial that was conducted across seven countries, participants with POMC or LEPR deficiency obesity were given setmelanotide. The main goal was to obtain a 10% weight loss from baseline within 12 months, with 80% of POMC trial participants and 45% of LEPR trial participants meeting this goal. Significant reductions in hunger scores were also noted. However, common side effects such as injection site reactions and hyperpigmentation were found as well. The findings of this revealed that setmelanotide could effectively treat obesity stemming from POMC or LEPR deficiencies.[506] In another study performed by Collet et al, setmelanotide induced weight loss in obese individuals with MC4R variants during a 28-day clinical trial, particularly among those with POMC defects. The drug was also found to be effective for individuals with MC4R deficiency.[507]

Semaglutide

A meta-analysis of 12 clinical trials revealed that semaglutide is both safe and effective for treating obesity, although some users reported GI side effects. Further research with larger samples and longer follow-up periods is needed to understand its long-term effects, optimal dosages, and appropriate treatment durations for a wider range of individuals with overweight or obesity.[508]

In a Phase 3 trial involving adults with obesity or overweight but without T2DM, the oral glucagon-like peptide-1 analog, semaglutide 50 mg taken once daily, was compared to a placebo to assess its effectiveness and safety. The findings of this trial, which was conducted in 50 outpatient clinics across Asia, Europe, and North America, confirmed that participants on semaglutide experienced an average weight loss of 15.1% over 68 weeks compared to 2.4% in the placebo group. Furthermore, 85% of participants on semaglutide achieved a body weight reduction of at least 5% in comparison to only 26% on the placebo. In conclusion, oral semaglutide 50 mg demonstrated significant weight loss benefits compared to a placebo in adults with obesity or overweight without T2DM.[509]

Another study by Ghusn et al investigated the effects of weekly semaglutide injections (1.7 mg or 2.4 mg) for 3–6 months in patients with obesity or overweight. On average, they experienced a weight loss of 6.7 kg (5.9%) after 3 months and 12.3 kg (10.9%) after 6 months. Interestingly, 87.3% of these patients shed over 5% of their weight by the 6-month mark. However, those with T2DM experienced less weight loss than those without T2DM. The results related to semaglutide's effectiveness in weight loss conform to the findings of a randomized clinical trial.[510] The STEP 5 trial evaluated the effectiveness of semaglutide 2.4 mg injections for weight loss in adults over 104 weeks. Compared to the placebo group (2.6%), those on semaglutide experienced an average weight reduction of 15.2%. However, more GI side effects were reported in the semaglutide group. Overall, semaglutide was significantly more effective than the placebo for weight loss over two years.[511]

Tirzepatide

Tirzepatide is a novel GLP-1 and gastric inhibitory polypeptide receptor agonist administered by once-weekly subcutaneous injection.[512] It is effective in the treatment of obesity in patients with and without DM.[513]

In an open-label trial including over 1,800 patients with diabetes, once-weekly tirzepatide, in varying doses, was compared with semaglutide 1 mg.[514] After 40 weeks, reduction in body weight with all doses of tirzepatide was greater compared with semaglutide (5 mg, 10 mg, and 15 mg of tirzepatide; -7.6 kg, -9.3 kg, and -11.2 kg, respectively: 1 mg of semaglutide; -5.7 kg).[514]

In addition, in a double-blind placebo-controlled randomized trial including over 2500 adults with obesity (but without diabetes), tirzepatide once weekly was compared with the placebo.[513] After 72 weeks, reduction in body weight at all tirzepatide doses (5 mg, 10 mg, and 15 mg) was more noticeable in comparison with the placebo (-16.1 kg, -22.2 kg, and -23.6, respectively, versus -2.4 kg).[513]

Gelesis100

Gelesis100 is a non-systemic hydrogel composed of modified cellulose combined with citric acid, designed for the treatment of overweight or obesity. When taken orally with water before meals, it rapidly absorbs water in the stomach, evenly mixing with food. The hydrated Gelesis100 occupies approximately one-fourth of the average stomach volume, forming thousands of small gel-like pieces with a consistency similar to solid foods such as vegetables yet containing no calories. While it retains its form in the small intestine, it starts to break down in the large intestine, releasing the absorbed water and leaving behind waste material.[515] Classified as a medical device, Gelesis100 operates mechanically and has received a non-significant risk designation from the FDA.[516]

A 24-week randomized, double-blind, placebo-controlled study evaluated the effectiveness and safety of Gelesis100 for treating overweight or obesity. The study findings demonstrated that Gelesis100 led to a significantly greater weight loss (6.4%) than the placebo (4.4%). Notably, 59% of Gelesis100-treated individuals achieved at least 5% weight loss, and 27% lost over 10%, compared to 42% and 15% in the placebo group, respectively. Moreover, participants on Gelesis100 had twice the odds of achieving 5% or 10% weight loss, and prediabetic or drug-naive type 2 diabetic patients were six times more likely to achieve over 10% weight loss. Gelesis100 displayed no additional safety risks and is

considered a promising treatment option for overweight and obesity issues.[515] However, despite the FDA approval, the American Gastroenterological Association guidelines currently list the use of Gelesis100 as a knowledge gap, highlighting the need for more research and evidence.

Bariatric Surgery

Several studies have confirmed the potential and efficacy of bariatric surgery as a therapeutic approach for treating obesity and obesity-related morbidities. These studies have explored various methods, all of which aimed to interfere with the physiological processes of eating, digestion, and absorption.[517] Sleeve gastrectomy (SG) and RYGB have emerged as the two most commonly performed procedures, accounting for 61% and 17% of primary bariatric surgeries, respectively, with RYGB considered the gold standard.[518] However, techniques such as jejunoileal bypass, vertical banded gastroplasty, and laparoscopic adjustable gastric banding (LAGB) have been largely abandoned due to concerns regarding side effects, frequent reoperation needs, or limited long-term effectiveness.[519]

The National Health System and other guidelines have established indicators for bariatric surgery, including a BMI ≥ 40 kg/m^2 or a BMI ≥ 35 kg/m^2 in patients with obesity-related morbidities. Furthermore, patients with poorly controlled T2DM and a BMI of 30–35, despite optimal pharmacological therapy, may also be candidates.[520,521] Multiple studies have consistently demonstrated the superior efficacy of bariatric surgery in achieving short- and long-term DM remission, particularly in earlier-stage patients before requiring multiple medications.[522,523]

The findings of RCTs comparing different bariatric procedures have been controversial. Some studies have found that SG and RYGB outperform each other in terms of weight loss outcomes, while other studies have reported similar levels of efficacy.[524] A systematic review and meta-analysis of six RCTs revealed no significant difference in BMI reduction between the two methods.[525] Another systematic review and meta-analysis, which included 20 RCTs comparing SG and RYGB, concluded that both methods achieved similar BMI reductions 1 month, 3 months, 2 years, and 5 years after surgery while favoring RYGB after 1 year. Additionally, excess weight loss at 3 months, 6 months, 12 months, and 24 months after surgery showed no significant differences between the methods; however, RYGB outscored SG by 11.93 and 13.11 percentage units after 3 years and 5 years, respectively.[526] Furthermore, another systematic review and meta-analysis, encompassing both RCTs and observational studies comparing SG and RYGB, indicated that RYGB had greater efficacy in total weight loss and the remission of T2DM, dyslipidemia, and HTN at five-year follow-ups.[527]

Beyond weight loss, bariatric surgery has shown substantial efficacy in managing obesity-related morbidities, including T2DM, dyslipidemia, HTN, sleep apnea, osteoarthritis, urinary incontinence, and cancer.[519] Multiple RCTs on obese patients with T2DM revealed that various bariatric surgeries were more effective than non-surgical therapies for glycemic control and remission of T2DM, with varying rates of remission at different time points ranging from 1 to 5 years post-surgery.[528-532] A systematic review and meta-analysis of these RCTs represented that single anastomosis (mini) gastric bypass (mini-GBP), SG, RYGB, LAGB, and a biliopancreatic diversion (BPD) without duodenal switch (DS) can all yield significantly more favorable outcomes in terms of T2DM remission and glycemic control in comparison to non-surgical interventions.[533] Among these methods, mini-GBP, which includes both simplicity and reversibility, had the highest efficacy.[534] Similarly, the significant preventive effects of bariatric surgeries and their superiority over medical treatments for both microvascular and macrovascular complications of T2DM have been well-established.[535-537]

Furthermore, several RCTs have evaluated the efficacy of bariatric surgery in treating dyslipidemia in patients with obesity. The findings of the largest RCT, involving 134 obese patients and comparing the effects of different bariatric surgeries with intensive medical therapy in terms of dyslipidemia resolution, confirmed that RYGB and SG reduced triglyceride levels by 40% and 29%, respectively, over 5 years from baseline, compared to 8% with intensive medical therapy.[532] Likewise, RYGB, SG, and intensive medical therapy enhanced HDL-C concentration by 32%, 30%, and 7%, respectively, demonstrating the superior performance of bariatric surgeries over medical therapies in ameliorating dysregulated lipid profiles in patients with obesity. An analysis of findings from 35 RCTs demonstrated that mini-GBP, RYGB with omentectomy, and DS had the best performance in reducing triglycerides, cholesterol, and LDL-C levels. On the other hand, SG with omentectomy was found to be most effective in elevating HDL-C concentrations.[538]

In terms of HTN, different findings have been made, depending on the length of the follow-up period and the type of surgery performed, with the majority suggesting promising outcomes. A meta-analysis of studies with a mean follow-up of 34 months indicated that bariatric surgery has been associated with a 68% decrease in obesity-related HTN.[539] Likewise, another meta-analysis reported that HTN was resolved in 38.4% of patients who received LAGB, 75.4% of patients who underwent RYGB, 72.5% of patients who received vertical banded gastroplasty, and 81.3% of patients who had BPD-DS.[540] Nevertheless, the long-term effects of these interventions on HTN are not known yet. A study suggested that within 10 years of follow-up, approximately 44% of patients who had previously achieved the resolution of HTN experienced its recurrence and required anti-hypertensive medication for blood pressure control.[541]

Public Health Policies and Interventions

Previous research highlighted obesity as a global concern, emphasizing that its control requires efforts beyond personal prevention.[542] Nutrition policies play a crucial role in enhancing the quality of diets and reducing the growing prevalence of obesity. Various measures, such as beverage taxes and recent nutritional modifications for women, infants, and children in programs such as the National School Lunch Program and School Breakfast Program, have been identified to be effective in promoting healthier consumption.[543] The implementation of calorie labeling on prepared foods has been associated with modest decreases in the calories purchased from such foods. Cost-effectiveness analyses suggest that beverage taxes, calorie labeling, and adjustments to federal nutrition assistance programs are expected to be economically beneficial in curbing the rise in obesity prevalence. Additionally, it is noted that a combination of multiple policies is more likely to succeed than relying on single policies.[543]

Calorie Labeling

Addressing obesity requires a comprehensive and multifaceted approach. One aspect of this solution may involve providing calorie information on menus for individual dishes and drinks. While the existing evidence does not strongly support a substantial reduction in calories ordered, the implementation of menu calorie labeling serves as a cost-effective educational strategy. It has the potential to influence consumers to make slightly lower calorie purchases.[544] The inclusion of calorie labels has the potential to assist consumers in making healthier choices. Furthermore, it motivates manufacturers to reformulate their products or offer a greater variety of lower-calorie options. While there is not extensive evidence indicating that menu labeling significantly impacts calorie purchases in fast-food establishments, some studies suggest that it does lead to a reduction in calories purchased in specific restaurant types and cafeteria environments. The limited available data on altered calorie labels indicate that they can promote the choice of lower-calorie options, although their effects may not significantly differ from those of standard calorie labels alone.[544,545]

Food Taxing

Taxation and increased strategies have shown promise in limiting calorie intake. For example, in studies involving university students, raising the prices of high-calorie foods resulted in a decrease in the proportion of selected calories. Therefore, implementing a tax on high-calorie foods has the potential to reduce calorie demand, making it a viable policy measure to combat the prevalence of obesity.[546] However, it is important to note that while small taxes could generate significant revenue, they may not significantly affect obesity rates. Conversely, high excise taxes could directly influence weight in at-risk populations but might face challenges in terms of political acceptance and sustainability.[547] A frequently cited objection to taxing unhealthy foods is the concern about infringing upon individual freedom. Nevertheless, it should be considered that the broader society bears the costs of obesity resulting from poor nutritional choices, including diminished productivity and costs to the healthcare system.[547]

A comprehensive systematic review and meta-analysis study assessed the impact of SSB taxes on the prevalence of overweight and obesity across countries with different income levels. Among the sixteen studies analyzed, most indicated a decrease in consumption, sales, and purchases with increasing SSB prices. Eight of the studies suggested the positive effect of SSB taxes on reducing the prevalence of overweight and obesity. A 20% tax was estimated to be more effective than a 10% rate in decreasing these health issues. Conversely, studies from high-income countries showed no significant effects, while those from upper-middle- and middle-income countries demonstrated notable reductions in purchase, consumption, and obesity prevalence. These findings indicate that a high SSB tax, especially if specific to beverage volume, could serve as an effective fiscal policy measure to lower SSB consumption and combat overweight and obesity.[548]

In a comprehensive study conducted in Kenya, it was revealed that implementing a 20% tax on SSBs, mandatory kilojoule menu labeling, changes in consumption patterns related to supermarket food purchases, and a shift in national consumption back to 1975 energy intake levels had significant impacts on health-adjusted life years (HALYs). The estimated effects ranged from 151,718 to 13.1 million HALYs, equating to 3 to 261 HALYs per 1,000 persons. Additionally, it was estimated to save between USD 0.08 billion and USD 6.2 billion, with productivity gains ranging from USD 1.2 billion to USD 92 billion. Both the 20% SSB tax and menu intake energy labeling were deemed cost-effective, promoting health and saving costs.[549]

Physical Activities Policies

Most children and adolescents do not engage in sufficient physical activity, which is considered a vital aspect of a healthy lifestyle. Public health initiatives must address this lack of physical activity among young people by implementing interventions such as school programs, educational initiatives, and after-school activities. It is crucial to ensure equitable access to community resources, promote youth sports, re-establish active transportation to school, and create environments conducive to physical activity in homes. Comprehensive national and international strategic planning is necessary to effectively implement these initiatives and promote a culture of physical activity among children and adolescents.[550]

Limitations

The present review article relies on existing published studies, which may have inherent limitations such as sampling bias, measurement errors, or variations in methodologies across studies. The accuracy and reliability of the data used in this review depend on the quality of the

sources. It is important to note that this study employed a narrative review rather than a systematic review and meta-analysis, making it harder to draw definitive conclusions. Given that obesity is a dynamic and evolving field, new research and developments may have emerged since our search was conducted. Therefore, this review may not capture the most up-to-date information and trends related to obesity. The review process may be biased, as the authors' perspectives and judgments may influence the selection of studies, data extraction, and synthesis of findings. Additionally, the quality and rigor of the included studies may vary, potentially affecting the overall validity and reliability of the conclusions drawn.

The findings presented in this review may not be universally applicable as they are based on studies conducted in specific populations or regions. The epidemiology, risk factors, and trends of obesity can vary across different geographic locations, socioeconomic groups, and cultural contexts. Hence, caution should be exercised when generalizing the results to other populations. Moreover, we focused solely on specific risk factors, although other potential risk factors may also warrant exploration. Additionally, some topics covered under risk factors may have needed a more balanced approach. While this review explored various risk factors associated with obesity, establishing causal relationships can be challenging due to the presence of confounding factors, unmeasured variables, or reverse causality in the original studies, which may limit the ability to attribute the observed associations to the discussed risk factors.

It is essential to consider these limitations when interpreting the findings of this study and to encourage further research to address these gaps and refine our understanding of the epidemiology and risk factors of obesity. Despite these limitations, our comprehensive review identified crucial gaps in our understanding and highlighted areas that require further investigation. Future research should prioritize conducting systematic reviews, with or without meta-analysis, on specific risk factors, especially those with inconsistent findings, to clarify whether there is a correlation.

Conclusion

In general, obesity remains a major public health concern worldwide. This review article highlighted its prevalence, risk factors, and trends, demonstrating its persistent rise and resulting in considerable health and economic burdens. Genetic, environmental, and behavioral factors contribute to the development of obesity. Understanding these risk factors is vital for effective prevention and management strategies. Addressing the obesity epidemic requires a comprehensive approach involving individuals, communities, healthcare systems, and policymakers. In addition, implementing evidence-based interventions, such as promoting healthy eating, regular physical activity, and supportive environments, is essential to combat this global health challenge. Continued research and surveillance play a crucial role in monitoring trends, identifying emerging risk factors, and evaluating the effectiveness of interventions in reducing the prevalence of obesity. By prioritizing prevention and implementing multidisciplinary strategies, we can work toward a healthier future, reducing the burden of obesity and its associated complications.

Acknowledgments

We would like to express our sincere gratitude to the Social Determinants of Health Research Center at Shahid Beheshti University of Medical Sciences for their invaluable support and contribution to this research. Additionally, we acknowledge the Global Burden of Disease Study, led by the Institute for Health Metrics and Evaluation, for providing publicly available data on global epidemiology, which was crucial to the development of this work.

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Funding

The present study was supported by the Social Determinants of Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran (Grant No. 43005963).

Data availability statement

Not applicable.

Ethical approval

Not applicable.

Consent for publication

Not applicable.

Conflict of interests

The authors declare that they have no competing interests.

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