

Review Article

Evolving landscape of obesity from genetic predisposition to public health intervention

Uzma Asif

Department of Biochemistry, Medicine Program, Batterjee Medical College, Jeddah, 21442, Saudi Arabia

*For correspondence: **Email:** uzma.aasif1@gmail.com; **Tel:** +966565299124; **ORCID:** <https://orcid.org/0000-0002-4659-9173>

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Abstract

Obesity is a global problem affecting billions of people worldwide and has increased substantially across the world. Researchers are trying to figure out its causes and possible interventions to control this problem. This review explores the genetic factors contributing to obesity, discusses challenges and treatment options associated with this condition, and provides a multidisciplinary perspective on this complex problem by thoroughly assessing genetic insights, challenges and therapeutic options associated with obesity. Furthermore, this review aims to support current techniques and advancements to combat obesity by improving the multimodal disease burden on society and healthcare. By understanding the various facets of this condition, it is possible to work towards developing effective solutions and improving the health of individuals worldwide.

Keywords: Obesity, Genes, Complications, Fat mass and obesity-associated gene (FTO), Proopiomelanocortin (POMC)

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INTRODUCTION

Obesity has become a serious global health issue, with excess body fat being the primary cause. However, this multifaceted condition is a combination of various other factors in which genetics plays a crucial role. While behavioral and environmental factors play a significant role in its development, research has shown that genetics and epigenetics also contribute as a major cause of obesity. This major health concern has its prevalence increasing not only in the United States but also in several other countries. According to several studies, obesity perception has been drastically shifted in recent times. Earlier, obesity was thought to be related to eating habits, sedentary lifestyle and lack of

physical activity but recently, genetic predispositions have also been included to play a significant role in determining cause of the obesity pandemic [1,2]. The prevalence of obesity among teenagers is predicted to increase by around 18 – 20 % by the end of 2035.

Previous reports have revealed a substantial connection between obesity and genetic predisposition [3]. Numerous genetic loci linked to obesity have been found by genome-wide association studies (GWAS), offering a framework for intricate interactions between genetic and environmental factors. These discoveries have spurred additional investigation into the molecular mechanisms governing

malnutrition, calorie consumption and accumulation of fat, providing a deeper understanding of the intricacies underlying obesity.

Additionally, obesity has impacts that go beyond what is apparent. Multiple health issues have been connected to it, including high blood pressure, metabolic syndrome, such as coronary artery disease, type 2 diabetes, dyslipidemia, insulin resistance, depression, sleep disorders and multiple types of cancers, including breast, colon, esophageal, ovarian, lung, rectal, stomach and gall bladder cancers [3,4].

METHODS

Search strategy

A comprehensive literature review was conducted to explore the evolving landscape of obesity over the last decade, with a focus on genetic predisposition, associated risk factors, complications and public health interventions. The review adhered to a structured search and selection protocol to ensure transparency and reproducibility. Systematic search was performed across five major electronic databases: PubMed, Scopus, Taylor & Francis Online, ResearchGate and Google Scholar. The literature search was conducted between January and March 2025, covering studies published from January 2014 to December 2024. The following combination of keywords and Boolean operators were used to capture relevant articles: "obesity" OR "overweight" and "genetics" or "genetic predisposition" and "causes" or "risk factors" and "complications" or "comorbidities" and "treatment" or "management" or "intervention" and "public health". Additional terms such as "epigenetics", "environmental factors", "behavioral interventions" and "obesity trends" were also used to refine the search.

Inclusion criteria

This review included peer-reviewed original research articles, reviews, and meta-analyses that were published in English between 2014 and 2024. In addition, studies focusing on genetic, environmental, and lifestyle factors contributing to obesity, as well as research addressing clinical, epidemiological, or public health interventions for obesity, including human-based studies, comprising adult and pediatric populations, were included in the search.

Exclusion criteria

Non-English publications, editorials, commentaries, conference abstracts, book chapters, animal studies, or studies focusing exclusively on molecular mechanisms without clinical or population-level relevance, as well as articles published before 2014, were excluded from the search.

Study selection process

After removal of duplicates, titles and abstracts were screened for relevance by two independent reviewers. Full texts of potentially eligible articles were then retrieved and evaluated for inclusion based on predefined criteria. Any disagreements during selection were resolved by consensus or consultation with a third reviewer.

Final dataset

Out of approximately 1,000 initially retrieved records, a total of 59 articles met the inclusion criteria and were selected for final analysis to capture the most current trends and emerging insights in obesity studies.

RESULTS

The impact of obesity on health and well-being

Obesity distorts physical and emotional health, raising risks for diabetes, heart disease, cancer, and a shorter lifespan. It also has a significant impact on both physical, mental health and emotional wellbeing of an individual [5]. High BMI (Body Mass Index) causes increased risk of weight stigma and psychological stress, especially in young adults. Several severe health risk factors are connected with obesity, including an increased likelihood of developing chronic conditions such as diabetes, heart disease and certain types of cancer. Along with these, several other problems like iron deficiency, osteoarthritis, obstructive sleep apnea, and polycystic ovarian syndrome-like problems make obesity a multisystem disease [6-8]. These health concerns lead to a decreased quality of life and a shortened lifespan for individuals affected by obesity [9].

In addition to several other consequences, most obese individuals suffer emotional and psychological effects quite often. People who struggle with obesity often face social stigma, discrimination, and low self-esteem. Depression and anxiety are also prevalent in obese people, further impacting overall well-being. Taking a

multi-faceted approach is key in addressing the impact of obesity on health and well-being. By focusing on education, support and access to resources for prevention and treatment, individuals, healthcare providers and communities work together to combat negative effects and promote healthier lifestyles. Prioritizing efforts to tackle physical and emotional challenges associated with obesity is crucial for improving overall quality of life.

Genomic perspectives on obesity

In order to understand and manage the global prevalence of obesity, it is crucial to have an in-depth understanding of the genetic foundations of this problem to enhance therapeutic techniques as well as promote personalized techniques for the universal management of this worldwide problem. By close monitoring as well as understanding the genetic basis of obesity, individualized and personalized approaches towards treatment and management options could be facilitated. It is quite clear that the landscape of management of obesity is evolving. There is a deviation from traditional methods of calorie restriction as well as intense exercise and the new paradigm shift is being accompanied by targeted therapies aimed at altering specific genetic pathways. Other approaches which are complemented by traditional therapies are adding pharmacological interventions to precision nutrition approaches. These methods leverage treatment and management options of this global multifaceted problem [10,11]. These deep genetic investigations reveal a more detailed explanation of the complicated nature of obesity. However, detailed analysis and investigations lead to an unparalleled inference of the genetic elements responsible for obesity. On the other hand, it shows a new approach for personalized treatment and interventions based on an individual's distinct needs.

Many recent studies show an association of adiposity related to genomics, which arises from various genetic factors. Certain genetic variations have been identified as leading causes of obesity as well as related metabolic disorders worldwide. It has been shown that a single gene defect leads to hyperphagia and endocrine disorders [12]. Genomic role in obesity and related disorders also affects the treatment option and response drastically [13,14]. Based on this knowledge and understanding of the underpinning mechanisms, individuals with high-risk factors are identified, and targeted therapies are designed to provide better outcomes and management [13]. It has also been hypothesized

that only 10 % of severe obesity has genetic causes; however, environmental factors elevate the risks of obesity without changing the genetic code, but along with present genetic factors in individuals [14]. These environmental changes are also linked with early-onset obesity, which is significantly affecting both developing and developed countries [15].

Epigenetic regulation of obesity, role of lifestyle modification along with therapeutic intervention

Epigenetics plays a crucial role in obesity and related metabolic disorders. Although it is difficult to relate epigenetics to obesity, a wealth of studies, however, support this hypothesis [16,17]. This could be because of age-related factors along with environmental, stress-related, or lifestyle changes that could make the condition worse. DNA methylation is the most common obesity-related epigenetic modification, which could result in cancer development. However, recent studies show that improved modification in lifestyle, along with potential dietary interventions, could reverse this issue and improve the outcome [18]. This epigenetics approach, along with addition of physical activity, could lead to improved outcomes in obese patients.

Possible genetic targets for intervention

For obesity and related syndromes, genetic defect identification could be challenging, costly and time-consuming. A study published in 2018 mentioned a Next-generation sequencing-based analysis to identify 52 simultaneous obesity-related mutations [19]. To understand its genetics, obesity could be classified as monogenic and polygenic obesity. Monogenic obesity could be rare and arise from a single mutated gene; however, polygenic obesity, which is more abundant, depends on multiple factors resulting from modification of numerous genetic variants. For early detection and implementation of protective and preventive measures, a genome-wide polygenic score has been established based on computational modeling and large dataset. These approaches integrate all common variants into projected possibilities for adults, specifically the young adult population, who are at risk of developing obesity. The most common genetic factors contributing to obesity are summarized in Table 1.

Leptin (LEP)

Leptin, a protein, acts as a proinflammatory adipokine and its importance in

immunometabolism was identified in mid 1990's and it is reported to be related to obesity and its related genetics. This protein is encoded by the obesity gene and high levels of this protein are associated with weight gain [20]. It is mainly produced by subcutaneous white adipose tissue and influenced by hormones like insulin and glucocorticoids. It is one of the main physiological body weight regulators in the system. Leptin receptors (Lep-R) are found in various tissues and activate multiple signaling pathways to regulate energy balance. Leptin helps in suppression of appetite by binding to its receptor LEPR-B in the brain and mutations in LEPR-B could cause early-onset obesity, even for normal birth weight individuals [21]. In obesity, there is often hyperleptinemia due to leptin resistance. Also, leptin is linked to cardiovascular disease events and reproductive processes. Certain factors contribute to fluctuations in the concentration of leptin, including fasting, hyperphagia and post-operative stress. Overall, leptin overexpression is identified in obese persons and this overexpression could cause resistance mechanism that leads to insufficiency of leptin to target cells and resulting in altered signaling [22].

Proopiomelanocortin (POMC) deficiency

Proopiomelanocortin deficiency is one of the causes of early onset and severe obesity [23]. Obesity linked to POMC gene mutations is quite rare, with a very low prevalence in normal population. Furthermore, POMC-derived neuropeptides play crucial roles in weight loss by elevating satiety levels in an individual. Thus, it provides a shield against obesity and related disorders through appetitive control.

Melanocortin-4 receptor

Melanocortin-4-Receptor (MC4R) gene is one of the most widely investigated genes related to obesity [24,25]. Its mutation results in the commonest monogenic form of obesity in ~5 % individuals worldwide. Studies also reveal that MC4R deficiency leads to hyperphagic state [26], delayed gastric emptying and disturbed satiety level [27] Contributing overall to circumstances leading to obesity. Studies also support evidence that activation of MC4R pathway results in decreased appetite and elevated energy expenditure [29,30]. However, on the other hand, modification or mutation in this pathway leads to compromised dietary habits and energy balance. This statement is supported by another study, which shows that MC4R agonist facilitates reduction in appetite along with regulation of body weight [29,30].

Fat Mass and Obesity Associated (FTO) Gene

Several studies revealed that modification of the FTO gene could lead to cancer progression in obese individuals. Furthermore, previous studies revealed the association of the first intron of FTO gene to obesity-related traits, including Type-2 diabetes, young adults early onset and obesity [28]. Also, FTO disturbs the levels of neuroendocrine hormones including leptin and ghrelin, thus resulting in less post-prandial satisfaction, increased diet intake and binge eating, thereby causing weight gain [29-31].

Brain-derived neurotrophic (BDNF) factor

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that impacts neuron growth. It is primarily found in the central nervous system, especially in the prefrontal cortex and hippocampus. Its receptor, neurotrophic tyrosine receptor kinase-2 (NTRK2), is also reported to play crucial roles in obesity, hyperphagia and developmental delay disorders specifically in children [32] and pregnant women resulting in gestational diabetes [33]. Research has shown its involvement in neuropsychiatric conditions such as epilepsy, depression, anorexia, obesity, schizophrenia, and Alzheimer's disease [34]. Along with other neuronal roles, BDNF is also known to be the metabokine linked with energy homeostasis and childhood obesity [35]. Studies report that there is a negative correlation between an individual's glycemic index and brain-derived neurotrophic factor and further demonstrating that obesity, as well as several other metabolic illnesses, are linked to a decrease in BDNF levels brought on by gene alterations [36]. According to a different study, regular exercise, a fitness regimen and physical activities also lower BDNF levels, which lowers obesity [37]. Furthermore, another study reported that the degree of caloric restriction may influence how weight reduction impacts circulating BDNF. Overall, several studies support the fact that increased levels of BDNF have a positive impact on metabolic health and obesity [38].

Table 1: Key genes associated with genetic obesity: mutations, mechanisms, and inheritance patterns

Gene	Chromosomal Location	Type of Mutation	Phenotype	Mode of Inheritance	Population	Mechanism	Reference
Leptin (LEP)	7q32.1	Frameshift mutation/ Loss of function mutation	Decreased satiety level, Hyperphagia, and obesity.	Autosomal recessive	Global/ Consanguineous families	Leptin deficiency affects hunger regulation, pituitary dysfunction	[40]
POMC	2p23.3	Loss-of-function mutations	Severe early-onset obesity, adrenal insufficiency	Autosomal recessive	Global	Deficiency in pro-opiomelanocortin affects appetite and adrenal function	[41]
MC4R	18q21.32	Missense mutation	Severe early-onset obesity	Autosomal dominant	Global	Impaired melanocortin signaling affects appetite	[42]
FTO	16q12.2	SNP (rs9939609)	Increased BMI, adiposity	Polygenic	European/ Asian	Alters fat mass regulation and energy balance	[43]
BDNF	11p14.1	Polymorphism (Val66Met)	Increased obesity risk	Polygenic	European/ Asian	Impairs neural control of energy balance and appetite	[44]
SIM1	6q16.3	Missense mutations	Severe obesity	Autosomal dominant	Global	Impaired hypothalamic development affecting satiety regulation	

Single-minded homolog 1 (SIM1)

With respect to the relationship between single gene defects and obesity, single-minded homolog 1 (SIM1) gene also takes part in obesity genetics [36]. This gene is known to be one of the underlying genetic causes of obesity by single gene disruption and it occurs abundantly in paraventricular nucleus of hypothalamus (HPV) along with some portions of amygdala neurons, and plays important roles in energy metabolism and hyperphagia in knockout mice [39]. Loss of function of SIM1 gene causes severe obesity.

Several studies have highlighted the established connection between loss of SIM1 variant and alteration in feeding pattern and severe obesity, especially in children and young individuals [36]. Table 1 shows the summary of key genes associated with obesity.

Contemporary strategies employed in the battle against obesity

Management of genetic obesity

Obesity is a significant global health issue with serious medical and mental health risks, including life-threatening conditions. Its prevalence continues to increase globally, leading to the development of modern management strategies. These approaches extend beyond traditional methods, such as diet and exercise, to focus on holistic approaches. Behavioral therapy, pharmacotherapy and bariatric surgery are among the options available; each tailored to individual needs to address the complexities of obesity. For pharmacotherapy approach, many drugs have been established to help with weight loss and have successfully shown promising results in obesity treatment. These drugs, including orlistat, naltrexone, phentermine and liraglutide, are used along with several other FDA-approved drugs. All these drugs target fat absorption and metabolism in addition to appetite control to facilitate weight loss. Additionally, one of the most popular treatments for obesity, especially severe obesity, is bariatric surgery, which is known to be an aggressive but efficacious intervention for severe obesity, leading to significant weight loss and improvement in obesity-related comorbidities. A careful risk-to-benefit assessment should be performed before considering surgical approach, especially when multiple complications are expected [45,46].

One of the contemporary approaches to managing obesity is the use of behavioral therapy. This includes addressing psychological and emotional factors resulting in overeating and sedentary behavior. This approach facilitates development of healthier habits as well as coping mechanisms to combat stress-related binge eating and thus reduces obesity [39,47]. Behavioral therapy is always needed, as most of the individuals who lose weight tend to regain it within a couple of months. Therefore, behavioral therapy is important to maintain lost weight and continue with healthy lifestyle [48]. Bariatric surgery is considered as gold standard approach in treatment and management of obesity. However, another much sought reason for weight regain even after surgery is the use of various drugs such as insulin, anti-depressants, glucocorticoids, oral contraceptives, hormonal implants, anti-psychotics and other related drugs.

For treatment of obesity due to deficiency of proopiomelanocortin (POMC), proprotein convertase subtilisin/keying type 1 (PCSK1), or leptin receptor (LEPR) deficiency, the melanocortin-4 (MC4) receptor agonist, Setmelanotide, is approved by US Food and Drug Administration (FDA) for patients above 6 years old. Setmelanotide stimulates the brain regions controlling appetite and fullness, assisting patients with certain brain defects to eat less and lose weight. It may also boost resting metabolism, thereby aiding in weight loss. While it helps patients with obesity related to these conditions shed weight, it does not address the genetic defects causing the condition or other symptoms [49]. In contrast to other MC4R agonists, Setmelanotide is well tolerated and patients haven't complained about high blood pressure, increased heart rates, or any other complications [50].

Leptin deficiency causes weight gain due to disturbances in energy metabolism. Administration of leptin, as a treatment option, in congenitally deficient individuals showed promising results [51]. An FDA-approved recombinant leptin analogue, metreleptin, could be used as management option, especially in children with known LEP gene defects. It not only controls hyperphagia but also controls body weight in both children and adults with congenital leptin deficiency [52,53].

Ethical and social implications for management in obese individuals

The most common phenomena related to obesity are disease stigma, discrimination and judgmental behavior of surrounding individuals. This could result in isolation of obese person, which leads to mental illness, drug addiction and other disorders. Poverty and below-the-bar earnings are known to be an impactful relationship with obesity. Unemployment, less healthcare and basic life facilities, absence of physical activities have a huge impact on a person's weight [54]. High-income countries' data showed that obesity is more prevalent among the poor due to these reasons. Overweight people often face disgrace and disparaging behavior in society and are often held responsible for their body weight despite the contribution of several genetic and environmental factors, which have been mentioned above. Obese people are often disrespected, disgraced and humiliated and their character has been portrayed as lazy, unhealthy, and incompetent by society, which makes them more prone to isolation. The societal stigma that fat people face and their culpability for their condition have been rendered possible by social media, entertainment and online advertising [55]. As research progresses on genetic insights into obesity, it is important to address ethical and social implications. Discussions on genetic

testing for obesity risk, potential stigmatization of genetically predisposed individuals, and disparities in access to genetic information and interventions are crucial in managing obesity ethically and socially [56].

Exploring behavioral therapy in managing obesity

Behavioral therapy is a contemporary approach that delves into the psychological and emotional aspects of obesity. It recognizes that overeating and sedentary behavior are often linked to deeper psychological issues, such as stress, trauma, or maladaptive coping mechanisms. By addressing the root causes of these behaviors, behavioral therapy aims to help individuals develop healthier habits and coping mechanisms for managing their weight. This approach often involves personalized counseling and support to guide individuals in identifying their triggers for unhealthy eating patterns. It also helps them build strategies to overcome emotional barriers that may hinder their progress in achieving a healthier lifestyle. By integrating behavioral therapy into obesity management, individuals gain a deeper understanding of their relationships with food and exercise, paving the way for sustainable and lasting changes (Figure 1).



Figure 1: Summary of genetic causes, environmental factors, management and complications related to obesity

CONCLUDING REMARKS

The global prevalence of obesity has become a significant public health concern. Innovations in obesity management are being explored to provide more effective solutions beyond traditional methods. New strategies aim to address the complex nature of obesity and improve public health outcomes by incorporating multifaceted approaches that go beyond simple calorie restriction and physical activity, but also effectively manage the hidden underlying causes of obesity and retain the results in the long run.

Public health policies and community-based initiatives are crucial in combating the obesity epidemic by promoting healthy lifestyles and regulating unhealthy food marketing to children. To effectively address obesity and its related complications, a comprehensive approach is needed that considers the physical, psychological and social aspects of the condition.

By focusing on prevention and treatment, as well as environmental and societal factors, efforts are made towards a healthier future for all.

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Ethical approval

None.

Use of artificial intelligence/large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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