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# Narrative Review of Genetic Contributions to Obesity

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## ABSTRACT

Obesity is a multifactorial condition influenced by complex interactions between genetic, environmental, and socio-behavioural determinants. Recent genomic studies underscore the significance of population and ancestry-related variation in obesity risk, highlighting disparities in the discovery and applicability of obesity-associated loci across global populations. While genome-wide association studies (GWAS) have identified over 150 loci linked to body mass index (BMI) and adiposity, most findings originate from populations of European ancestry, limiting transferability to African, Asian, Hispanic, Latino, and Indigenous groups. Differences in allele frequency, linkage disequilibrium patterns, and genetic architecture underscore the necessity of cross-population analyses and ancestry-specific polygenic risk models. Environmental and lifestyle factors, including diet, physical activity, socioeconomic status, and developmental conditions, further modulate genetic predisposition through gene–environment interactions. Early-life influences, such as intrauterine genetic risk and maternal nutrition, play a crucial role in shaping metabolic outcomes and behavioural susceptibility to obesogenic environments. Methodological challenges persist, including sampling bias, measurement errors, and limitations in causal inference due to over-reliance on self-reported BMI and predominantly European datasets. Advances in bioinformatics, rare-variant sequencing, and Mendelian randomisation hold promise for disentangling causality and improving prediction models. Addressing ancestry-specific variation, improving study design, and integrating environmental context are essential to ensuring equity, accuracy, and applicability in obesity genetics research. This integrated approach will advance understanding of the interplay between genetic architecture and environmental exposures, promoting more inclusive and effective global strategies for obesity prevention and management.

**Keywords:** Obesity genetics; Population ancestry; Gene, Environment interaction; Genome-wide association studies (GWAS); and Causal inference.

## INTRODUCTION

Obesity is a multifactorial condition characterised by excess body fat, affecting over one-third of the worldwide population [1, 2]. The rising rates of obesity over the past several decades reflecting a higher degree of overweight and obesity among younger cohorts have led to its designation as an epidemic [3]. Obesity significantly increases the risk of multiple debilitating conditions, including type-2 diabetes, cardiovascular diseases, and certain cancers [1]. The aetiology of obesity involves an imbalance between caloric intake and expenditure, where environmental factors such as diet and reduced physical activity contribute [2]. However, the phenotypic expression of obesity is irreducibly influenced by biological factors, indicating that genetics has an important role 2. Family studies show heritability estimates between 40 and 70%, indicating strong genetic contributions to risk [3]. Many genes associated with energy homeostasis or appetites, including MC4R, FTO, LEP, LEPR, POMC, and NPY, have been identified, alongside still-uncharacterised genes of unknown function [23]. Recent advances in whole-genome sequencing have elucidated rare coding variants with potent effects on body mass index (BMI), and genome-wide association studies (GWAS) have identified common non-coding variants outside of established obesity genes. In parallel, work on monogenic forms of obesity has detailed the

involvement of central regulatory circuits governing appetite and energy expenditure [13]. The aim of this narrative synthesis is threefold. First, the discussion reviews the genetic architecture, key loci, and biological pathways implicated in common obesity [15]. The emphasis throughout is on genes shaping liability rather than on dietary behaviours or other lifestyle factors. The second aim is to present methodological and practical issues. The synthesis concludes by outlining translational implications across research, clinical, and health-equity domains [14].

## Scope and Aims

Obesity is a complex trait influenced by genetic and environmental factors [11]. Understanding the genetic contribution to obesity may further elucidate pathogenetic mechanisms, support the prevention and treatment of obesity, and offer individualized health care [10]. Derived from genetics, the heritability of obesity is ~40% to ~70%. Based on genome-wide association studies (GWAS) data from multiple ethnically diverse populations, polygenic scores constructed from common genetic variants account for ~6% to ~8% of obesity variance [13]. Enhancing knowledge of genetic risk factors for obesity has both scientific and clinical relevance [17]. A detailed understanding of the genetic architecture of obesity across the spectrum of monogenic to polygenic and gene-environment interactions elucidates mechanisms that could serve as strategic targets for therapeutic intervention. A focus on specific, high-impact genetic loci, associated genes, and biological pathways has the potential to direct clinical and translational activities [19]. Genuine insight into the contribution of rare variants and monogenic causes of obesity can be obtained through sequencing and Mendelian approaches [2]. Available high-throughput sequencing data from individuals of diverse populations offer opportunities to examine rare variants in different geographical settings beyond European populations. Global GWAS integrating genetic, anthropometric, and environment data across diverse populations identify fitness and allow safety and health decisions to tackle the challenges of a healthy lifestyle regardless of genetic backgrounds [3]. Cross-population studies enable a better understanding of shared and novel obesity mechanisms resulting from population history, evolution, and adaption under different environments. Such efforts contribute to the ongoing pursuit of challenges related to prediction, prevention, and treatment of obesity that derive from the extensive use of GWAS in ethnic-generalized studies [4, 5].

## Overview of Obesity as a Complex Trait

Overweight and obesity are worldwide health problems that have increased dramatically over the last several decades, resulting in a major public health burden [3]. According to the World Health Organization (WHO) projections, the number of overweight individuals is expected to exceed 2.16 billion by the year 2030, with 1.12 billion of those classified as obese; this number is predicted to rise to 2.3 billion overweight and 1.7 billion obese by 2035[1]. In addition to the burden on individual health, overweight and obesity are ranked second in attributable mortality, behind only tobacco [5]. The clinical consequences associated with increased body weight include type 2-diabetes; hypertension; cardiovascular disease; dyslipidemia; certain types of cancer; and premature mortality. Excess body weight is caused by a positive energy balance, with more energy consumed than is expended; consequently, the amount of fuel stored in the human body increases over time [6]. Triglyceridedropped stored in adipose cells are released as free fatty acids into the plasma [8]. The genetic contribution to obesity risk and the active research in genetic epidemiology, including genome-wide association studies, sequencing of rare variants, and genetic epidemiological approaches, underscore the need for an understanding of genetic events that shape obesity risk [10]. Over 800,000 genome-wide association study (GWAS) samples have been analyzed globally, allowing nearly 50 loci to be identified that robustly influence the risk of obesity [9].

## Genetic Architecture of Obesity

Genetic architecture encompasses monogenic syndromes and polygenic variants, each conferring risk across a range of environments [3]. Forming distinctive pathways, risk loci contribute to appetite, energy expenditure, and adiposity; some also affect imprinting and early-life exposures [9]. Mechanisms under these loci engage neurobiology, endocrine signalling, metabolism, and microbiota. Interactions predicated on early life, diet, and activity amplify or attenuate heritable risk, and highly heritable traits, disorder-like trajectories, and early sensitivity indicate critical periods of exposure [6].

## Monogenic forms and Syndromic Obesity

Obesity is a highly heritable polygenic trait greatly influenced by the environment [21]. Monogenic obesity syndromes and chromosomal abnormalities contribute to extremely rare cases of early-onset obesity, generally arising due to mutations in genes associated with the central regulation of body weight [27]. A dual monogenic polygenic model provides a unified explanation for obesity risk, whereby the majority of affected individuals bear a polygenic genetic load [28]. At the opposite end of the risk spectrum, syndromic obesity forms part of complex multiple-defect syndromes such as Prader–Willi, Bardet–Biedl, and Cohen syndromes, or a host of imprinting

disorders affecting early-life development, including 15q11–q13 and 11p15 disorders [29]. Individuals severely affected by genetic obesity offer insights into the developmental and physiological regulation of appetite and energy metabolism; the core processes remain incompletely elucidated [30]. While the combination of early-onset severe obesity with mental delay provides particular modeling opportunities, other established syndromes also warrant deeper exploration [23].

## Polygenic and Heritable Risk

A growing number of studies indicate that obesity is governed by a polygenic architecture. Genetic studies provide compelling evidence for a genetic contribution to obesity predisposition. Collected estimates show heritability values of body mass index (BMI) of 74% in adults and 70% in children [3]. Classic twin studies and the heritability of specific phenotypes consistently suggest that the obesity heritability value is situated between 0.6 and 0.9 [7]. Searching for plausible loci, three recent genome-wide association studies (GWAS) for BMI have uncovered less than 20 such variants, each accountable for only a few percent of the genetic contribution. Understanding how individuals can be genetically different yet phenotypically similar remains challenging: it requires deciphering genetic effects that, instead of acting as a unidirectional trajectory, shape the final phenotype. Individuals who are genetically susceptible to obesity develop and care more about elaborate food regimes [17]. Their changes in body mass would be significantly different, and the early developmental environment appears to program the sensitivity of energy–substrate homeostasis in response to perinatal nutrition [18]. In light of the genetically determined differences in the behaviour of eating and exercise, the substantial discrepancy in effective imitation of the success of mates arise [19]. As twins grow older, especially in childhood, the environmental variance shrinks; anyway, such selection theory is not in opposition to the genetic–environment simplicity because allogenic mates become more important [20].

## Gene-Environment Interactions

Obesity arises from a multifactorial combination of biological and environmental mechanisms [7]. The global epidemic of obesity has been accompanied by environmental changes such as unhealthy dietary patterns, physical inactivity, and cultural shifts that have increased the exposure of populations to obesity-promoting environments, particularly in high-income and middle-income countries [23]. Individuals' genetic predisposition to obesity influences responses to an increasingly obesogenic environment [21]. Specific variants in the gene for the Melanocortin-4-Receptor (MC4R), for example, are associated with higher levels of appetite, food intake, and food reward, and variants regulating affective and emotional responses towards food have been identified [25]. Predicting risk for obesity based purely on genetic variants is complicated by interactions between genetic variants and environmental factors; hence, understanding these interactions is critical to developing effective prevention and management strategies [8]. Genetic variants associated with the metabolic efficiency towards utilising excess caloric energy from a short ephemeral diet have also been reported, emphasising the need for an integrative view of diet genes interactions [10]. Early-life and developmental context, in utero exposure to maternal obesity, and consequently the epigenome, together with non-epigenomic risk factors can all magnify genetic susceptibility[11].

## Key Genetic Loci and Pathways

An overview of over 700,000 subjects on an exome array uncovered eight novel loci associated with body mass index (BMI) and revealed involvement of the melanocortin pathway in energy balance [4]. Genes controlling mammalian production of pro-opiomelanocortin (POMC) and agouti-related peptide (AGRP), key agonist and antagonist, respectively, of the MC4 receptor (MC4R), participate in appetitive behaviours [4]. Loci additionally linked to appetite regulation include those for leptin, leptin receptor, neuropeptide Y and neuropeptide Y receptor [2, 9]. MC4R presents a strong candidate for pharmacological intervention targeting obesity. Fifty-eight additional loci exert influence primarily on energy expenditure, body fat distribution and adiposity [3]. Experimental disruption of β3 adrenergic receptors in mice produced hyperphagic obesity with increased energy expenditure; humans rarely express β3 adrenergic receptor antagonists at most and maintain intact β3 adrenergic receptor genes [2]. Other loci associated with adiposity include those for perilipin 1. Key imprinted genes exert influence during early life [1]. Genetic predisposition correlates strongly with childhood obesity; early-life genome–BMI associations shown within first years of life indicate risk established early [4].

## MC4R and melanocortin pathway

The melanocortin system is implicated in the regulation of body weight and energy balance [2]. The pro-opiomelanocortin (POMC) gene encodes peptides that play a role in melanocortin receptor signaling [1]. Among these receptors, none is more critical than MC4R. Mutations in MC4R and in other components of the melanocortin pathway produce obesity in mice [7]. In humans, loss-of-function mutations in MC4R also lead to monogenic obesity, confirming its role as a major regulator of energy homeostasis [12]. More than 280 mutations

causing either loss or gain of MC4R function have been identified in mice [8]. Certain mutations associated with monogenic human obesity can affect receptor trafficking, intracellular signaling, and ligand binding. Multigenic obesity represents another significant form of this disease [9]. Some of its genetic causes, including variation in MC4R and in other components of the melanocortin system, have been confirmed by genome-wide association studies (GWAS)[9]. Genes associated with monogenic and multigenic forms of obesity converge on the same signaling pathway that reflects information about energy and nutrient availability obtained throughout life [10]. Melanocortin receptors regulate energy processes in physiological models of caloric deficiency and excess. Unlike in the laboratory, however, the dynamic and integrated nature of the food environment faced in the wild starkly contrasts with the artificial experimental paradigms used to study the melanocortin system [15]. The modern food landscape poses unprecedented challenges to mice and humans alike. Melanocortin signaling is likely the first step in a broader system that integrates numerous other signalling pathways [11].

**Other appetite-regulation genes**

The single-nucleotide polymorphism (SNP) near the gene NEGR1 and deletions affecting the gene DDX1 have emerged from genome-wide association studies (GWAS) as significant common variants influencing body weight and appetite regulation [4]. Common variants at three further locinear the genes BDNF, SH2B1, and POMC associate with satiety and energy intake [5]. Deletions affecting the gene POMC also stand out among rare variants discovered through sequencing. Other appetite-regulation genes linked to insertion-deletion variants, copy-number variation, or rare non-synonymous mutations include DBH, DCDC2, and the imprinted gene MAGEL2. In addition, additional common variants at TAS2R38 and ZHX2 in prospective studies correlate with food choice and diet [3]. Translational applications of these findings may include pharmacological or surgical interventions targeting the melanocortin pathway to mitigate genetically programmed obesity. MC4R-targeted therapies are in early development, while the stimulus to consider selective POMC agent development has strengthened given the independent modulation of appetite and energy expenditure by MC4R and POMC insertion-deletion variants coupled with the recent identification of selective POMC compounds [4].

**Energy Expenditure and Adiposity Pathways**

An astonishing array of genetic contributions to obesity has emerged from research into monogenic forms, the impact of the early-life environment, and polygenic variants, including those identified in genome-wide association studies (GWAS)[9]. Causal insights from monogenic forms and certain polygenic variants have further illuminated mechanisms involved in energy intake and expenditure, the function of which is thought to underlie many polygenic variants implicated in appetite regulation [12]. The excess of high and low-frequency variants at these genes contributes to universal traits such as adiposity and appetite. A second category of obesity-related genetic variants controls energy expenditure and fat distribution [10]. These variants persist at significant allele frequencies across diverse populations, reflecting their clear selective advantage in environments that promote obesity [13]. Studies of rare-mendelian forms of obesity illustrate the fundamental role of the central nervous system in the regulation of energy homeostasis [12]. Monogenic variants, affecting the function of genes such as POMC, LEP, LEPR, and, most notably, MC4R, acting primarily on the leptin–melanocortin pathway, confer massive increases in body weight. An extensive collection of mouse obesity models with phenotypes mimicking those observed in patients is available that enables the investigation of the downstream neuronal circuits and molecular mechanisms affected by these variants in detail [13]. For example, expression analysis has revealed that, among the pomc-targeted mouse models, deletion of the Mc4r is sufficient to reproduce the massive obesity conferred by total removal of the POMC system. Adiposity and energy expenditure are tightly linked because excessive caloric intake, in the absence of a compensatory increase in energy expenditure, leads to gradual weight gain [14]. A substantial body of evidence indicates that, in humans, a differential genetic susceptibility to energy expenditure may contribute to obesity risk [15]. There is, for instance, a well-established genetic contribution to resting energy expenditure, and a number of candidate genes have been shown to influence the metabolic activity of pharmacologically inducible brown adipose tissue in rodent models [16].

**Imprinted Genes and Early Life Effects**

Offspring exposed to an adverse in utero environment during fetal development are at increased risk of obesity, dyslipidemia, and impaired glucose tolerance later in life [12]. Both maternal and paternal pre-pregnancy obesity raised the risk of childhood obesity among children delivered at full-term [14]. A substantial body of literature suggests that epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNA activity, play an important role in mediating the effects of early life adverse environmental exposures on long-term metabolic health [15]. These data suggest that maternal obesity and excessive GWG during gestation may affect the obesity risk and metabolic health of subsequent offspring by altering the epigenome characteristic and gene expression of key metabolic and obesity-related genes during early embryo development [3].

## Genomic Technologies in Obesity Research

Genome-Wide Association Studies (GWAS) represent a recent, ubiquitous approach to discover new genetic variants that may affect complex traits such as obesity [16]. Leveraging these resources, it was possible to ascertain which of the signaling pathways influencing body weight were most heavily affected by common genetic variation [11]. Because the variants identified in GWAS studies are either uninterpretable or far from the functional variant, the analysis of rare-variant sequences adds specificity regarding the relevant genes [17]. Monogenic and syndromic disorders are the oldest methods to query human genes with the potential to alter weight [10].

## Genome-wide Association Studies (GWAS)

Genome-wide association studies (GWAS) provide a scalable framework for uncovering the genetic variants that shape human diversity and disease susceptibility [18]. Their lowest common denominator is the genome-wide analysis of hundreds of thousands of single-nucleotide polymorphisms (SNPs) preferably diverse and polymorphic ones distributed evenly across the entirety of genomic DNA using samples that are typically fixed short-upstream-to-short-downstream (ex vivo) DNA-derived and well-phenotyped [16]. GWAS have demonstrated their potential as discovery engines in obesity research by illuminating the milieu of genetic risk on an unprecedented scale [17]. They pinpointed the first common-risk polymorphisms at or near pro-opiomelanocortin (POMC) and melanocortin-4 receptor (MC4R) two genes intimately associated with appetite regulation and energy homeostasis [19] and identified new obesity-related susceptibility loci involving brain-derived neurotrophic factor (BDNF), insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2), and the diacylglycerol acyltransferase [1] (DGAT1) gene cluster. They also revealed trans-acting rare variant associations at mohocutaneous dystrophy and fissured tongue 3 (MDTF3), a gene hypothesized to influence early-life metabolic programming [23].

## Rare Variant Sequencing and Mendelian Approaches

Many genes implicated by GWAS show ubiquitous effects on related anthropometric traits or behaviours; in some, the associations are stronger with obesity or metabolic variables than with height or BMI [19]. About 20% of loci are close to targets of known obesity medications; genes via energy intake, output and storage are thus prime candidates for discovery, supporting pathways suggested by rare-variant data and classical physiology[18]. The identification of all genetic variants influencing obesity risk remains an elusive goal; determining how those mechanisms operate post-genotyping is a greater chal- lenge [11]. Obesity thus presents an opportunity to study how complex genetic effects act on human behaviour and physiology, and the fraction of damaging alleles shared across populations remains a hotly debated topic. GWAS point to common variants with small effects on obesity risk, and sequencing studies complement these findings [12]. Several Mendelian conditions, each due to a single-gene mutation with strong effects on appetite, fatness and timing of food intake, have been recognized [9]. Their commonness (weight gain often begins early in life) and the heterozygosity of variants from large cohorts in mega-analysis of simple-to-severe paediatric obesity suggest that they are unlikely to explain significant proportions of risk [10].

## Translational and Clinical Implications

Obesity is a major health problem threatening the health of individuals and populations and imposing an enormous economic burden [22]. The understanding of the genetic determinants of obesity and the associated mechanisms is therefore critical to guide early prevention strategies aimed at reducing this ever-growing epidemic [7]. Due to its complexity, physical observation alone cannot capture all aspects of obesity [9]. Genomic techniques provide a more reliable and accurate way to study obesity [13]. The genome can be interrogated in many different ways, and the choice of a methodology has large consequences on the nature of the knowledge extracted regarding the genetic architecture of obesity [22]. Genetic studies have led to many insights regarding the developmental origin and drivers of obesity at multiple levels: identification of genetic loci associated with obesity-associated traits and elucidation of the associated pathways, elucidation of an extensive genetic architecture comprising monogenic, syndromic, polygenic heritable, and gene-environment interactions, evaluation of the contribution of ancestry to the genetic architecture of obesity, specification of the properties of non-genetic factors that affect obesity or mitigate genetic risk, and examination of the multiple implications of these findings for intervention and clinical translation[3]. Population diversity therefore represents a fundamental requirement for health equity and the identification of the most appropriate translational research strategy [20].

## Risk Prediction and Polygenic Risk Scores

Studies investigating the genetic architecture of obesity have facilitated the identification of actionable biomarkers that reliably inform risk prediction and susceptibility [20]. Monogenic forms of obesity resulting from rare, high-impact mutations are well characterized; the implicated genes encode proteins that influence hypothalamic circuits regulating appetite and energy expenditure [3]. These very few well studied genes impact mechanisms upstream of a broader collective of polygenic obesity genes and pathways that emerge from genome-wide association studies

(GWAS) involving hundreds of thousands of individuals [21]. Obesity polygenic risk scores (PRS) combining thousands of single nucleotide polymorphisms (SNPs) associated with body mass index (BMI) further reinforce genetic predisposition and indicate marked trans-ancestry transferability [22]. Validated environmental, lifestyle, and gene–environment interactions modulate the risk predicted by PRS and provide a framework for translating these findings into personalized health care that, within broad population-based obesity-prevention efforts, may improve obesity management and reduce obesity-related chronic conditions [23].

## Targeted Therapies and Personalized Medicine

The potential for targeted therapies and personalized medicine in obesity management has gained attention following the genetic dissection of obesity and related metabolic conditions [24]. The obesity-causing variants uncovered through genome-wide association studies (GWAS) and the analysis of rare variants support the notion that individuals with lower susceptibility can be considered for personalized approaches. Sequencing of exomes has led to the identification of variants that are associated with protection from obesity [23]. Whole-genome and exome sequencing can, therefore, allow identification of individuals at low risk of obesity, healthy long-term weight gain, or at risk of healthy weight loss from a diet [25]. The identification of genomic variants associated with specific dietary patterns supports modeling of food prescriptions tailored to genetic risk. Individuals less prone to obesity appear to benefit more from higher carbohydrate and sugar consumptions, indicating that more personalized dietary interventions could improve adherence to healthy dietary patterns and, consequently, facilitate long-term weight management and metabolic health[26]. Polygenic prediction models have been applied to estimate weight and obesity trajectories starting at birth, as well as to forecast response to lifestyle changes. Monogenic obesity syndromes provide a clear demonstration of the importance of hypothalamic and other central nervous system circuits in appetite regulation [16]. GWAS analyses have identified multiple genetic variants associated with obesogenic dietary habits, exposing another dimension through which genetic variations influence body-weight regulation [20]. Even in healthy-weight individuals, genetic risk appears to enhance the propensity to develop characteristics typically connected to obesity. Genetic studies of body-fat distribution and the metabolic influence of early life have also been pointed to as relevant dimensions for developing and refining personalized approaches. Overall, the findings underscore the potential of targeted therapies and a personalized framework in the management of obesity and metabolic health [23].

## Ethical, Legal, and Social Considerations

Obesity is a major public health concern, being one of the leading preventable causes of death. Furthermore, the increased prevalence of obesity has contributed to the epidemic increase in type 2 diabetes, hypertension, and other serious diseases [15]. Determinants of obesity are complicated and include environmental, social, demographic, and genetic factors [11]. Genetic contributions to obesity are recognized, and research on genetic factors has rapidly progressed due to new genomic technologies and the large databases available from various sequenced organisms. Understanding the genetic bases of obesity is an important area of research in order to identify high-risk groups, improve disease prediction, and develop personalized medicine [16]. Genetic variation leads to individual differences in body weight and fat distribution [1]. Analysis of large human populations has shown that approximately 70% of BMI variance and 80% of BMI variance in childhood are attributable to genetic heritability. Identification of genetic factors that are associated with obesity continues to be an active area of research [17]. To date, >160 loci associated with BMI have been demonstrated in genome-wide association studies (GWAS) in multi-ethnic populations that include European, Asian, African, and Hispanic ancestry. Understanding the genetic factors that are associated with obesity has implications for the design of novel intervention strategies to combat the epidemic [5]. Genome-wide association studies (GWAS) have identified >160 loci also indicating that obesity is a complex trait; most obesity-associated genetic variants have very small effect sizes(<0.1kg/\( m^{2} \)). Nevertheless, a polygenic risk score (PRS) derived from GWAS analyses provides a powerful predictor of individual genetic risk of obesity and its associated traits widely applied in population-scale genome sequencing and genetic risk research[2]. Furthermore, inputting the large-scale, high-quality polygenic signal into various population groups with distinct ancestry provides an opportunity to probe the genetic architecture across populations [2].

## Population and Ancestry Considerations

Obesity is a multigenic trait influenced both by genetic and environmental factors, including inter and intrapopulation variability [26]. Genetic architecture shows population differences, including low statistical power to detect the classical loci and relevant pathways in some minority populations [27]. Genetic variability in loci and pathways collectively contribute to the risk of the disease [7]. Either predicted polymorphisms via inclusion in clump-based PGIS or ancestry-specific associated variants enable the prediction of BMI across diverse population settings [14]. Bioinformatic modelling identifies several environmental variables that modulate the effect of the predicted risks derived from classical GWAS variants and related pathways [9]. Early-life phenotype varies

across populations, and biological environmental modifications, including socio-economics, appear to be population specific [8].

**Cross-population Differences in Genetic Architecture**

Human populations have not been strategically sampled for obesity genetics, and a comparative advantage exists in the Hispanic–Latino population [13]. Genetic variants that explain obesity-related phenotypic variation are underexplored outside of non-Hispanic European ancestry. Outside of Europe, the risk shown by adiposity factors remains strong in the United States but diminishes elsewhere [23]. The association between common obesity variants and essential fat is stronger in individuals of African ancestry than of European ancestry [28]. Following GWAS, the absence of widely replicated associations demonstrates clearly that common genetic variants communicated by large studies remain effective in populations outside of European-ancestry and that these connections might be captured in low-PGS groups of early ZIP or POF size [27].

**Implications for Health Disparities**

Obesity is a global health problem, affecting approximately 400 million adults worldwide, more than 60 million of whom live in the United States [13]. The increasing prevalence of obesity among children is alarming, especially considering the association between obesity and a range of serious health conditions, such as stroke, coronary heart disease, type 2 diabetes, hypertension, certain cancers, and cardiovascular diseases [18]. Furthermore, although varied and multidimensional methods of assessing body composition exist (e.g., percentage body fat, waist-to-hip ratio), the World Health Organization (WHO) recognizes body mass index (BMI), defined as weight in kilograms divided by height in meters squared, as a fundamental measure for the classification of obesity. The WHO defines obesity as a BMI equal to or higher than 30 kg/m2 [19]. Studies have shown that variation in body fat has a substantial genetic component, and family studies suggest that BMI-related measures are heritable. Recent advances in genotyping technology have enabled the identification of a variety of genetic variants associated with obesity-related phenotypes through genome-wide association studies (GWAS), principally in populations of European ancestry [17]. However, the consistency of these findings across diverse ancestries, specifically African American, Asian, and Indigenous groups remains uncertain [25]. To evaluate the consistency and magnitude of associations between genetic variants previously implicated in BMI and obesity, a study investigated a sample of 69,775 individuals from 25 diverse racial and ethnic backgrounds who participated in the Population Architecture using Genomics and Epidemiology (PAGE) Study [12].

**Environmental and Lifestyle Contexts**

Within modern environments the early life of children and adolescents–their dietary, physical activity, and developmental experiences exert decisive influences on risk for obesity [14]. The potency of non-genetic factors both those stemming from exogenous such as the wider diet regime and exercise of the surrounding population and those that reflect individual characteristics, such as socio-economic status, health awareness, and behaviour patterns, adaptive or otherwise is well documented[10]. Notably, the wider diet regime exogenous to hereditary predispositions generates both gene-environment interactions and polygenic-wide association studies [15]. Such factors therefore exert a strongly modulatory influence on risk elaborated in the preceding sections on loci and pathways, with the overall totality of evidence indicating that longitudinal studies reveal the outsized influence of the wider diet regime [7].

**Diet, Physical Activity, and Gene-environment Interactions**

The 21st century has witnessed an alarming increase in obesity rates globally, prompting widespread initiative to tackle the issue [23]. Obesity is now recognized by the World Health Organization as a global epidemic that poses greater risk of death than underweight and the factors that lead to obesity have become a focal matter for multiple scientific disciplines [22]. Obesity has been recognized as a challenging trait for biologists. Attention has been drawn to the interactions between biological and environmental factors leading to obesity [25]. Environmental changes such as unhealthy diets and sedentary lifestyles have been implicated in what some call an obesity epidemic [20]. Nevertheless, such modifications do not act independently; sensitivity to such changes is influenced by biological factors [12]. Genetic factors, for example, influence adiposity and may modulate behaviours such as appetite, energy intake, food preferences, and parental feeding style and so on [23]. The interactions between these external changes and biological susceptibility to obesity have been labelled "gene-by-environment", "gene-environment", "DNA-by-environment" 8 or environmental moderation [24]. Recent largescale genome-wide association studies (GWAS) targeting directly obesity-related traits have identified more than 150 independent loci, stressing the polygenic nature of the trait [17]. However, understanding genetically-based body weight and fat distribution regulation remains complex due to the multifactorial nature of the trait and the impossibility to link phenotypes at the physiological level to the new loci discovered in other GWAS approaches [7].

## Early life and Developmental Environment

The early-life and developmental environment influences obesity via genetic and environmental pathways. Metabolic defects and appetite regulation genes are linked to childhood obesity and childhood BMI is influenced by intrauterine genetic risk and maternal genetic risk mediated by the intrauterine environment [14]. During childhood, BMI becomes increasingly susceptible to genetic variance, particularly via heritable variants in the FTO region [29]. Affected individuals exhibit heightened behavioral susceptibility to an obesogenic environment through gene-environment interaction, which also influences appetite and adiposity [18]. In early life, appetite-associated and weight-gain-associated single nucleotide polymorphisms affect dietary intake of protein and carbohydrates, respectively, highlighting how early-life exposure to obesogenic dietary components, particularly protein and sugar, in conjunction with genetic susceptibility, can drive rapid weight gain already in infancy [15]. From early childhood to adolescence, non-genetic components including parental influences predominantly determine weight, which began progressively being captured by genetic heritability from the early teenage years onward [30].

## Methodological Reflections

While obesity research has broadly relied upon self-reported weight and body mass index (BMI) in technology now facilitate the collection of more precise, continuous measures of fat mass, fat distribution, and the deposition rates of lipid and lean tissues [2, 26]. Despite technical innovations, however, study designs remain vulnerable to bias and complexity. Increased sample sizes can reduce sampling bias associated with selection and exposure. Genetic variation can further assess sufficiency and selection bias, yet imprecision in genetic expression hinders accuracy; studies cannot ascertain the extent to which bias, sufficiency, and conditional variation propagate through predictive models [25]. A principal concern relates to causal inference. ID and BL, for example, have experimental character; where resistance is applied, individuals become fatter, and if reduced, they become leaner. Such clear cause-and-effect relationships render them semantically distinct to C, PR, and G 6. Conversely, once the variant is in place, determinants of food intake, energy expenditure, or the behaviour of animals do not differ [3]. The understanding of genetic-related pathways is, hence, scientifically interesting but conceptually complex [27].

## Study Design and Bias

Associating obesity with genetic polymorphisms has been a topic of interest in clinical and epidemiological studies; nevertheless, most of the research relies on data from European populations, which could limit opportunities to guess genetic polymorphisms related to obesity risk in the Arab world [28]. Obesity is too complex since environmental factors alone could influence the genetics where a larger variation in genetic composition has been observed among Individuals from the Arab world due to factors such as different migrations that have occurred across the region [5]. A vast amount of new information has been assembled from diverse sources about how gene-environment interactions allow the environment, through diet composition, lifestyle, etc., to alter the genetic architecture by modifying the contribution of genes and genetic background concerning environmental factors in order to enable researchers to improve health in a fair and equitable manner, creating opportunities to contribute to preventive measures and treatment [7].

## Causal Inference in Genetic Obesity Research

As the genetic basis of obesity emerges, so too does the challenge of causality. Although the rising tide of obesity owes much to the adoption of energy-dense diets and sedentary lifestyles, both genetic and environmental factors contribute to individual differences in the response to these risk factors [3]. Cross-sectional surveys of believed causes of obesity reinforce the idea that the excess caloric intake and low energy expenditure only represent proximate causative factors, but these have not helped disentangle genetic from other causes [31]. Genetic studies uniformly find that genotypes affect predisposition to environmental influences, thus making it a paramount question whether genetic models for obesity allow inferences of causality that extend beyond the population, particularly in the direction of feasible prevention or intervention strategies[32]. As a starting point to address the causal role of genetic polymorphisms in obesity, the focus can be placed on genome-wide association studies (GWAS), rare-variant sequencing, and Mendelian approaches before extending the discussion to gene-environment interactions and cross-population validation [30]. Specific attention is given to how these aspects affect the interpretation of recent findings, alongside appropriate caveats concerning the potential pitfalls of exposing genotype data and the discouragement from over-interpretation of genetic information [29]. The Causal role of genes that are implicated in obesity through the type and size of sample used is another facet determining the overall causal inference from genotype to phenotype [33-36]. GWAS alone, despite facilitating the detection of associations, resists use for further inference, nor do rare-variant sequencing and analysis of Mendelian forms shed much light in this regard. Shifting the focus to the nature of the lifestyles that lead to overweight, Davidson et al. build an argument that can equally address the monogenic versus polygenic nature of the monogenically and polygenically inherited obesity forms without any bias from the type of data[37-40].

## CONCLUSION

The genetic basis of obesity is deeply intertwined with environmental, social, and developmental factors, making it a quintessential example of a complex, polygenic trait. The evidence reveals substantial heterogeneity in genetic architecture across populations, driven by ancestry-related variation in allele frequency and gene-environment interactions. Despite major advances in genome-wide association studies (GWAS) and polygenic risk scoring, obesity genetics remains disproportionately informed by data from individuals of European ancestry. This imbalance limits the accuracy and predictive power of genetic models in non-European populations, perpetuating global health disparities. Population and ancestry considerations are therefore critical for understanding obesity's genetic diversity and for developing equitable prevention and treatment strategies. African and Hispanic, Latino populations, for example, exhibit distinct associations between adiposity and genetic loci, necessitating ancestry-specific approaches in study design and risk assessment. Environmental influences, including diet, physical activity, socioeconomic status, and developmental factors, exert powerful modulatory effects on genetic susceptibility, particularly during early life when heritability progressively increases. Methodological limitations, such as sampling bias, inconsistent phenotype definitions, and difficulties in establishing causality, continue to challenge interpretation. Integrative methodologies, including bioinformatics modelling, geostatistical analysis, Mendelian randomisation, and longitudinal cohort studies, are vital for clarifying causal relationships and reducing confounding. A paradigm shift toward inclusive, diverse, and environmentally contextualized genetic research will improve translational accuracy and fairness. Ultimately, a comprehensive understanding of obesity must bridge biological, behavioural, and environmental domains. Achieving this integration requires not only scientific innovation but also policy commitment to expand genomic research beyond Eurocentric confines. By embracing diversity and methodological rigor, future obesity genetics can inform precision medicine, equitable healthcare, and culturally adaptive interventions that address the multifaceted roots of the global obesity epidemic.

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