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REVIEW

Integrating Genetic Insights, Technological Advancements, Screening, and Personalized Pharmacological Interventions in Childhood Obesity

Robert Šket · Barbara Slapnik · Primož Kotnik · Klementina Črepinšek · Barbara Čugalj Kern · Tine Tesovnik · Barbara Jenko Bizjan · Blaž Vrhovšek · Žiga I. Remec · Maruša Debeljak · Tadej Battelino · Jernej Kovač

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ABSTRACT

Childhood obesity is a significant global health challenge with rising prevalence over the past 50 years, affecting both immediate and long-term health outcomes. The increase in prevalence from 0.7% to 5.6% in girls and 0.9% to 7.8% in boys highlights the urgency of addressing this epidemic. By 2025, it is estimated that 206 million children and adolescents aged 5–19 years will be living with obesity. This review explores the complex interplay of genomics and genetics in pediatric obesity, transitioning from monogenic and polygenic obesity to epigenetics, and incorporating advancements in omics technologies. The evolutionary purpose of adiposity, systemic evaluation of hyperphagia, and the role of various genetic factors are discussed. Technological advancements in genotyping offer new insights and interventions. The integration of genetic screening into clinical practice for early identification and personalized treatment strategies is emphasized.

Keywords: Childhood obesity; Genomics; Genetics; Screening; Technological advancements; Personalized treatment strategies

Key Summary Points

Accurate assessment of childhood obesity involves evaluating both body mass index standard deviation scores (BMI-SDS) and hyperphagia to identify factors contributing to excessive hunger and food intake.

Technological advancements have deepened our understanding of genetically conditioned obesity by enabling exploration of its complexities, including single nucleotide variants (SNVs), structural variants (SVs), copy number variations (CNVs), and epigenetics.

Prior Presentation: Limited segments of this review regarding genetic insights in childhood obesity were presented at the 17th International Conference on Advanced Technologies and Treatments for Diabetes, held in Florence between March 6 and 9, 2024.

R. Šket · B. Slapnik · P. Kotnik · K. Črepinšek · B. Čugalj Kern · T. Tesovnik · B. Jenko Bizjan · B. Vrhovšek · Ž. I. Remec · M. Debeljak · T. Battelino · J. Kovač (✉)
University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia
e-mail: jernej.kovac@kclj.si

R. Šket · B. Slapnik · P. Kotnik · K. Črepinšek · B. Čugalj Kern · T. Tesovnik · B. Jenko Bizjan · M. Debeljak · T. Battelino · J. Kovač
Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

We have the tools, but we lack the guidelines and policies required to effectively integrate genetic screening into clinical practice.

Health interventions and new therapeutic strategies are increasingly focusing on targeting specific molecular pathways that regulate appetite and energy expenditure, like the *GLP1R* and *MC4R* gene, shifting from one-size-fits-all treatments to more personalized care plans.

INTRODUCTION

Childhood obesity is a global health challenge, affecting both immediate and long-term health outcomes [1, 2]. Over the past 50 years, its prevalence has risen significantly: from 0.7% to 5.6% in girls and from 0.9% to 7.8% in boys [3]. The World Obesity Federation projects 206 million children aged 5–19 will be obese by 2025, increasing to 254 million by 2030. Of the 42 countries projected to have over one million obese children by 2030, only seven are high-income nations [1, 4].

The idea that body weight is a modifiable risk factor, easily changed by eating less and/or increasing physical activity, is not entirely accurate [5]. Along with environmental influences, genetics play a crucial role in the development of obesity. Genetic studies have identified several genes associated with obesity that importantly affect energy balance and body weight regulation, including the *FTO* gene, the *MC4R* gene, and others involved in the leptin melanocortin (LEP-MCH) signaling pathway [6–12].

Beyond single gene variants, obesity often results from the cumulative effects of many genes. Genome-wide association studies (GWAS) have identified numerous loci linked to obesity and use polygenic risk scores to estimate genetic predisposition. However, genetic variations alone cannot explain the recent surge in obesity rates [13–15]. Addressing pediatric obesity requires a multifaceted approach, including identifying underlying drivers, implementing appropriate lifestyle interventions, and, when necessary, using pharmacotherapy or surgical procedures [16].

This review examines the complex interplay of genetic factors influencing pediatric obesity, transitioning from monogenic and polygenic obesity to epigenetics. It also addresses the integration of various omics technologies, providing insights into the mechanisms controlling body weight [17]. We have advanced from identifying single gene variants to exploring structural variants (SVs) and epigenetic mechanisms at both the DNA and RNA levels [18]. These analyses can now be performed within a one-go sequencing using long-read technologies [13–15]. On the other hand, interest in whether genetic findings can be applied in the clinical setting to improve risk prediction and facilitate personalized therapy for obesity remains relevant today [19, 20]. Several challenges remain in the widespread adoption of genomic medicine, including the need for robust genetic data, the development of effective interventions based on genetic information, and the ethical management of genetic data. Once these are properly addressed, the importance of early genetic screening should be considered in therapeutic decision-making.

METHODS: INCLUSION AND EXCLUSION CRITERIA

This literature review was conducted using both disease- and intervention-related keywords to capture relevant studies. References were identified through searches on Google Scholar, PubMed, and Science Direct for articles and studies published from January 2018 to July 2024, focusing on combinations of research topics such as "child," "adolescent," "obesity," "pediatric obesity," "body mass index," and "body weight." It also included methodological concepts like "genomics," "genetics," "genetic screening," "epigenetics," "sequencing," and obesity prevention strategies such as "obesity prevention" and "pharmacotherapy." Clinical trials of all types from clinicaltrials.gov were included. Three independent reviewers, R.S., B.S., and J.K., reviewed and collected the data. Any systematic reviews or meta-analyses found in the searches

were checked for relevant references. The search was restricted to articles published in English, without any geographical limitations.

THE EVOLUTIONARY PURPOSE OF ADIPOSITY

Adiposity, or the accumulation of body fat, served several evolutionary purposes that contributed to the survival and reproductive success of humans and animals. It provided essential energy reserves during food scarcity and supported reproductive health by ensuring sufficient energy for pregnancy and lactation. In the modern era, especially in developed countries with abundance of available energy-dense food, this mechanism seems to result in widespread obesity as fat is stored in preparation for famines that never occur [21]. Moreover, it has been suggested that the laws of thermodynamics do not entirely support the idea that obesity is solely an energy intake problem or an energy balance problem since a positive caloric balance can be a result rather than a cause of the condition. For example, physiologic metabolic processes controlling satiety/hunger could be the ones that established a positive or negative energy balance, and not the other way around [5]. Although the mechanistic background of obesity development is not fully understood, it is undeniable that excess weight, especially in childhood, often leads to health problems once considered adult issues, such as metabolic, cardiovascular, orthopedic, neurological, liver, lung, and kidney disorders (Fig. 1). These issues can manifest early and continue into adulthood, severely impacting physical health, social and emotional well-being, self-esteem, academic performance, professional career, and overall quality of life [22–24]. Furthermore, both boys and girls who are obese as children have been shown to experience puberty earlier, albeit the strength

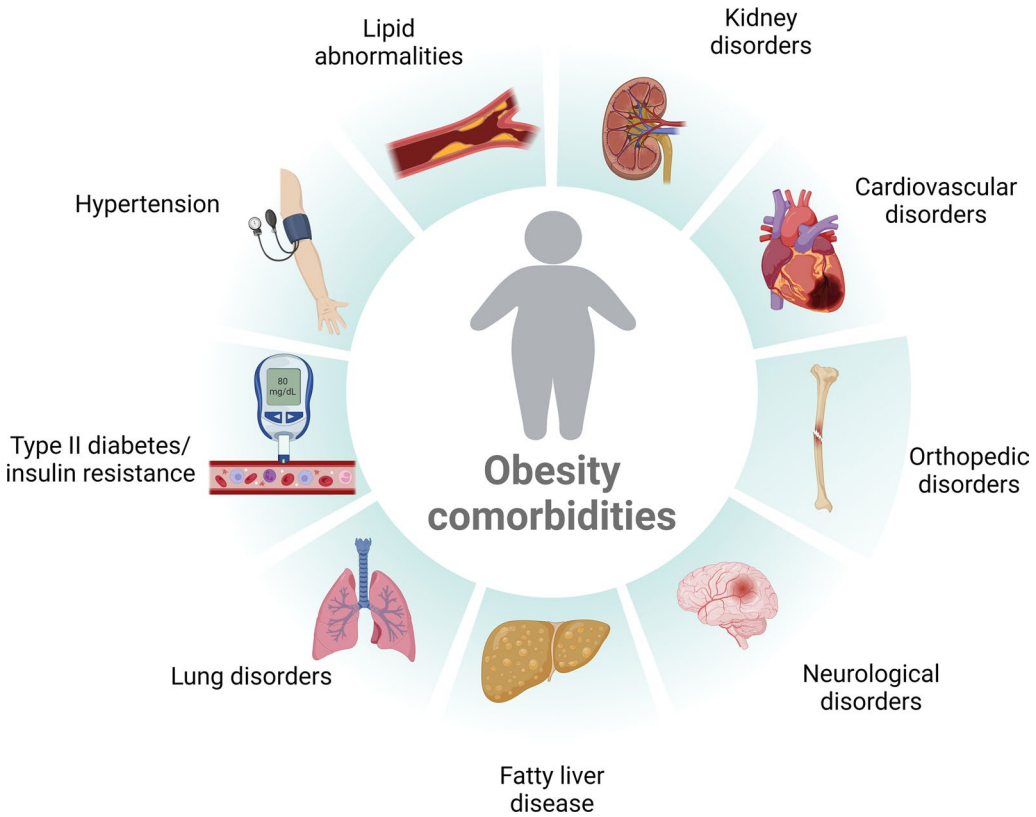

Fig. 1 Common comorbidities associated with obesity (Created in BioRender.com)

of this correlation varies by race and ethnicity [25, 26].

EVALUATING OBESITY AND SYSTEMATICALLY ASSESSING HYPERPHAGIA IN PEDIATRIC POPULATION

Etiologically, obesity is classified into acquired (adult-onset), which is linked to behavioral factors like reduced physical activity, and inherited (childhood-onset), related to prenatal development or genetic disorders such as leptin deficiency [27]. Additionally, obesity subtypes include metabolically healthy obese, metabolically abnormal obese, metabolically abnormal normal weight, and sarcopenic obese, though terminology remains inconsistent [28]. In epidemiology and clinical practice, body mass index (BMI), calculated as weight divided by height squared (kg/m^2), is commonly used to screen for and diagnose excess body fat. Based on BMI, the categories include severely underweight (BMI < 16.5 kg/m^2), underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), and obesity (BMI ≥ 30 kg/m^2). Obesity is further divided into class I (BMI 30–34.9 kg/m^2), class II (BMI 35–39.9 kg/m^2), and class III (BMI ≥ 40 kg/m^2, also known as severe or extreme obesity) [29]. However, BMI has limitations—it lacks sensitivity in detecting excess adiposity, does not account for fat distribution, and may be inaccurate for certain racial and ethnic groups [30, 31].

Adjusting BMI for sex and age, or using body mass index standard deviation scores (BMI-SDS), provides a more precise marker for pediatric obesity [32]. This method takes into account sex, age group, growth indicators, and utilizes specific *Z* score curves based on the Centers for Disease Control and Prevention or World Health Organization (WHO) standards [11, 33, 34]. Arbitrarily, mild underweight is defined as weight-for-height between more than 2 standard deviations (SD) below the WHO Child Growth Standards median and 1 SD below the median (approximately below the 2nd to the 15th percentile). A healthy weight falls between 1 SD below and 1 SD above the median (approximately the 15th to 85th percentile). More than 1 SD to 2 SD above the median (85th to 97th percentile) is considered overweight but not obese, while obesity is classified as more than 2 SD above the median (above the 97th percentile) [2, 4]. For example, severe childhood obesity is defined as having a BMI at or above 120% of the 99th percentile for age and sex, or 35 kg/m^2 or more at the age of 18 years [35].

Waist circumference and the waist-to-height ratio exceeding 0.5 are increasingly used as indicators of abdominal adiposity [3]. Following the clinical practice guidelines, pediatricians and healthcare providers should measure height, weight, and BMI annually for children aged from 2 to 18 to identify overweight and obesity. Moreover, body composition can also be assessed through various imaging techniques including magnetic dual-energy X-ray absorptiometry, air displacement plethysmography, bioimpedance analysis, computed tomography, magnetic resonance imaging, and ultrasound aimed at measuring the distribution of body fat [15].

In addition to the physiological aspects of obesity, evaluating eating behaviors, particularly hyperphagia, is crucial. This evaluation helps in identifying and assessing the effectiveness of new pharmacological therapies aimed at reducing weight and managing hyperphagia [36, 37]. Hyperphagia is linked to binge eating, hormonal imbalances (e.g., glucocorticoid excess, leptin abnormalities), obesity-related syndromes, and cognitive impairment [38]. The hyperphagic drive is typically evaluated using the Dykens questionnaire, designed for patients with Prader-Willi syndrome (PWS), to assess food obsession and invasive thoughts about seeking food [39]. However, this tool may not be suitable for adolescents or adults with genetic obesity who do not have intellectual disabilities. Recently, an impulsivity questionnaire was proposed to evaluate an individual's inability to control responses to food stimuli, aiming to better characterize food impulsivity [37, 40]. The immunoassay evaluation of appetite and satiety hormones, such as leptin, ghrelin, and insulin, can help predict an individuals' susceptibility to

obesity and monitor weight loss and weight loss maintenance after interventions [36].

FACTORS CONTRIBUTING TO OBESITY

Obesity represents a multifaceted challenge with numerous contributing factors, making environment, lifestyle choices, and cultural context crucial to its growing prevalence [41–47]. Low socioeconomic status and parental education are major risk factors, often due to limited enabling environments or reduced awareness and prioritization of healthy living. This situation frequently leads to reliance on inexpensive, low-quality food, resulting in an energy imbalance characterized by high consumption of empty calories [48–51]. Neighborhood socioeconomic status significantly impacts the development of childhood obesity, with children in lower socioeconomic areas having a higher risk of becoming overweight or obese [52, 53]. Lifestyle choices, such as physical activity, diet, sedentary behavior, and sleep duration, are crucial factors that should be promoted irrespective of genetic background [43]. Poor sleep hygiene frequently contributes to weight gain by fostering bad eating habits and reducing the advantages of a balanced diet and regular exercise [54]. According to recent findings from the LONCAAFS study, decreased physical activity, compounded by increased sedentary behavior, raises the likelihood of adolescents being overweight by roughly 40% [55]. Additionally, endocrine-disrupting chemicals, commonly known as obesogens, interfere with normal hormonal regulation, disrupting key processes such as metabolism, adipose tissue development, appetite regulation, and overall energy balance [56].

Social disruption, unhealthy behaviors, chronic stress, and adverse childhood experiences can drive individuals to seek comfort in hedonic junk food binge eating [57–60]. This behavior can evolve into a form of addiction, potentially increasing the likelihood of adult obesity by 46% [61]. Although this type of addictive behavior might not cause intense cravings or withdrawal symptoms, its subtle nature makes it hard to detect and, consequently, challenging to manage through therapeutic interventions.

GENETICS AND GENOMICS OF OBESITY ADVANCING WITH TECHNOLOGY

In contexts of adverse environments and socioeconomic status, food cravings can be partially intensified but are typically most pronounced in cases where biological pathways related to satiety, energy expenditure, and taste are dysregulated [7]. Even with a healthy diet and adequate physical activity, these measures may only mitigate but not fully prevent the development of overweight and obesity. Many genes predispose individuals to obesity, with heritability estimates ranging from 40% to 80% based on genetic studies of twins, families, and adoption cases [15, 62–64]. Research utilizing case–control or gene candidate methods is essential for discovering new genetic variants linked to obesity susceptibility. Additionally, the techniques for identifying genes related to obesity differ depending on the type of obesity and the genotyping technology available at that time (Fig. 2) [65].

Where Are We Looking and What Are We Analyzing?

The choice of biological sample is crucial for accurate genetic analysis. Whole blood, which contains genomic DNA (gDNA), RNA, and cell-free DNA (cfDNA), is commonly used owing to its ease of collection and processing [66, 67]. Adipose tissue, on the other hand, is directly relevant for studying obesity-related genes and provides insights into tissue-specific gene expression and epigenetic modifications [68, 69]. While subcutaneous and visceral adipose tissues share many similarities, visceral adipose tissue exhibits higher rates of lipolysis, reduced insulin sensitivity, and increased inflammatory activity compared to the metabolically benign subcutaneous adipose tissue. Although subcutaneous adipose tissue is easier to access and requires less invasive procedures, visceral

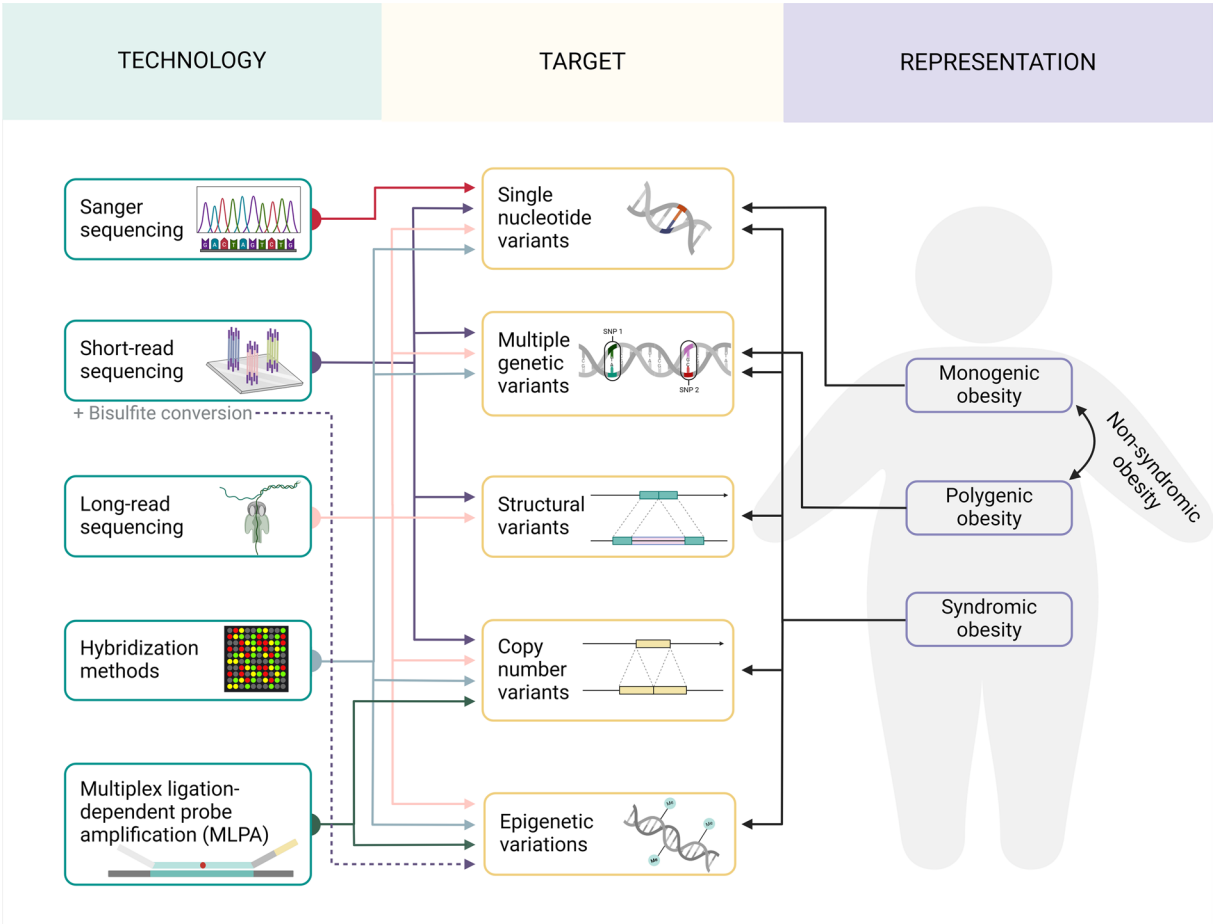

Fig. 2 Use of different genotyping techniques to identify genetic variations responsible for varying obesity phenotypes (Created in BioRender.com)

adipose tissue is more appropriate for research focused on metabolic disorders or cardiovascular health [70, 71]. While whole blood is a convenient and widely used sample, it is important to evaluate its compatibility with adipose tissue. Intravenous blood withdrawals are generally less invasive and more straightforward compared to adipose tissue sampling. It is important to determine if genetic and epigenetic markers identified in blood reflect those in adipose tissue, ensuring that blood-based findings are relevant for understanding obesity mechanisms at the tissue level [72]. In addition to whole blood and adipose tissue, other samples are also important, especially in research settings. Studies investigate cord blood samples, neonatal blood spots, buccal swabs, saliva samples, adipose stem and precursor cells, and embryonic stem cells. These diverse samples contribute valuable information, enhancing our understanding of genetic and epigenetic influences across different tissues and developmental stages [73–78].

In biological samples, one can analyze various components of DNA, either in cells or cfDNA, and look for single nucleotide variants (SNVs), SVs, copy number variations (CNVs), methylation patterns, and transposons, as well as RNA, including gene expression profiles and noncoding RNAs, such as miRNAs [79–82]. These various approaches provide specific insights into the genetic mechanisms underlying the development of obesity, which will be further discussed in the subsequent sections.

Exploring Monogenic Obesity Through Individual Gene and Gene Panel Analysis

Studies of severe, early-onset obesity have employed methods such as Sanger sequencing or small gene panels using next-generation sequencing (NGS) to investigate single gene dysfunctions that characterize monogenic obesity. This condition is typically caused by small or large chromosomal defects inherited in a Mendelian pattern among affected individuals and their families and presents as severe and early-onset, with minimal environmental impact on its development [12, 17, 83]. If obesity is the only symptom, it is referred to as nonsyndromic monogenic obesity. However, when any combination of symptoms such as dysmorphic facial features, developmental delays, hypotonia, short stature, organomegaly, skeletal abnormalities, endocrine disorders, behavioral issues, and skin or hair anomalies is present, the condition is classified as syndromic obesity, enabling differentiation between its types.

In nonsyndromic obesity, most genes and pathways causing monogenic obesity led to spontaneous obesity and hyperphagia, primarily involving components of the LEP-MCH pathway. For instance, congenital leptin deficiency due to disease causing genetic variants (DCVs) in the *LEP* gene results in rapid weight gain and severe early-onset obesity [8]. DCVs in the *LEPR* gene also lead to increased body weight in carriers of heterozygous variants [11]. Autosomal recessive inheritance of *POMC* deficiency can cause red hair and severe obesity; a few studies have found *POMC* genetic variants in individuals with obesity but no other symptoms [11]. Both autosomal dominant and recessive DCVs in *MC4R* cause increased appetite, with heterozygous DCVs being the most frequent drivers of monogenic childhood obesity, occurring in 5% of affected children [10, 11]. Analyzing the BMI trajectories of children with genetic obesity reveals that these genetic variants significantly contribute to increased weight. Variants in the *MC4R* gene have been shown to increase BMI-SDS by 1.62 and add approximately 15 kg of body weight by age 18 [11]. Homozygous *ADCY3* (adenylate cyclase 3) DCVs result in early-onset hyperphagia and obesity [84]. Other genes implicated in monogenic pediatric obesity include *SIM1* (single-minded homolog 1), *NTRK2* (neurotrophic receptor tyrosine kinase 2), *BDNF* (brain-derived neurotrophic factor), *SH2B1* (SH2B adaptor protein 1), *KSR2* (kinase suppressor of ras 2), *PCSK1* (proprotein convertase subtilisin/kexin type 1), *TUB* (tubby bipartite transcription factor), and *CPE* (carboxypeptidase E) [15]. Additionally, age-specific investigations have identified rare variants in the genes *OBSCN* and *MADD*, which are implicated in recalled childhood adiposity [85].

In contrast, syndromic obesity is often associated with multiple comorbidities, including cognitive delays [15, 86, 87]. There are 23 obesity syndromes that exhibit significant phenotypic variability, with obesity not always appearing in early childhood. These syndromes arise from three primary mechanisms: genomic imprinting, transcriptional regulation, and defects in cellular cilia function [86]. The study of syndromic obesity is difficult because of its heterogeneity and the small number of cases globally. Genetic heterogeneity includes SVs such as deletions, insertions, inversions, and complex rearrangements. Bardet-Biedl syndrome (BBS) is one example, involving over 20 different genes [78]. PWS is influenced by epigenetics/imprinting alterations that are consequences of microdeletions at chromosome 15, and PWS-like syndrome can be caused by deletions in *SIM1*. Albright's hereditary osteodystrophy arises from alterations in the *GNAS* gene, and Wilms tumor-aniridia (WAGR) syndrome from deletions on chromosome 11. The clinical similarity of these syndromes complicates diagnosis and phenotyping [15].

Identifying SVs has facilitated the characterization of new genetic forms of syndromic obesity, primarily due to CNVs [88]. Chromosomal microarray analysis (CMA) has implicated many genes previously associated with obesity, among others *PTBP2* and *SIM1*. Additionally, CMA has revealed other possible relevant genes such as *TAS1R3*, *ALOX5AP*, and *GAS6* [89]. Using short-read sequencing techniques, detecting SVs remains challenging because of their size

or location in complex genomic regions such as centromeres, telomeres, and segmental duplications. However, long-read sequencing technologies, such as Pacific Biosciences (PacBio) and Oxford Nanopore Technologies (ONT), can span these regions in single reads, effectively capturing the complete extent of SVs, including their breakpoints and precise genomic context [90]. Recently, SVs in the *WWP2* gene impacting among others height, weight, and fat distribution have been reported but are yet to be fully evaluated [91].

Deciphering Polygenic Obesity: GWAS and NGS in Identifying Genetic Variants

In contrast, obesity of polygenic origin arises from the cumulative effects of an obesogenic lifestyle and multiple genetic variants, each contributing subtly to body weight gains [17, 62, 92]. Genetic variants were initially identified through GWAS that pinpoint pre-selected variants using microarrays. This initially provided strong coverage for common variation with a minor allele frequency (MAF) > 5%, but with the development of NGS and the application of whole-exome sequencing (WES) and whole-genome sequencing (WGS), detection of rare variants (MAF < 1%) has become increasingly feasible [15, 62, 63].

GWAS have identified more than a thousand loci associated with BMI, obesity, and related comorbidities. The first discovered was *FTO*, which was then linked to obesity in both childhood and adulthood, highlighting the relatively consistent genetics of obesity throughout the lifecycle [93, 94]. However, these signals explain only about 5% of the variance in BMI [95]. Therefore, a GWAS has also been performed on more specifically defined obesity phenotypes, including waist-to-hip ratio, body fat percentage, and circulating leptin and leptin receptor levels [15]. Additionally, genetic associations with obesity can be influenced by sex and vary across different ethnicities and populations. There is significant transferability across ancestries, although allele frequencies and effect sizes can vary considerably. Implementing transcriptome-wide association studies, which excel in detecting functional genes regulated by disease-associated variants, is expected to further expand the list of converging genes [96].

Mechanisms and Technological Advances in Understanding the Epigenetic Basis of Obesity

Epigenetic changes in gene expression resulting from gene–environment interactions can help explain some of the missing heritability of obesity [13, 97]. Epigenetic mechanisms regulate gene expression by silencing genes through DNA methylation, controlling gene accessibility by modifying histones and altering chromatin structure, and influencing mRNA stability and translation through microRNAs and long non-coding RNAs. One of the earliest findings was the increased DNA methylation on the *FTO* obesity susceptibility haplotype, identified using methylated DNA immunoprecipitation on a targeted array (MeDIP-chip) [13, 98]. While DNA methylation is widely studied [6, 13, 66, 67, 99–102], evidence of its causative role in disease pathogenesis remains limited. Therefore, integrating data, employing innovative approaches and new technologies to investigate the impact of methylation on obesity and associated comorbidities is crucial.

Confined to DNA methylation array-based techniques, these approaches offer only a limited insight of the DNA methylome. This is due to the presence of around 28 million CpGs in the genome, along with the potential for non-CG modifications [103]. In contrast, whole-genome bisulfite sequencing offers improved coverage—in theory, up to 100% of the CpG sites. However, whole-genome bisulfite sequencing remains a highly complex and costly procedure [104].

Recent studies combining epigenome-wide association studies and integrative genomics identified over 500 target genes that statistically and functionally connect extreme obesity-associated methylation variations with transcriptomic changes [68, 69, 105, 106]. To explore the functional consequences of *POMC* methylation variability, studies on human embryonic stem cells revealed that

reduced *POMC* gene expression is associated with increased *POMC* methylation in *POMC*-expressing neurons. An epigenetic obesity risk variant at the *POMC* gene has been identified, which could be targeted by *MC4R* agonist treatment to reduce body weight [77]. Effects of weight loss induced by bariatric surgery on DNA methylation in rectal mucosa and cfDNA from blood were investigated and reversibility of DNA methylation was observed [107, 108]. Additionally, novel and significant metabolic changes have been discovered, with some alterations linked to changes in DNA methylation patterns and levels of DNA methyltransferases [109–111].

Evidence suggests that the trajectory leading to childhood obesity is established early in life [112, 113]. Consequently, recent studies have focused on the pediatric methylome in the first year and transmitted epigenetic signatures. Researchers have identified DNA methylation biomarkers at regions involved in fatty acid metabolism and mitochondrial bioenergetics (*CPT1B*, *SLC38A*, *SLC35F3*, *FN3K*), which track maternal differences during pregnancy and persist through the first year of life [114]. An association between cord blood DNA methylation in genes related to lipid metabolism (*ARID5B*, *KLF9*) and rapid weight gain has been observed, linking prenatal exposures to childhood obesity and highlighting early prevention opportunities [73]. A study of genome-wide DNA methylation profiles in 48 infants found associations with methylation profiles of *PLIN4*, a regulator of lipid storage, *UBE2F*, associated with BMI in children, and *PPP1R16B*, which plays a role in obesity [115].

Long-read sequencing technologies, such as PacBio and ONT, can assess both DNA sequence and modifications genome-wide directly on native DNA, providing a more comprehensive view of the epigenetic landscape compared to previous microarray and bisulfite sequencing techniques [79, 104]. For example, ONT sequencing with 10× coverage depth produces 5′-mC methylation frequencies consistent with those obtained by 450k microarray, digital restriction enzyme analysis of methylation, and reduced representation bisulfite sequencing [116].

In a research setting, cases of PWS and Angelman syndrome (AS), both imprinting disorders, were used to assess the efficacy of ONT sequencing. The analysis of SVs, SNVs, CNVs, and CpG methylation patterns from a single sequencing dataset demonstrated that CpG sites, typically fully methylated on the maternally derived allele and unmethylated on the paternally derived allele within the *SNRPN* gene promoter region, were nearly all methylated on both alleles in PWS samples. In contrast, these sites were almost entirely unmethylated on both alleles in AS samples [117].

To date, few studies have characterized methylation on a whole-genome scale in rare disease cohorts. This is also the goal of ONT and Genomics England, which aim to sequence up to 7500 samples from individuals with a range of genetic or suspected genetic disorders to improve diagnostic outcomes in rare diseases [118]. As a proof of principle applicable in obesity research, direct DNA methylation ONT sequencing in cases of prolonged hyperglycemia in individuals with type 1 diabetes (T1D) without clinical manifestations of diabetes-related complications has revealed multiple differentially methylated CpG sites in crucial genes and pathways known to be linked to chronic complications in T1D [119].

SCREENING FOR GENETIC PREDISPOSITIONS TO OBESITY

The American Academy of Pediatrics and the American College of Medical Genetics and Genomics (ACMG) recommend newborn screening for specific inherited metabolic and genetic disorders that are treatable but not clinically evident in the newborn period [120–123]. In contrast, genetic screening in pediatric care emphasizes the importance of targeted screening based on family history, known risk factors, and key clinical indications [124]. Consequently, genetic screening for youth with obesity, in the absence of syndromic findings, has not been part of obesity management. However, in children with early onset obesity, genetic screening is recommended before 5 years of age for those

who have clinical features of genetic obesity syndromes (including hyperphagia) and/or a family history of severe obesity [78]. The optimal age of onset cutoff for genetic screening is suggested to be ≤ 3.9 years to enable early intervention [125]. Here, highly penetrant variants associated with severe early-onset or syndromic forms of obesity, such as DCVs in the *MC4R* or *LEPR* gene, may serve as first diagnostic tools (Fig. 3) [9, 11, 20, 125].

Integrating genetic screening into clinical practice still presents challenges. There is a need for guidelines, regulatory frameworks, and policies to effectively use genetic information for treatment decisions while addressing privacy concerns, misuse of information, and social stigma [122, 124, 126, 127]. Healthcare providers must be trained to communicate genetic risks and integrate them into patient care, despite the challenge of interpreting genetic susceptibility given the influence of environmental and lifestyle factors on obesity [35].

When it comes to evaluating the causality of identified variants, the ACMG guidelines provide a clear framework where genetic variants are classified as "pathogenic," "likely pathogenic," "variant of uncertain significance" (VUS), "likely benign," and "benign" [128]. While "likely benign" and "benign" variants are not included in reports, genetic variants identified as VUS often leave providers and families with inconclusive results based on current evidence. The same phenomenon is observed in the molecular testing in newborn screening of inherited metabolic disorders, partly due to the lack of diversity in currently sequenced populations

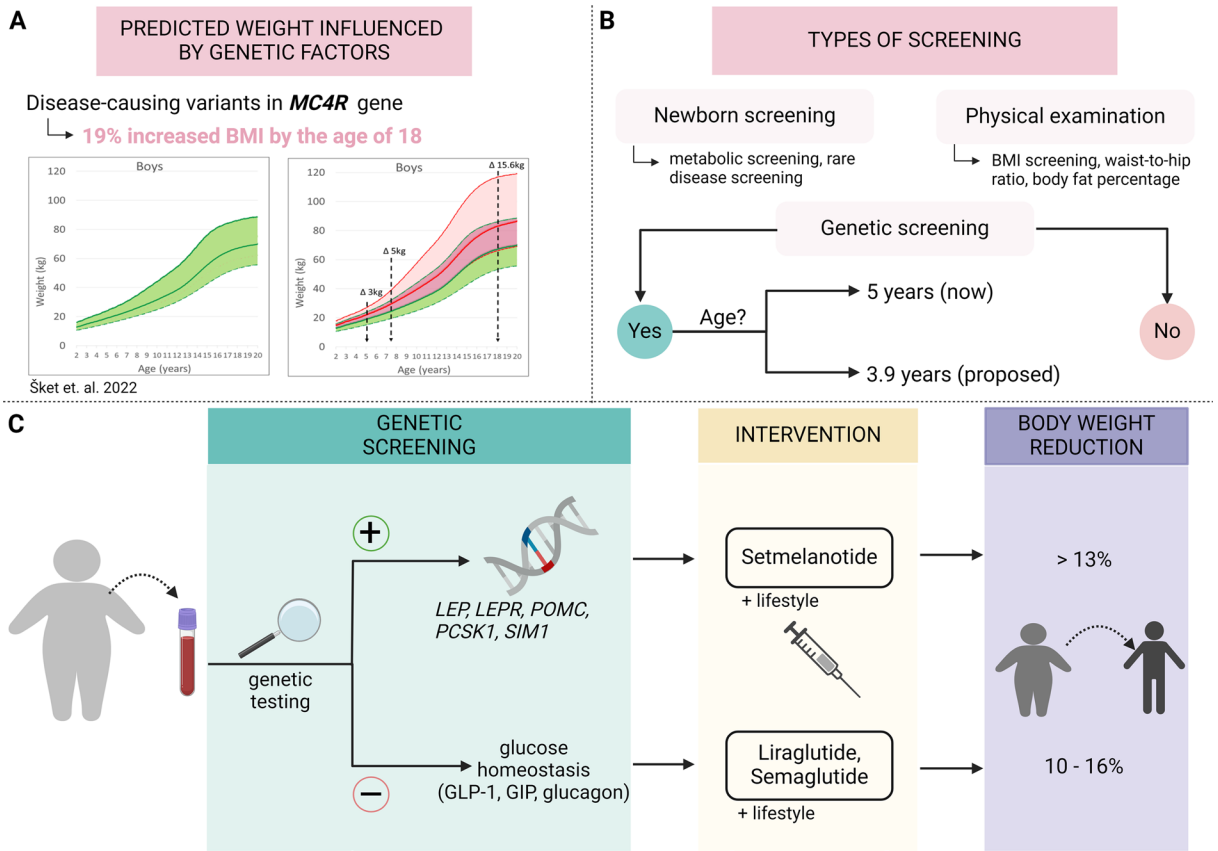

Fig. 3 **A** Proposed body weight trajectory, using disease-causing variants in the *MC4R* gene as an example, highlighting the genetic influence on obesity [11]; **B** principles of screening approaches used to identify genetically conditioned obesity; and **C** tailored interventions based on genetic screening results, enabling personalized treatment strategies and body weight reduction after 1 year of use (Created in BioRender.com)

and consequently a lack of knowledge to either confirm or refute the causality of candidate variants [129].

Nevertheless, effectively treating obesity requires first identifying the underlying etiology and then developing comprehensive, long-term management strategies, as outlined in the following sections.

IMPLEMENTING GENOMIC INFORMATION IN CLINICAL PRACTICE: TREATMENT OF CHILDREN AND ADOLESCENTS WITH OBESITY

Addressing pediatric obesity necessitates a multifaceted approach that includes lifestyle interventions, pharmacotherapy, and, in certain cases, surgical procedures [35, 81, 130]. This approach should also involve medical monitoring to manage associated comorbidities and ensure continuous access to obesity management resources.

Lifestyle interventions are the first line of obesity treatment, involving dietary modifications, increased physical activity, behavioral changes, and proper sleep habits [130]. For children older than 12, pharmacotherapy becomes the next step in treatment. Several anti-obesity medications approved by the US Federal Drug Administration (FDA) target the neurohormonal dysregulation that causes weight gain and prevents sustained weight loss and it should be used for lifetime (detailed in the next section). The FDA also approves certain medications for short-term weight management, such as sympathomimetic anorexigenic agents (phentermine, diethylpropion) [131]. On the other hand, the FDA has not approved metformin as a stand-alone weight loss drug; however, its FDA-approved use may lead to weight loss as a side effect [132]. Metabolic and bariatric surgery is another option for adolescents with severe obesity when other interventions have failed. This approach has been shown to be an effective and well-tolerated treatment, resulting in substantial weight loss and improvements in various aspects of metabolic health and physical quality of life over 2 years. However, it carries potential risks and long-term implications, necessitating careful patient selection and thorough pre-surgical evaluation [133, 134].

Microbiota-centered therapies promise to manage metabolic disorders through diet and microbiome interactions. Prebiotics can reduce obesity symptoms by maintaining healthy gut microbiota and activating relevant metabolic pathways [135]. Fecal microbiota transplantation also enhances microbial diversity and stability [136, 137]. Technological advancements, especially in sequencing, again play a crucial role in monitoring and analyzing microbial diversity, which is essential for assessing the effectiveness of these therapies [136].

Innovative therapies are needed, and gene therapy using adipose tissue-derived mesenchymal stem cells shows promise for cell therapy. Adipocytes with a constitutively active form of carnitine palmitoyltransferase 1A (CPT1AM) for mitochondrial fatty acid oxidation implanted into high-fat diet mice result in lower body weight, reduced hepatic steatosis, improved serum insulin and cholesterol levels, better glucose tolerance, and enhanced mitochondrial function, indicating potential for future clinical gene therapy [138].

GENOTYPE-INFORMED TREATMENTS

With advancements in the post-genomic era, there is increasing potential for the use of genetic insights to predict, treat, and prevent obesity [65]. The treatment landscape for obesity includes a variety of pharmacological options. However, before prescribing weight-loss medications, which are intended to be used in conjunction with diet, exercise, and behavior modifications, it is important to identify the appropriate recipients. In adults, anti-obesity medications are indicated for individuals with a BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with one or more comorbidities [16]. Pharmacological treatments can also be considered for severe cases of obesity where lifestyle changes are insufficient. Medications used to treat obesity work by suppressing appetite, increasing satiety, or reducing the absorption of

fat. A comprehensive search on ClinicalTrials.gov from January 2020 to July 2024 identified 81 ongoing studies focused on childhood obesity and its treatment for children from birth to 17 years old [139]. Our findings include eight observational studies and 74 interventional studies. Among these, 20 studies are in various phases of clinical trials, examining drugs or biological products based on FDA definitions.

Treatments targeting genetic defects in the LEP-MCH pathway can effectively manage monogenic obesity syndromes, crucial for regulating hunger and energy expenditure. Setmelanotide, an *MC4R* agonist, reduced hunger scores by 43.7% and body weight by 12.5% after 1 year ($p < 0.0001$) [140]. Additional findings support setmelanotide as a novel and effective treatment for acquired hypothalamic obesity, improving weight reduction, hunger, and quality of life also in patients aged 4 years and older [141, 142].

Medications such as orlistat, phentermine/topiramate, naltrexone/bupropion, and glucagon-like peptide 1 (GLP-1) analogues like semaglutide and liraglutide are approved for non-syndromic obesity [16, 143–145]. GLP-1 analogues mimic incretin hormones produced after eating, improving glycemic control and promoting weight loss in adolescents. Semaglutide and lifestyle intervention resulted in a 10–16.1% body weight reduction and improvements in cardiometabolic risk factors compared to placebo [146, 147]. Furthermore, weight loss was sustained over 4 years [146]. Liraglutide plus lifestyle intervention led to a 4.64% reduction in BMI-SDS compared to placebo. Importantly, after discontinuation, the BMI in the liraglutide group increased more than in the placebo group [148].

The GIP/GLP-1 dual agonist tirzepatide reduces food intake by modulating hypothalamic pathways and delays gastric emptying [149, 150]. Approved in 2022 for type 2 diabetes and in 2023 for chronic weight management, it showed a 12% average body weight reduction in a randomized study at the highest dosage (15 mg once weekly) [151, 152]. The efficacy and safety of tirzepatide in adults were assessed, revealing that the most frequent adverse events were mild to moderate nausea, diarrhea, and vomiting, with few leading to treatment discontinuation (< 5%) [153]. Simulated studies and clinical trials are now assessing tirzepatide use, dosage, safety, and tolerability in children. Physiologically based pharmacokinetic modeling provides dosage recommendations: 62.5–75% of the adult dose for children with obesity and 75–100% of the 5-mg adult dose for early adolescents with obesity [154]. Furthermore, ClinicalTrials.gov lists four ongoing clinical trials evaluating the safety and tolerability of tirzepatide in children and adolescents under ID NCT05696847, NCT06075667, NCT06439277, and NCT06533527. Next in line is an experimental glucagon and GLP-1 receptor dual agonist survodutide, currently in dose-finding phase 2 trials. It reduced body weight in adults by 14.9% with a 4.8-mg once-weekly dose over 46 weeks. The weight reduction was dose-dependent, and all doses were well tolerated with primarily gastrointestinal adverse events in 75% of participants [155]. It is important to acknowledge significant differences among regulatory agencies in approving anti-obesity drugs, especially for pediatric use (Table 1). These variations arise from high dropout rates, small sample sizes, poor methodological quality, and considerable heterogeneity in clinical trials [156].

CLINICAL PRACTICE GUIDELINES FOR THE EVALUATION OF OBESITY INTERVENTIONS

It is important to recognize that the treatment of obesity is integral to the treatment of its comorbidities and that conditions such as lipid abnormalities, abnormal glucose metabolism, and abnormal liver function should be treated concurrently (Fig. 1) [35].

Treatment effects vary, particularly in children with severe obesity, physical activity limitations, or disabilities. Additionally, intervention studies often lack detailed information on dose, duration, and specific components [35]. Limited research with long-term follow-up exists to determine the sustainability of weight improvements. The long-term effects are difficult to

Table 1 Comparison of different weight-loss medications, detailing their targets, effectiveness in percentage weight loss, associated side effects, and Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval status for use in adults, children, or both

Anti-obesity medications	Mechanism	FDA approved		EMA approved		Weight loss [%]	Adverse effect
		Adults	Children	Adults	Children		
Orlistat	Gastric and pancreatic lipase inhibitor	Yes	Yes (> 12 years old)	Yes	No	5.3–5.9	Oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, fecal incontinence
Phentermine/topiramate	Norepinephrine agonist/GABA agonist, glutamate antagonist	Yes	Yes (> 12 years old)	Yes	No	9.8–10.9	Paraesthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth, depression, arthralgia, pyrexia, influenza, ligament sprain
Naltrexone/bupropion	Opioid receptor antagonist/dopamine and norepinephrine reuptake inhibitor	Yes	No	Yes	No	8.1–11.5	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea
Setmelanotide	MC4R agonist	Yes	Yes (> 4 years old)	Yes	Yes (> 6 years old)	13.0	Skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, spontaneous penile erection

Table 1 continued

Anti-obesity medications	Mechanism	FDA approved		EMA approved		Weight loss [%]	Adverse effect
		Adults	Children	Adults	Children		
Semaglutide	GLP-1 agonist	Yes	Yes (> 12 years old)	Yes	Yes (> 12 years old)	10.0–16.1	Nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia in patients with type 2 diabetes, flatulence, gastroenteritis, gastroesophageal reflux disease, nasopharyngitis
Liraglutide	GLP-1 agonist	Yes	Yes (> 10 years old)	Yes	Yes (> 12 years old)	4.6	Nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation
Tirzepatide	GIP/GLP-1 dual agonist	Yes	No	Yes	No	12.0	Nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, abdominal pain
Survodutide	Glucagon and GLP-1 dual agonist	No	No	No	No	14.9	Nausea, vomiting, diarrhea, and constipation

maintain, and trajectories often return to baseline obesity levels or exceed them [36, 157].

Nevertheless, evidence for successful treatment shows that lifestyle randomized controlled trials in general were effective in reducing adiposity in children, indicating that pediatricians can successfully assess and address obesity with an individualized approach [35]. Additionally, in implementing genomic information in clinical practice, artificial intelligence has offered personalized health assessments and predictive analytics to identify obesity risk as early as at the age of 2 years and thus aiding early intervention and prevention [30, 158, 159].

CONCLUSIONS

While significant progress has been made in understanding the genetic underpinnings of obesity, the multifactorial nature of the disease poses ongoing challenges. The identification of numerous genetic loci associated with obesity, combined with advancements in epigenetic profiling and sequencing technologies, offers promising avenues for personalized interventions and treatments. Effective use of genetic information requires robust guidelines, ethical management of genetic data, and appropriate training for healthcare providers. Additionally, the potential adverse effects of pharmacological treatments necessitate careful monitoring and risk management. In conclusion, while there are significant hurdles to overcome, the integration of genomics and advanced technologies into clinical practice holds great promise for the future of obesity management. Personalized and data-driven approaches that consider the unique genetic and environmental factors contributing to each individual's condition are essential.

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Declarations

Conflict of Interest. Robert Šket, Barbara Slapnik, Primož Kotnik, Klementina Črepinšek, Barbara Čugalj Kern, Tine Tesovnik, Barbara Jenko Bizjan, Blaž Vrhovšek, Žiga Iztok Remec, Maruša Debeljak, Tadej Battelino, and Jernej Kovač have no conflicts of interest.

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