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Epigenetics of Childhood Obesity

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Abstract
Background: Childhood obesity has become a global pandemic and is one of the strongest risk factors for cardiovascular disease later in life. The correlation of epigenetic marks with obesity and related traits is being elucidated. This review summarizes the latest research and its challenges in the study of epigenetics of (childhood) obesity. ***Summary:*** Epigenome-wide association studies helped identify novel targets and methylation sites that are important in the pathophysiology of obesity. In the future, such sites will become essential for developing methylation risk scores (MRS) for metabolic and cardiovascular diseases. Although MRS are very promising for predicting the individual risk of obesity, the implementation of MRS is challenging and has not been introduced into clinical practice so far. ***Key Messages:*** Future research will undoubtedly discover numerous methylation sites that may be involved in the development of obesity and its comorbidities, especially at a young age. This will contribute to a better understanding of the complex etiology of human obesity. From a clinical perspective, the overarching aim was to generate MRS that is robust for reliable and accurate prediction of obesity and its comorbidities.

Introduction

The Global Burden of Disease 2015 Obesity Collaborators report the mean global prevalence of obesity in children and adolescents as approximately 5%, with rates rising faster than in adults since 1980 [1]. A recent meta-analysis estimated the global obesity prevalence at 8.3% between 2020 and 2023 [2]. While obesity rates stabilized in some high-income countries during the early 21st century [3–5], global rates continue to rise, with sharp increases observed during the COVID-19 pandemic, especially in younger children [6, 7]. Childhood obesity significantly raises the risk of lifelong obesity and related metabolic conditions, such as type 2 diabetes, cardiovascular diseases (CVDs), and psychiatric disorders

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[8–11]. Obesity reduces healthy life years and increases disability-adjusted life years lost [1, 12].

The accelerated increase in obesity prevalence is not caused by genetic factors alone – the drivers are often environmental. However, the genetic component of obesity is undeniable, with early evidence provided by family [13], twin [14], and adoption [15] studies, which have estimated heritability rates for BMI between 40 and 80%, with higher heritability in individuals with obesity [16]. Genome-wide association studies (GWAS) have significantly enhanced our understanding of the genetic architecture of common obesity, identifying hundreds of risk variants from which, in a recent study, 74 key genes were derived as potential therapeutic targets [17]. However, the proportion of BMI variability attributed to genetic variation remains poorly understood [18]. The primary challenge lies in integrating genetic factors with environmental influences such as energy intake, physical activity, and smoking. Epigenetics represents a possible link between genetics and the environment [19]. The associations between epigenetic marks and obesity, including its sequelae, have now been investigated for more than 15 years [20, 21]. This review highlights current research and its challenges in epigenetics of (childhood) obesity. It largely follows an overview article authored by some of us earlier [22] but extends it to childhood obesity issues.

Obesity is a multifactorial disease influenced by both genetic and environmental factors [13, 23]. During the last decades, it has been especially aggravated by the spread of so-called "obesogenic environments" – living environments promoting a sedentary lifestyle with reduced energy expenditure and high-calorie, ultra-processed diets [23]. Differential genetic predisposition interacting with these obesity-promoting environmental factors introduce additional inter-individual variability in weight development, highlighting the complex and dynamic etiology underlying obesity's pathophysiology.

Moreover, previous research showed an increasing, cohort-dependent heritability of obesity, suggesting that obesogenic environments enhance the influence of obesity-related genes [24–26] (Fig. 1). Epigenetic mechanisms, such as DNA methylation and histone modifications, play a critical role in gene-environment interactions and may influence susceptibility to obesity. Among these, DNA methylation is the most extensively studied epigenetic mark in obesity research due to its stability and ease of measurement. This process involves the addition of a methyl group to the carbon 5 position of cytosine bases, forming 5-methylcytosine. Mediated by DNA methyltransferases, DNA methylation primarily occurs in the cytosines within CG dinucleotides, known as "CpG" sites, in mammalian genomes. When present at gene promoters and enhancers, it is commonly associated with gene silencing [27]. Epigenetic analyses have rapidly advanced in recent years, with epigenome-wide association studies (EWAS) leading the field. Numerous genes and novel CpG sites associated with changes in methylation profiles in obesity have been identified [28, 29]. Epigenetics is also proposed to contribute to metabolic alterations in the offspring of mothers with obesity or mothers exposed to environmental agents, such as endocrine disrupting chemicals [30–32]. However, the causal relationships are still debated, though several studies support that both obesity and environmental agents induce changes in methylation levels [33–35].

Efforts to apply experimental knowledge to clinical practice have focused on developing predictive tools for obesity, such as polygenic risk scores and, more recently, methylation risk scores (MRS). These scores combine several genetic variants or methylated CpG sites across the human genome. However, applying such scores is challenging and not yet recommended for use in clinical care because of the current lack of reliable predictions.

Nonetheless, significant progress has been made in understanding the genetic architecture of obesity and the correlation of epigenetic marks with obesity and related traits [22]. Some of us have recently collected data on genetic and epigenetic risk scores for obesity and put it down in a previous review [22]. This short narrative review summarizes mainly the epigenetic part of that review and extends it into the general topic of obesity at a young age.

The Relevance of Epigenetic Mechanisms in Obesity

Epigenetic marks and mechanisms such as DNA methylation, histone modifications, and gene-environment interactions are crucial for understanding the role of genetics in the pathophysiology of obesity. Although several hundred genetic variants have been discovered and the number of studies on gene-environment interactions is growing, the results are often inconclusive and prone to be rather population-specific than universally applicable. Lifestyle factors like exercise, smoking, and dietary components interact with the genetic predisposition, modifying the individual's risk of obesity. As epigenetic marks are modifiable, they offer new strategies for obesity prevention and treatment strategies.

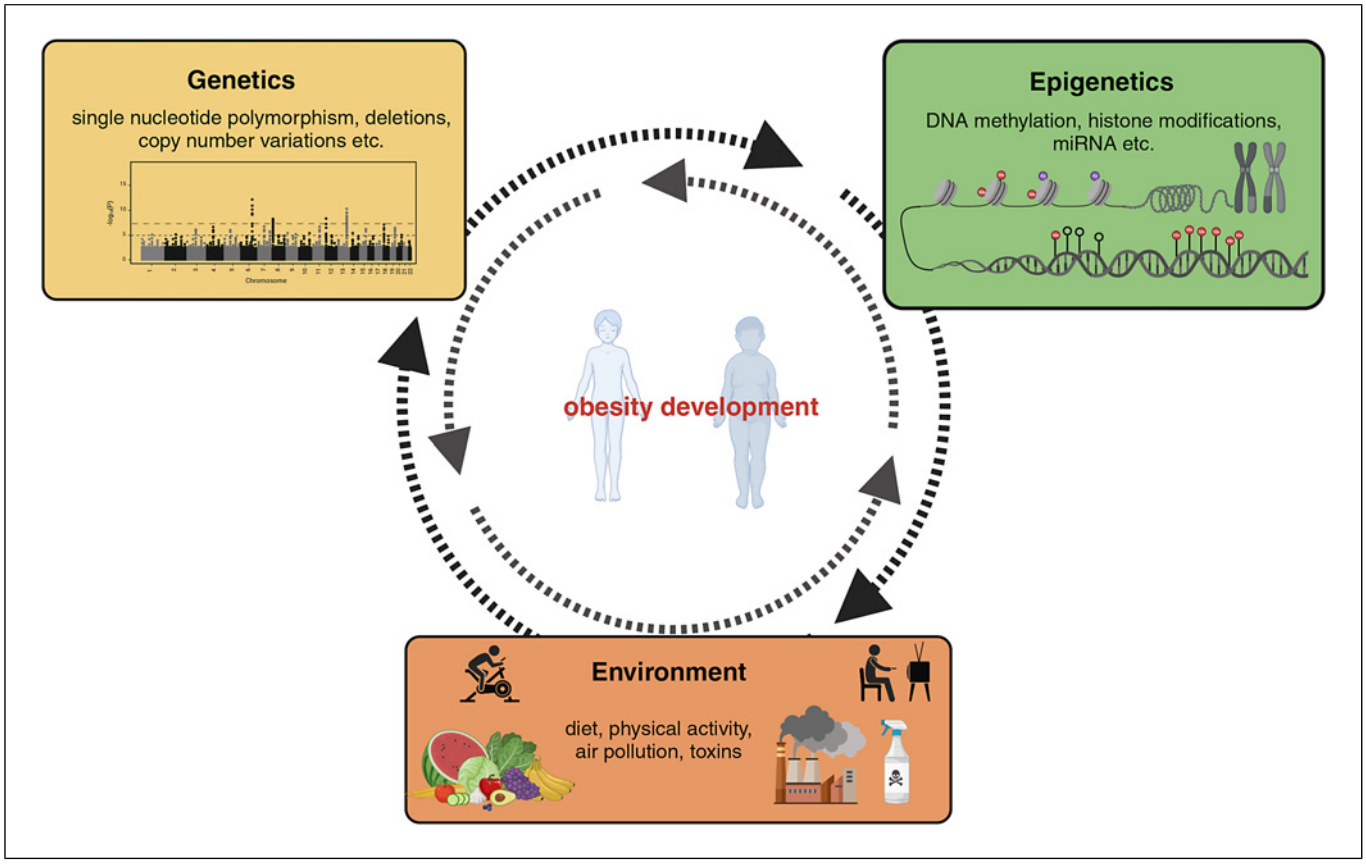

Fig. 1. Interplay of genetics, epigenetics, and environmental factors in obesity development: obesity results from a complex interaction between genetics, epigenetics, and environmental factors. Single nucleotide polymorphisms (SNPs) and variants (SNVs), short insertions and deletions (indels), as well as copy number variations (CNVs) are genetic variations contributing to obesity susceptibility. Modifications such as DNA methylation, histone modifications, and microRNA (miRNA) regulation influence gene expression without altering the DNA sequence, playing a crucial role in obesity. Lifestyle and environmental exposures, including diet, physical activity, air pollution, and toxins, also contribute to obesity risk, e.g., by causing changes in methylation patterns.

A recent review found that the most SNP-environment interactions involved alcohol consumption, sleep time, smoking, and physical activity [36]. Notably, the association between the genetic risk score [37] or MC4R variants [38] and childhood obesity seems to be modulated by diet quality, where a high-quality diet characterized by a high share of vegetables, legumes, polyunsaturated fatty acids, and nuts acts as protective factor, whereas a low-quality diet marked by a high share of trans fat, processed meat, sugar-sweetened beverages, and sodium (highly processed food) exacerbates the genetic risk (Table 1). Moreover, physical activity can attenuate genetic risks [26]. The growing number of large-scale studies, including cohorts like the UK Biobank, will uncover new and more robust gene-environment interactions, enabling more precise treatment opportunities in the long-term. However, the causative mechanisms underlying most of the observed risk variants remain not well understood.

Obesity-Related Epigenetic Programming in Children

Maternal and paternal overweight and obesity are linked to an increased risk of overweight and obesity and metabolic impairments in children [71–73]. A current review lists the correlation between current obesity in one or both parents and obesity at age 15 as $r = 0.29$, reflecting both genetics and a shared lifestyle [74]. The underlying mechanisms contributing to this heightened susceptibility and its associated health consequences in children are not yet fully understood [30]. Additionally, maternal factors such as weight gain during pregnancy [75, 76],

Table 1. Summary of bioactive dietary compounds influencing obesity-related outcomes through epigenetic mechanisms

Dietary compound	Food source	Health effects	Ref.
Polyphenols			
Curcumin	Turmeric (*Curcuma longa*)	• Antioxidant, anti-inflammatory, immunomodulatory • Reduces pain and swelling • Alleviate arthritis • Improves wound healing • Boost memory and mood • Tumor cell suppressing • Antiangiogenic	[39–43]
Catechins	Green tea leaves, beans, black grapes, cherries, cacao, apples, pears, chocolate, cider, red wine	• Antioxidant • Anti-inflammatory • Tumor cell suppressing • Antibacterial • Anti-obesity, anti-diabetic • Antihypertensive, cardioprotective • Weight loss • Anti-hyperlipidemic	[39, 42–47]
Resveratrol	Grapes, berries, tomato, peanuts, walnuts, plums, pines, rhubarb, apples, red wine	• Anti-diabetic (amelioration of diabetic nephropathy) • Anti-obesogenic • Antihypertensive • Anti-aging (inhibition of 'metabolic memory' of endothelial senescence) • Anti-inflammatory • Chemo-preventive • Antioxidant • Cardioprotective • Neuroprotective • Antitumorigenic	[39, 42, 43, 45, 47, 48]
Ellagitannins and ellagic acid	Pomegranate, berries, nuts, wolfberry, apples, peaches, pears, guava, mangoes, legumes, cereal grains, wine, cognac, tea	• Antioxidant • Anti-mutagenic • Anti-carcinogenic • Anti-adipogenic • Anti-inflammatory (BANC) • Glucose-lowering • Anti-glycation effects	[39, 43, 49, 50]
Organosulfur compound			
S-allyl cysteine (SAC)	Onion, garlic, shallots	• Improving immunity • Hypolipidemic, improving cardiovascular health • Diabetes- and cancer-preventive • Anti-mitotic potential against many cancers • Neuroprotective • Anti-inflammatory	[39, 51–54]
Diallyl disulfide/trisulfide (DADS)	Garlic	• Improving immunity • Improving cardiovascular health, anti-atherosclerosis • Diabetes- and cancer-preventive • Anti-mitotic potential against many cancers • Anti-obesogenic (esp. in combination with green tea)	[39, 55–57]

Table 1 (continued)

Dietary compound	Food source	Health effects	Ref.
Bioactive compounds of cruciferous vegetable			
Isothiocyanates (SFN), sulforaphane (most popular isothiocyanate SFN), indole-3-carbinol (I3C), and 3,3′-diindolylmethane (DIM)	Broccoli, cauliflower, cabbage, kale, brussels sprouts, collards, watercress, radishes, mustard	• Antimicrobial • Cancer-preventive • Tumor cell suppressing • Anti-obesogenic • Anti-inflammatory • Antioxidant • Prevention/therapy of the metabolic syndrome	[39, 42, 58, 59]
Isoflavones			
Genistein	Lupine, fava beans, raisin, nuts, and soybeans	• Antioxidant • Anti-fibrotic • Anti-carcinogenic • Cardioprotective • Improves glucose and lipid metabolism	[39, 42, 43, 45]
Quercetin	many seeds, buckwheat, nuts, flowers, shallots, barks, broccoli, olive oil, apples, onions, green tea, red grapes, red wine, tomatoes, and berries, *Ginkgo biloba*, *Hypercium perforatum*, and *Sambucus Canadensiss*	• Cardiovascular protection • Anti-carcinogenic • Anti-diabetic • Imunomodulatory • Antihypertensive • Anti-viral • Anti-inflammatory • Anti-fibrotic • Antioxidant • Antioxidant	[39, 45, 60, 61]
Citrus flavonoids			
Naringin, hesperidin, nobiletin, tangeretin	Citrus fruits	• Anti-inflammatory • Antioxidant	[42, 43]
Alkaloids			
Caffeine	Tea and coffee, cacao beans, yerba mate, guarana berry	• Decreases diabetes type II risk • Increases energy expenditure • Increasing mental alertness • Relieving fatigue • Improving concentration and focus	[39, 62]
Berberine	Barberry (diverse varieties)	• Anti-adipogenic • Antimicrobial • Improving cardiovascular health (lowering LDL) • Improved the insulin sensitivity • Anti-carcinogenic	[39, 63–65]
Vitamins			
Vitamin B	• B2 (riboflavin): eggs, cereal grains, sunflower seeds, brown rice, whole-grain rye, asparagus, kale, cauliflower, lean meat, and leafy vegetables • B3 (nicotinamide): eggs, meat, fish, and mushrooms • B9 (folate): green leafy vegetables, whole grains, beans, lentils, liver, beef • B12 (cobalamin): fish, fowl, meat, eggs, liver from lamb, veal, beef, and turkey, shellfish, crab meat	• Cardioprotective • Anti-cancerous • Folic acid is essential for the maintenance of normal methylation patterns • Folic acid supplementation ameliorates obesity-associated decrease in leptin methylation • Folate is protective against methylation changes caused by obesity, Alzheimer's, and cancer	[39, 42, 47]

Table 1 (continued)

Dietary compound	Food source	Health effects	Ref.
Vitamin C	Citrus fruits, red and green peppers, broccoli, tomatoes, and potatoes	• Antioxidant • Anti-cancerous • Reverse some of obesity-caused methylation changes	[39, 66]
Vitamin D	Produced in the body on exposure to light (80–90%), fatty fish, egg yolk, mushrooms	• Suspected to be related to insulin sensitivity • Deficiency suspected to be involved in subclinical atherosclerosis • Bone formation • Muscle contraction • Nervous functioning • Anti-cancerous • Anti-inflammatory	[39, 67, 68]
Vitamin E	Vegetables, oils, grains, nuts, etc.	• Antioxidant • Treatment of Parkinson's disease • Up-regulating tumor-suppressor genes • Improved glycated hemoglobin profiles under energy restriction	[39]
Other dietary micronutrients			
Choline and betaine	Liver, egg, soybeans, meat, fish, potatoes, kidney beans, etc.	• Important for the development of the fetal nervous system • Anti-cancerous • Mitigated high-fat diet-induced non-alcoholic fatty liver disease	[39, 69]
Apigenin	Celery, tea, mint, oregano	• Anti-inflammatory • Antioxidant • Alleviation of obesity-associated metabolic syndrome	[42, 43]
Gomisin N	Magnolia berry (*Schisandra chinensis*)	• Anti-obesity effects in high-fat diet	[70]

The table outlines bioactive compounds, their sources, and their associated health-related effects. The most common epigenetic mechanisms include the inhibition of DNA methyltransferase, of histone acetyltransferase or histone deacetylase and changes in miRNAs and histone expression. For detailed information about the mechanisms, we refer to the listed references.

prenatal nutrition [77, 78], and physical activity [79] directly impact fetal health. These intrauterine stimulants can lead to epigenetic remodeling, influencing health outcomes in the offspring [80, 81]. A low-protein diet, e.g., changes epigenetic marks (methylation, histone modification) in pregnant rat, mouse, and pig models, affecting the expression of leptin [82], hepatic glucose production [83], and glucose metabolism [84] in the offspring. Likewise, a high-fat diet for pregnant mice changed the leptin and adiponectin expression in the offspring [85, 86]. Moreover, a recent study showed that a preconception high-fat diet in fathers-to-be increases obesity risk in children [87].

Studies have also shown that dietary micronutrients, both postnatal and during early life, alter gene expression and subsequently affect health and disease outcomes later in life [88]. Longer duration of breastfeeding, considered the most appropriate way to feed newborns, is associated with favorable alterations in leptin gene expression [89–91]. In general, sufficient dietary methyl sources are required for methylation processes during epigenetic (re-)programming during the perinatal period [82, 92, 93] as well as later in life. Low birth weight, especially a birth weight too small for gestational age, is a known risk factor for an unfavorable lipid profile [94] and for developing type 2 diabetes or CVD in later life [95, 96].

Epigenetics provides a link between malnutrition-induced intrauterine growth restriction and higher adult BMI, increased lipids, and increased CVD risk [97].

Dietary intake is not always correlated with a sufficient supply of nutrients. The gut microbiome influences the bioavailability of different micro- and macronutrients by extraction and synthesis [98]. An impaired functioning of the gut microbiome might lead to choline deficiency, affecting methylation processes. Studies have shown that different gut microbiome profiles are associated with specific epigenetic risk profiles [99, 100]. The maternal microbiome links directly to the baby's health – through metabolic provisioning during pregnancy and vertical transmission during and after birth. The latter depends strongly on delivery mode (Cesarean section or vaginal delivery) and breastfeeding. There is growing evidence that the gut microbiome plays a crucial role in the transgenerational epigenetic programming, e.g., DNA methylation and microRNA expression, for the better or the worse [98, 100].

Besides nutrition-related factors, methylation patterns are also thought to be influenced by adversities, especially during childhood. A study on CpG sites in children from the ALSPAC childhood cohort found that the ages between 3 and 5 years is a particularly sensitive period for epigenetic changes caused by adverse events, including physical or emotional abuse, maternal psychopathology, and financial hardship [101]. Evidence of altered methylation related to childhood maltreatment has also been found in several other studies [102]. Abuse of mothers has also been linked to changes in methylation in the newborns' cord blood, as well as poorer mental health at age 7 [103]. Other factors related to changed methylation profiles comprised poverty and neighborhood deprivation [104], exposure to environmental pollutants [105], noise [106], stress [107], sleep deprivation [108, 109], or sleep apnea [110], etc. All or any of these changes may or may not contribute to a change in obesity risk. To our knowledge, there are no studies on causal pathways, which would allow the drawing of conclusions.

Novel Knowledge from EWAS in Obesity

Epigenetic mechanisms, such as DNA methylation and histone core protein modification, are believed to mediate gene-environment interactions and, thereby, modify the individual's susceptibility to obesity. A multitude of studies have analyzed DNA methylation, which is a stable, straightforward, and well-studied epigenetic mark that has been of substantial interest in (childhood) obesity research.

EWAS dissect genome-wide DNA methylation to uncover methylation pattern that correlate with manifestations of obesity or fat distribution. Over the past decade, well-powered EWAS, combined with multi-omics strategies and large case-control studies in twins, families, or independent subjects, have identified novel targets involved in the epigenetic dysregulation of obesity. In the first table by Keller et al. [22], we listed and summarized 45 genome-wide methylation studies. The major part of these studies included subjects of European origin and examined genomic DNA derived from either whole adipose tissue, whole blood, or specific blood cells. While DNA methylation analyses identify novel candidate CpG sites and genes, the underlying causative mechanisms often remain elusive. Therefore, it is crucial to integrate information from genetic, transcriptome, and proteomics/metabolomics studies to provide better understanding of the causative relationships underlying disease-relevant clinical traits. For example, genetic variants may influence methylation at specific CpG sites, potentially creating co-methylation patterns that translate into changes in clinical traits, suggesting a genotype-phenotype correlation. As a result, an increasing number of studies focus on multi-omics epigenetic associations with obesity and related traits, facilitated by advances in high-throughput technologies and analytical approaches.

The largest study so far comprised more than 5,000 subjects from four discovery cohorts [34]. Across loci, the BMI change associated with a 10%-change in methylation (0.1 change in methylation β-value) varied between 0.6 and 4 kg/m^2 [34], comparable with a change of 2–13%/1–8%, for a reference BMI of 30/50 kg/m^2, respectively. A meta-analysis of EWAS in neonatal blood from more than 8,800 babies found effect sizes up to 180-g-changes in birthweight (approximately 5%) [111]. A sub-analysis in blood taken later in life (2–13 years, 16–18 years, 30–40 years) found less than 2% of the identified sites still associated with birth weight [111]. These results are in line with Madden et al. [112], who found no association between birthweight and DNA methylation in adults. Another EWAS meta-analysis found few associations between BMI-standard deviation score and methylation during childhood and adolescence [113]. As we can see, effect sizes differ not only by locus but also by age at sample collection and age at outcome measurement, respectively, by the difference between these two. Further sources of variation are tissue type and potentially the body part from which the sample was taken.

More studies found weaker links between BMI (or related measures) and methylation during childhood and adolescence than later in life: One mother-child study reported 10% explained variance of the maternal BMI for mothers in their late forties/early fifties, whereas about 10 years earlier, during pregnancy, only 2% could be explained by differential methylation. For the children, they reported 1, 2, and 3% at birth, 7 years, and between 15 and 17 years of age, respectively [114]. The trend of increasing explained variance with age seems to continue: a study in subjects mainly in their 50s to 70s reported approximately 25–30% BMI variance explained by differential methylation [115]. The pattern may hint to obesity rather causing differential methylation patterns than resulting from it. To further our understanding, we need to shift the focus of studies from identifying novel candidate sites to investigating methylation change in longitudinal designs [29, 116].

To better understand how genes related to BMI are affected by changes in DNA methylation, we previously analyzed data from the EWAS catalog (all $p < 1 \times 10^{-8}$ [29]; accessed 08.03.2023 [22]) and identified the most frequently studied genes linked to BMI. Among these, *ABCG1* was the most commonly replicated, followed by *CPT1A*, *SREBF1*, *SBNO2*, and *SOCS3*. These genes were consistently found in at least three studies and were reported across different ethnic groups, including Europeans, African Americans, Africans, and Asians [117].

Research further supports the role of genes like *ABCG1* and *CPT1A* in obesity. For example, ABCG1 is important for cholesterol transport in cells, and its dysfunction can lead to excessive fat accumulation [118–121]. Changes in the methylation of ABCG1 and SREBF1 are also linked to type 2 diabetes (T2D) [122], suggesting that these genes influence the metabolic issues associated with obesity.

CPT1A is crucial for breaking down fatty acids in mitochondria and regulating inflammation [123]. Studies have shown that diets high in fat can reduce CPT1A activity and fat metabolism, while blocking fructose metabolism can increase CPT1A activity [124]. This demonstrates the potential impact of diet on gene function and obesity-related health outcomes.

In summary, identifying new methylation sites related to obesity and its comorbidities through EWAS highlights the importance of epigenetics in obesity development. However, the underlying functions of newly discovered candidate genes are not well understood, and the relevance of methylation signals derived from the whole blood for obesity pathophysiology is still debated. More comprehensive studies are needed; more so, since current genome-wide methylation array studies cover only about 1–3% of methylation sites, leaving a large portion of the epigenome understudied [125].

The Utility of MRS in Predicting Disease Risk

In clinical practice, easily available and low-cost prediction markers are highly warranted. Therefore, MRS are a promising tool (mirroring the concept of genetic risk scores) to be used as prediction markers for obesity and in assessing the relevance of environmental factors. However, the generation, as well as the application of MRS presents methodological challenges, as all epigenetic marks are, per se, susceptible to potential confounders, such as environmental factors, age, sex, ethnicity, and technological differences in DNA methylation assessment [126].

For instance, Lariviere et al. [127] constructed MRS using methylation profiles from placenta and cord blood to predict weight-related outcomes at birth and 6 months of age. The in-sample explained variance reached values up to and above 90%. But when applied to an independent control cohort, the association between MRS and the weight-related outcomes vanished [127]. On the other hand, one methylation-based, gene-specific blood test for colorectal cancer has already been approved by the FDA [128] and a multi-cancer blood test based on more than 100,000 methylation sites received FDA Breakthrough Device Designation in 2019 [129, 130]. Its final approval is expected for 2026.

Moreover, epigenetic predictors based on DNA methylation at CpG sites were shown to be valuable tools in predicting morbidity, mortality and exposure to environmental factors such as smoking [131–133]. A recent study supported this, showing that MRSs outperformed polygenic risk scores in explaining the variance of (prenatal maternal) smoking and BMI in adults, but not in children, suggesting that epigenetic changes may be consequences of weight or weight change rather than causes [133]. Methylation scores also outperformed polygenic risk scores for multiple outcomes [131].

In summary, although MRSs show great potential as valuable markers for clinical decision-making, conflicting results still exist. Current issues can be addressed by increasing statistical power through larger sample sizes, better accounting for potential confounders, and combining polygenic risk scores with MRS in future research. However, to date, their practical application remains limited as their predictive accuracy is still unreliable or often insufficiently precise.

Conclusion

Progress was made by using GWAS and EWAS to identify novel targets being involved in the development of obesity and its comorbidities. While the mechanistic details for many genetic and epigenetic risk variants remain to be fully understood, substantial progress has been made for several crucial components.

Applying novel tools such as MRS, best combined with polygenic risk scores, to establish reliable prediction scores may prove successful in the long-term, but is currently in its early stages. So far, their utility in predicting disease risk in clinical practice remains limited. To date, neither polygenic risk scores nor MRSs are valid clinical prediction tools, especially for day-to-day practice and young children. However, with the described improvements in score construction, there is high potential for these tools to become more reliable in the future. Indeed, solid methods are urgently needed to identify high-risk populations early and develop personalized preventive and therapeutic measures to combat the childhood obesity pandemic.

Conflict of Interest Statement

The authors have nothing to disclose.

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Author Contributions

Wieland Kiess conceptualized the review and prepared a preliminary draft. Maria Keller and Peter Kovacs authored the initial sections on epigenetics and obesity. Mandy Vogel adapted the manuscript to align with the pediatric context. Wieland Kiess, Maria Keller, Peter Kovacs, Antje Garten, Stina Ingrid Alice Svensson, Elena Rossi, Yvonne Böttcher, and Mandy Vogel reviewed and revised the manuscript several times during the writing and the revision process. Mandy Vogel incorporated the suggestions and wrote the final version. All authors approved the final version.

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