Diabetes, Metabolic Syndrome and Obesity

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REVIEW

Maternal Nutrition, Toxicants, and Epigenetic Programming of Obesity Across Generations

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Background: The developmental origins of health and disease (DOHaD) framework highlights the importance of the intrauterine environment in shaping lifelong health outcomes. Maternal nutrition, toxic exposures, and epigenetic reprogramming are key factors influencing offspring susceptibility to obesity and cardiometabolic disorders. However, prior reviews have typically addressed nutrition and toxicants separately, limiting insights into their combined effects on the fetal epigenome. This review integrates current evidence on how maternal nutrition and toxicant exposures converge through epigenetic mechanisms to influence obesity risk, while outlining translational opportunities for mitigating intergenerational metabolic disease.

Methods: A narrative review was conducted of studies published from 2000 to 2025, sourced from PubMed, Scopus, and Web of Science, supplemented by manual screening. Search terms included maternal nutrition, environmental toxicants, epigenetic mechanisms, and offspring obesity outcomes. Studies on animal models, human cohorts, and intervention trials were included, focusing on links between maternal exposures, epigenetic changes, and metabolic disease.

Results: Maternal dietary imbalances, such as deficiencies in one-carbon donors or excess caloric intake, cause persistent epigenetic changes on genes regulating adipogenesis and energy homeostasis, increasing offspring obesity risk. Prenatal exposure to environmental toxicants, including endocrine disruptors and heavy metals, amplifies these vulnerabilities by altering DNA methylation, histone modifications, and noncoding RNA networks. Combined nutritional deficits and toxicant exposures, particularly in low- and middle-income countries (LMICs), create a "dual burden" that intensifies epigenetic instability. Nutrients like methyl donors and antioxidants may mitigate toxicant-induced epimutations, offering potential for precision maternal nutrition interventions.

Conclusion: Maternal nutrition and toxicant exposures interact through epigenetic mechanisms to program obesity and related diseases. Addressing these factors through precision nutrition, stricter environmental regulations, and early-life epigenetic biomarkers offers promising prevention strategies. Large, diverse, multi-generational cohorts and multi-omics approaches are needed to strengthen causal inference and inform equitable policies to break the intergenerational cycle of metabolic disease.

Plain Language Summary: This study explores how a mother's diet and exposure to environmental pollutants during pregnancy can shape her child's future risk of obesity and related diseases such as diabetes and heart disease. It explains that what happens in the womb can "program" a baby's metabolism for life through changes in gene activity known as epigenetic modifications which are chemical tags that switch genes on or off without changing DNA.

Poor maternal nutrition, whether from eating too much fat and sugar or lacking key vitamins like folate and B_{12} can alter these epigenetic marks, increasing the child's tendency to gain weight. At the same time, exposure to environmental toxicants like plastics (which contains BPA), heavy metals, or pesticides can make these effects worse. When both poor nutrition and toxic exposure occur together, especially in low-income settings, the risk becomes even greater.

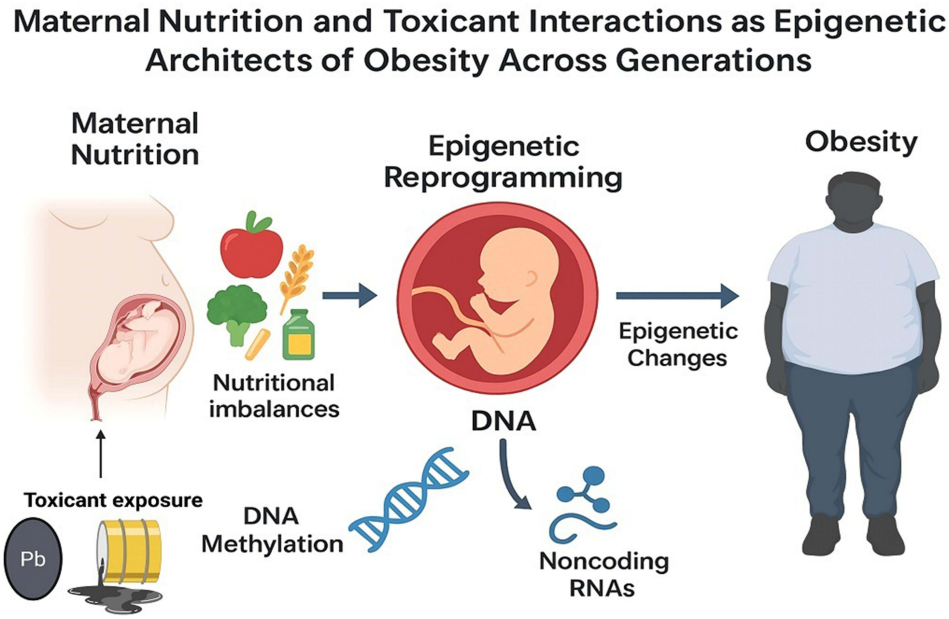
Received: 5 November 2025
Accepted: 18 December 2025
Published: 31 December 2025

The review also highlights that healthy diets rich in folate, antioxidants, and omega-3 fats may help protect against these harmful effects. New technologies that study genes, metabolites, and gut bacteria together (multi-omics) are helping scientists identify early biomarkers of risk.

Ultimately, the study calls for integrated maternal health policies that combine good nutrition with stronger environmental protections to prevent obesity from being passed down across generations.

Keywords: toxic exposures, epigenetics, histone modifications, endocrine disruptors, fetal programming, maternal precision nutrition

Graphical Abstract



Introduction

Obesity and its associated metabolic disorders represent one of the most pressing global health challenges of the 21st century. The prevalence of obesity has tripled over the past four decades, with current estimates indicating that more than 890 million adults and over 160 million children and adolescent are affected worldwide. Unfortunately, the prevalence of this menace has been predicted to surge by 2050 with the overall number of adults and children with overweight and obesity projected to reach 3.80 billion and 186 million, respectively.[1,2] Obesity not only increases the risk of type 2 diabetes, cardiovascular disease, and nonalcoholic fatty liver disease but also contributes to reduced life expectancy and escalating healthcare costs.[3,4] Traditional explanations centered on lifestyle and genetic predisposition cannot fully account for the rapid rise in obesity, suggesting that early-life determinants play a pivotal role in shaping lifelong metabolic risk.[5]

At the same time, global populations, particularly those in low- and middle-income countries face rising exposures to environmental toxicants. Biomonitoring surveys indicate that >90% of pregnant women in the United States have detectable levels of endocrine disruptors such as bisphenol A (BPA) and phthalates in their urine, while similar findings have been reported in European birth cohorts.[6] In South Asia, especially Pakistan and Bangladesh, tens of millions of people are chronically exposed to arsenic in drinking water, with exposure rates reaching up to 60 million individuals in Pakistan and 28–46% of the Bangladeshi population exceeding WHO safety limits.[7,8] Moreover, global food safety reports estimate that approximately 25% of food crops are contaminated with mycotoxins like aflatoxins, and in some regions detection reveals contamination in up to 60–80% of staple crops, notably maize and groundnuts in sub-Saharan Africa.[9,10]

The World Health Organization further estimates that environmental pollution accounts for 24% of global deaths and disproportionately affects women and children.[11] Together, these statistics reveal a "dual burden" in which widespread maternal exposure to obesogenic toxicants coincides with the escalating prevalence of obesity.

Growing evidence supports the concept that the intrauterine environment exerts a profound influence on long-term health outcomes, as articulated by the developmental origins of health and disease (DOHaD) hypothesis.[12] Maternal nutrition, exposure to environmental toxicants, and other gestational factors can induce biological changes in the developing fetus that persist well into adulthood. These developmental "programming" effects create a biological memory of early exposures, predisposing offspring to obesity and metabolic syndrome long before lifestyle factors take effect.[13]

At the molecular level, epigenetic programming provides a mechanistic framework for understanding how intrauterine exposures shape disease susceptibility without altering the DNA sequence.[14] Epigenetics refers to the study of inheritable modifications in gene expression that transpire without changes to the fundamental DNA sequence. These alterations are facilitated by mechanisms including DNA methylation, histone modification, chromatin remodelling, and non-coding RNAs, which govern the activation or repression of genes in response to developmental or environmental stimuli.[15,16]

Beyond DNA methylation and histone acetylation/methylation, several emerging epigenetic mechanisms may also mediate the impact of maternal nutrition and toxicants on obesity risk. Histone lactylation, derived from glycolytic lactate, links cellular metabolic state directly to chromatin regulation and may be particularly relevant in obesogenic, high-glycolytic intrauterine environments. Altered maternal fuel availability and placental hypoxia could, in principle, shift lactate flux and histone lactylation marks at genes controlling adipogenesis, inflammation, and energy expenditure.[17] According to Li et al,[18] changes in chromatin accessibility and nucleosome positioning, evaluated by ATAC-seq method, offer a more integrated view of how maternal exposures remodel cis-regulatory landscapes in adipose and hepatic lineages. Additionally, 3D genome architecture including chromatin looping, topologically associated domains, and long-range enhancer–promoter contacts may orchestrate coordinated transcriptional programs in developing metabolic tissues.[19] Although human pregnancy data remain sparse, early animal and in vitro work suggest that maternal dietary imbalance and toxicant exposure can rewire higher-order chromatin organization, with potential long-term consequences for obesity-related gene networks. Together, these processes are highly responsive to nutritional inputs and environmental insults during critical windows of development, establishing long-lasting alterations in metabolic pathways such as adipogenesis, insulin sensitivity, and energy homeostasis.[20]

Despite significant progress, several critical knowledge gaps remain. First, most studies examine maternal nutrition or toxicant exposures in isolation rather than within an integrated maternal "exposome" that reflects real-world co-occurrence of dietary imbalances and multi-toxicant burdens. Second, much of the mechanistic insight derives from animal models, which, while invaluable, may not fully capture the complexity of human pregnancy, placental function, and long-term metabolic outcomes. Third, human evidence largely comes from high-income cohorts, with relatively few data from LMICs where the dual burden of maternal undernutrition and pollution is greatest. Third, longitudinal, multi-omics studies that link specific maternal exposures to epigenetic marks and subsequent obesity phenotypes are still sparse, limiting causal inference and translational application. Observational cohort studies demonstrate associations between maternal exposures and offspring obesity but cannot establish causality. Few randomized controlled trials have tested nutritional or exposure-reduction interventions during pregnancy, and ethical considerations limit experimental manipulations in human populations.[21] Lastly, many studies rely on single-exposure assessments, overlooking the real-world complexity of combined nutritional deficiencies, excesses, and multi-toxicant exposures that constitute the maternal exposome.

Therefore, the aim of this narrative review is to fuse current knowledge on how maternal nutrition and toxic exposures individually and synergistically reconfigure the fetal epigenome to amplify intergenerational risk for obesity and related disorders. Specifically, we seek to: (i) summarize epigenetic mechanisms linking maternal macronutrient, micronutrient, and bioactive intake to offspring adiposity and metabolic disease; (ii) examine how major classes of environmental toxicants reconfigure the fetal epigenome to promote obesogenic phenotypes; (iii) evaluate evidence for interactive nutrition–toxicant effects, including microbiome-mediated and sex-specific pathways; and (iv) identify key knowledge gaps and translational opportunities for precision maternal nutrition, exposure-reduction approaches, and policy actions aimed at mitigating intergenerational cycles of obesity.

Methodology

This review adopts a narrative approach, aiming to integrate evidence across disciplines rather than constrain the synthesis to rigid systematic review protocols. Literature was identified through extensive searches of PubMed, Scopus, and Web of Science, complemented by manual screening of reference lists from relevant reviews and primary research papers. Search terms included maternal nutrition, macronutrient and micronutrient imbalances, epigenetics, DNA methylation, histone modifications, non-coding RNAs, obesogens, endocrine disruptors, and offspring obesity. To balance breadth with relevance, we focused on publications in English from 2000 to 2025, ensuring inclusion of both seminal studies and recent advances.

Studies were considered if they examined the relationship between maternal dietary exposures or toxicant burdens during pregnancy and epigenetic outcomes relevant to obesity risk. Evidence was drawn from animal experiments that provide mechanistic insights, observational human cohorts that capture real-world exposures, and randomized controlled trials or intervention studies where available. Reports without direct relevance to epigenetic mechanisms or obesity outcomes were excluded. In synthesizing the literature, emphasis was placed on mapping exposures to epigenetic modifications (DNA methylation, histone changes, chromatin remodeling, or non-coding RNA regulation), identifying the molecular targets most frequently implicated (IGF2, LEP, PPARγ, insulin signaling genes), and highlighting offspring outcomes such as adiposity, insulin sensitivity, and metabolic syndrome. Human cohort studies including famine exposures, prospective birth cohorts, and multi-omics investigations were particularly valued for their translational relevance, while animal models were used to fill mechanistic gaps that cannot be ethically or practically addressed in humans.

Because this is a narrative rather than a systematic review, the synthesis privileges integration and critical interpretation over exhaustive cataloguing. Findings are presented thematically, beginning with the effects of maternal macronutrient and micronutrient status, moving to the impact of environmental toxicants, and finally exploring their synergistic or antagonistic interactions. Throughout, attention is drawn to research gaps such as the underrepresentation of low- and middle-income countries, challenges in distinguishing causality from correlation, and the need for multi-omics approaches that frame opportunities for advancing both science and policy.

Maternal Nutrition and Epigenetic Programming of Obesity

Maternal nutrition during pregnancy is a critical determinant of the intrauterine environment, exerting profound influence on fetal growth trajectories and long-term metabolic health.[22] Beyond the direct supply of substrates for fetal development, maternal diet regulates the establishment of epigenetic marks that shape gene expression patterns in tissues central to energy balance, including adipose tissue, liver, pancreas, and hypothalamus. Nutritional perturbations, whether deficiencies or excesses, can induce lasting epigenetic alterations in pathways governing adipogenesis, appetite regulation, and insulin signaling, thereby programming an increased risk of obesity in offspring.[23]

Macronutrient Imbalances and Epigenetic Regulation

High-Fat Diets

Maternal overnutrition and high-fat intake have been consistently linked to obesity in offspring.[24] Mechanistically, excess maternal fat induces DNA methylation changes at adipogenic regulators such as *PPARγ* and *C/EBPα*, leading to enhanced adipocyte differentiation and lipid storage.[20] Histone acetylation changes in fetal liver further promote lipogenic gene expression, while alterations in hypothalamic DNA methylation disrupt appetite-regulating neurocircuitry.[2] Animal studies demonstrate that maternal high-fat feeding enhances activating histone marks (H3K9ac, H3K4me3) in lipogenic gene promoters, establishing a chromatin landscape permissive for obesity-related phenotypes.[25,26] Importantly, systematic reviews of human cohorts (eg, ALSPAC and Generation R) confirm that higher maternal dietary fat intake during pregnancy is associated with differential DNA methylation at obesity-related loci, including *LEP* and *IGF2*, which in turn correlate with childhood BMI trajectories.[27,28] Meta-analyses further suggest that maternal overnutrition during pregnancy increases offspring risk of obesity by 30–40%, partly mediated by epigenetic alterations.[29,30]

High-Sugar Diets

Gestational exposure to high-sucrose or high-fructose diets promotes epigenetic dysregulation of glucose–insulin signaling pathways.[31] In rodent models, maternal high-sugar intake reduces DNA methylation at *IGF2* and *IRS1*, genes central to insulin signaling, resulting in hyperinsulinemia and early-onset adiposity.[23,32] Histone deacetylase (HDAC) activity is also altered, shifting chromatin states toward increased glycolytic and lipogenic capacity.[2] Human studies support these findings: the Project Viva cohort reported that higher maternal intake of sugar-sweetened beverages was linked to epigenetic modifications in cord blood insulin signaling genes, which predicted higher adiposity in early childhood.[33] A meta-analysis review of 2003 mother-offspring pairs from three cohorts concluded that maternal glycemic load during pregnancy is consistently associated with methylation changes in glucose–insulin pathways, though replication across diverse populations is still limited.[34]

Protein Restriction

Low-protein maternal diets induce a "thrifty phenotype," whereby offspring develop enhanced metabolic efficiency that predisposes them to obesity in nutrient-rich postnatal environments.[35] Mechanistically, protein restriction is associated with hypomethylation of glucocorticoid receptor (NR3C1) and peroxisome proliferator-activated receptor alpha (PPARα) genes, altering stress responses and lipid metabolism.[36] Reduced histone acetylation in the pancreas and liver further modifies energy partitioning, enhancing susceptibility to metabolic syndrome.[37]

The "thrifty phenotype" hypothesis proposes that poor nutrition during fetal development and early life leads to long-term metabolic adaptations that help the individual survive in a nutrient-scarce environment. These adaptations include reduced insulin secretion and sensitivity, and altered energy metabolism. While these changes may be beneficial in conditions of chronic undernutrition, they increase susceptibility to metabolic disorders such as type 2 diabetes, obesity, and cardiovascular disease if the individual later encounters a nutrient-rich environment.[38]

The "thrifty phenotype" hypothesis, originally derived from low-protein diet models in rodents, has human parallels. Evidence from the Dutch Hunger Winter and Chinese Famine cohorts demonstrates that prenatal protein-energy restriction is associated with hypomethylation of *NR3C1* (glucocorticoid receptor) and *IGF2*, leading to long-term dysregulation of stress responses and metabolic pathways.[23] A meta-analysis and systematic analysis combined study confirmed persistent DNA methylation differences at these loci decades after exposure, directly linking undernutrition to increased obesity and cardiometabolic risk in adulthood.[39]

Micronutrients and One-Carbon Metabolism

Methyl Donors (Folate, Choline, Vitamin B_{12}, Methionine)

One-carbon metabolism provides substrates for DNA and histone methylation, making maternal micronutrient status a cornerstone of epigenetic regulation. Deficiency in folate or vitamin B_{12} during pregnancy disrupts S-adenosylmethionine (SAM) availability, leading to global hypomethylation and instability in obesity-related genes.[40] Classic evidence comes from the Dutch Hunger Winter cohort, where prenatal famine exposure altered DNA methylation at IGF2 decades later, linking nutritional stress to lifelong obesity risk.[41] Conversely, optimal methyl donor intake supports stable imprinting and healthy metabolic programming. Human evidence is particularly robust: maternal folate and B_{12} deficiencies have been associated with altered DNA methylation at *IGF2, LEP*, and other obesity-related genes in multiple cohorts (ALSPAC, Pune Maternal Nutrition Study).[40,42] A systematic review of 46 studies concluded that inadequate maternal folate and B_{12} significantly increase the risk of obesity and insulin resistance in offspring, highlighting the importance of optimal one-carbon donor status.[43]

Minerals and Trace Elements

Micronutrients such as zinc and selenium act as cofactors for epigenetic enzymes (eg, DNA methyltransferases, histone demethylases). Deficiency alters enzyme activity, promoting aberrant methylation patterns in metabolic genes. For example, in pregnant mice, zinc deficiency in pregnancy has been associated with altered methylation at leptin (LEP) and adiponectin (ADIPOQ) genes, affecting appetite regulation and adipocyte function.[44]

Rodent studies implicate zinc and selenium in maintaining DNA methyltransferase and histone demethylase activity. Human reviews note associations between zinc deficiency and altered gene-specific methylation, and state that zinc influences key epigenetic processes.[45,46] Selenium status has been inversely associated with offspring insulin resistance, although evidence is less consistent across populations.[47]

Dietary Bioactive Compounds as Epigenetic Modulators

Polyphenols (Resveratrol, Epigallocatechin Gallate, Curcumin)

Maternal consumption of polyphenol-rich diets exerts protective epigenetic effects against obesogenic programming. Resveratrol, for instance, activates sirtuin 1 (SIRT1), promoting histone deacetylation of pro-inflammatory genes and reducing adipogenesis.[2] Epigallocatechin gallate (EGCG) inhibits DNA methyltransferases (DNMTs), modulating methylation at metabolic genes involved in lipid oxidation.[48] These effects suggest bioactive polyphenols function as natural "epigenetic regulators" capable of mitigating toxicant- or nutrient-induced epimutations. In animals, polyphenols act as natural epigenetic regulators by modulating sirtuins and DNMT activity. Human intervention studies remain scarce, but small randomized trials indicate that maternal polyphenol-rich diets improve oxidative stress markers and may influence placental methylation patterns.[49] A recent systematic review of randomized control trials concluded that evidence in humans is promising but insufficient, calling for larger, well-controlled trials.[50]

Omega-3 Fatty Acids

Long-chain polyunsaturated fatty acids (PUFAs), especially docosahexaenoic acid (DHA), regulate histone acetylation and microRNA expression in pathways linked to inflammation and adipogenesis. Maternal omega-3 supplementation has been linked in human trials to altered cord blood DNA methylation at inflammatory genes (TNFα, IL6) and regulators of adipogenesis.[51] These changes are associated with improved offspring insulin sensitivity and lower risk of childhood obesity. A systematic review of 13 RCTs supports the role of omega-3s in modulating epigenetic markers relevant to metabolic programming.[52]

Other Bioactives

Rodent studies highlight sulforaphane (from cruciferous vegetables) and butyrate (a microbial metabolite of dietary fiber) as histone deacetylase inhibitors, enhancing protective chromatin remodeling.[53,54] In humans, evidence is still emerging, but observational data suggest that maternal high-fiber intake (increasing butyrate production) is associated with beneficial cord blood methylation signatures in metabolic pathways.[23,55] These findings point to the possibility of maternal dietary interventions as epigenetic therapeutics in preventing obesity programming.

To integrate mechanistic insights from experimental models with evidence from human populations, Table 1 summarizes maternal nutritional factors, their associated epigenetic mechanisms, key gene targets, and the corresponding obesity-related outcomes observed across animal and human studies.

As summarized in Table 1, maternal nutrition exerts profound epigenetic effects on pathways central to energy balance, adipogenesis, and insulin sensitivity. A consistent pattern emerges: macronutrient excesses (high-fat, high-sugar diets) and deficiencies (protein or one-carbon donor insufficiency) leave persistent epigenetic marks at loci such as IGF2, LEP, and PPARγ, which predict obesity and metabolic dysfunction in offspring. While rodent studies provide mechanistic detail on chromatin remodeling, systematic reviews and cohort data confirm that these associations extend to human populations, particularly in famine cohorts and prospective birth studies. Nonetheless, knowledge gaps remain, especially regarding the long-term persistence of epigenetic marks, the relative contributions of specific micronutrients, and the interactions between maternal diet and other exposures. Future research integrating epigenomics with metabolomics and microbiomics is needed to move from associations toward causal inference, and ultimately to inform precision maternal nutrition strategies.

Maternal Exposure to Environmental Toxicants and Obesity Risk

Beyond nutrition, the intrauterine environment is shaped by maternal exposure to environmental toxicants, many of which function as obesogens, chemicals that perturb developmental pathways to predispose offspring to obesity. These

Table 1 Maternal Nutritional Factors, Epigenetic Mechanisms, and Offspring Obesity Outcomes

Nutritional Factor	Epigenetic Mechanism (s)	Key Genes/ Pathways Affected	Evidence from Animal Models	Evidence from Human Cohorts/Reviews	Offspring Outcomes
High-fat diet	DNA methylation ↓, histone acetylation ↑	PPARγ, C/ EBPα, lipogenic genes	Rodents: enhanced adipocyte differentiation; activating histone marks (H3K9ac, H3K4me3)[25,26]	Cohorts (ALSPAC, Generation R): maternal fat intake linked to LEP, IGF2 methylation; meta-analysis: ↑ offspring obesity risk (30–40%)[27,28]	Increased adiposity, insulin resistance, fatty liver
High-sugar diet	Hypomethylation, altered HDAC activity	IGF2, IRS1 (insulin signaling)	Rodents: reduced methylation, hyperinsulinemia, early adiposity[23,32]	Project Viva: maternal sugary beverage intake → methylation changes in insulin pathways; systematic review: consistent links to glucose–insulin dysregulation[33]	Early-onset adiposity, impaired insulin sensitivity
Protein restriction	Hypomethylation, histone acetylation ↓	NR3C1, PPARα, IGF2	Rodents: 'thrifty phenotype,' altered stress and lipid metabolism[56]	Dutch Hunger Winter, Chinese Famine: persistent IGF2 hypomethylation; meta-analysis: higher adult obesity and cardiometabolic risk[23,39]	Increased visceral adiposity, metabolic syndrome
Methyl donors (Folate, B12, Choline, Methionine)	DNA methylation stability via SAM availability	IGF2, LEP, PPARγ	Rodents: deficiency → global hypomethylation, imprinting instability[57]	Pune Maternal Nutrition Study, ALSPAC: low maternal folate/ B12 → altered methylation, ↑ childhood adiposity; meta-analysis: ↑ obesity risk[41–43]	Obesity, insulin resistance, impaired glucose handling
Zinc, Selenium	Cofactors for DNMTs, HDACs; affect methylation/ demethylation balance	LEP, ADIPOQ, mitochondrial genes	Rodents: deficiency disrupts adipogenesis and mitochondrial metabolism[44]	Zinc deficiency → altered LEP/ADIPOQ methylation; selenium linked to reduced offspring insulin resistance (less consistent)[45–47]	Altered appetite regulation, adiposity, insulin resistance
Polyphenols (Resveratrol, EGCG, Curcumin)	SIRT1 activation, DNMT inhibition	Inflammatory & lipogenic genes	Rodents: resveratrol ↓ adipogenesis, EGCG modulates lipid oxidation[48]	Small RCTs: maternal polyphenol intake → changes in placental methylation; systematic review: promising but limited[49,50]	Reduced adiposity, improved insulin sensitivity (preliminary)
Omega-3 fatty acids (DHA, EPA)	Histone acetylation modulation, miRNA regulation	TNFα, IL6, adipogenic regulators	Rodents: restored balanced methylation, ↓ inflammation[58]	omega-3 supplementation → cord blood methylation changes; systematic review (13 RCTs): protective metabolic effects[51,52]	Lower obesity risk, improved insulin sensitivity
Dietary fiber/ Butyrate	HDAC inhibition, DNA demethylation via TET enzymes	Lipid oxidation, insulin signaling genes	Rodents: butyrate → histone acetylation ↑, metabolic flexibility[53]	Observational data: high maternal fiber intake → beneficial cord blood methylation profiles[23,55]	Improved energy metabolism, protection from obesity

Notes: This table summarizes key maternal dietary exposures, the associated epigenetic mechanisms, and their impact on offspring metabolic health. Evidence is drawn from both animal models (mechanistic insights) and human cohorts or systematic reviews (translational relevance). Arrows indicate the direction of change in epigenetic marks: ↓ = decrease or reduction (eg, hypomethylation, reduced histone acetylation). ↑ = increase or elevation (eg, hyperacetylation, increased offspring obesity risk). → = leads to.

https://doi.org/10.2147/DMSO.S579409

exposures can reconfigure the fetal epigenome through DNA methylation drift, histone modification changes, and altered noncoding RNA expression, thereby disrupting energy metabolism, adipogenesis, and endocrine regulation. The effects are often compounded when toxic exposures coincide with maternal dietary imbalances, amplifying the risk of obesity and related metabolic disorders.[59,60] The evidence linking toxicants to obesity risk is growing, but it is important to critically distinguish between correlative associations in human cohorts and causal mechanistic insights from experimental models. Additionally, while numerous studies link toxicants to metabolic dysfunction, translational relevance is strengthened by examining dose–response relationships and identifying exposure thresholds associated with obesity risk.

Endocrine Disruptors (Obesogens)

Bisphenols (BPA and Analogues)

Bisphenol A (BPA), widely used in plastics and food packaging, crosses the placenta and accumulates in fetal tissues. Prenatal BPA exposure has been linked to altered DNA methylation of PPARγ, LEP (leptin), and ADIPOQ (adiponectin), key regulators of adipogenesis.[61,62] Histone modifications at estrogen receptor–related genes further enhance lipogenic programming. Emerging evidence suggests that BPA analogues (BPS, BPF), marketed as safer alternatives, may exhibit similar obesogenic epigenetic effects.[63] BPA readily crosses the placenta and has been associated in observational studies with altered methylation of PPARγ and LEP, correlating with increased childhood BMI.[62] However, most cohort findings are correlative and often rely on single urine measurements, which may not reflect chronic exposure. In contrast, mechanistic animal studies provide stronger evidence, showing that prenatal BPA exposure induces persistent promoter hypomethylation and chromatin remodeling at adipogenic loci.[64] Human biomonitoring shows that >90% of pregnant women have detectable urinary BPA.[65,66] Multiple birth cohorts report a positive dose–response relationship: higher maternal BPA quartiles correlate with greater offspring BMI scores and altered methylation as well as mesoderm-specific transcript.[67] However, most studies use spot urine samples, which may underestimate chronic exposure variability. Animal models show that even low-dose BPA exposure (below current regulatory thresholds of 50 μg/kg/day) induces DNA hypomethylation at adipogenic loci, suggesting that "safe" limits may not adequately protect fetal development.[68] BPA analogues (BPS, BPF) demonstrate similar epigenetic effects, but dose–response data remain sparse.[63] These findings suggest causality, but the translational gap remains, particularly as human studies often cannot rule out confounding dietary and socioeconomic factors.

Phthalates

Phthalates, commonly found in cosmetics and food contact materials, act as PPARγ agonists, promoting adipocyte differentiation. Epigenetically, maternal phthalate exposure induces hypomethylation at adipogenic and lipid metabolism genes, while altering microRNA networks (such as miR-27 and miR-143) that regulate adipogenesis.[69] Human cohort studies (Project Viva, CHAMACOS) have associated prenatal phthalate exposure with increased childhood adiposity, implicating fetal epigenome remodeling as a mechanistic driver, but effect sizes are modest and sometimes sex-specific.[23] The strength of evidence here lies in convergence: human cohorts show consistent associations, while animal studies provide plausible molecular mechanisms. Still, a lack of dose–response data in human populations limits causal inference. Epidemiological studies reveal that higher prenatal urinary concentrations of DEHP metabolites are associated with greater childhood adiposity, with some cohorts showing threshold effects above the 75th percentile of exposure.[70,71] Mechanistic studies confirm dose-dependent activation of PPARγ and hypomethylation at lipid metabolism genes, but inconsistencies across phthalate subtypes complicate risk assessment.[72] Current tolerable daily intakes (TDIs) for phthalates may not account for these epigenetic effects, raising questions about regulatory adequacy.

Heavy Metals

Arsenic

Observational studies link prenatal arsenic exposure with higher obesity and diabetes risk in adulthood, supported by Epigenome-wide association studies (EWAS) findings of persistent methylation changes decades later.[73,74] Yet, these human data are largely associative, with limited ability to disentangle arsenic exposure from concurrent nutritional deficiencies (such as low folate). Animal studies provide stronger causal evidence, demonstrating global hypomethylation and specific hypermethylation of GLUT4 and IRS2, leading to impaired insulin signaling. Together, the human and

mechanistic evidence is compelling, but further intervention studies (such as folate supplementation trials in exposed populations) are required to establish causality. Dose–response analyses from Bangladeshi and Mexican cohorts demonstrate that higher prenatal arsenic exposure is associated with increased BMI z-scores and insulin resistance in offspring, with risk accelerating at water arsenic levels above 50 μg/L.[75] EWAS data reveal progressive global hypomethylation with rising exposure.[73] Animal studies corroborate these findings, showing dose-dependent hypermethylation of GLUT4 and IRS2 promoters at environmentally relevant concentrations.[76] Notably, the WHO guideline of 10 μg/L may not provide complete protection against epigenetic effects.[77]

Cadmium and Lead

Both cadmium and lead readily cross the placenta, accumulating in fetal tissues.[78] Epidemiological studies suggest that prenatal exposure to cadmium and lead correlates with higher offspring adiposity, but results are inconsistent across cohorts and often confounded by co-exposure to other pollutants.[79] Cadmium exposure alters methylation patterns of genes involved in adipogenesis and mitochondrial metabolism, while lead disrupts histone acetylation in neural and metabolic tissues, affecting appetite regulation. These modifications predispose offspring to energy imbalance, early weight gain, and metabolic dysfunction.[80] Thus, while biological plausibility exists, human evidence remains heterogeneous, highlighting the need for harmonized exposure measurements and multi-pollutant modeling. Prospective cohorts suggest nonlinear associations, with increased adiposity risk primarily observed in the upper exposure quartiles. For cadmium, cord blood concentrations above 0.44 μg/L have been linked to differential methylation at adipogenic genes.[81] Animal studies reveal dose-dependent mitochondrial dysfunction and epigenetic remodeling. Lead exposure shows stronger effects when maternal blood lead levels exceed 5 μg/dL, consistent with public health thresholds, although subtle epigenetic changes occur even below these levels, indicating that no truly safe threshold may exist.[82]

Food-Borne and Agricultural Toxicants

Aflatoxins

Produced by *Aspergillus* species in contaminated food, aflatoxins are potent hepatotoxins with emerging roles in metabolic programming. Evidence linking prenatal aflatoxin exposure to obesity risk remains preliminary. While some human studies report associations with impaired growth and liver function, few directly assess obesity outcomes.[83] Animal models suggest epigenetic modifications in hepatic metabolic genes, but stronger epidemiological data are needed before causality can be inferred.[84]

Pesticides and Herbicides

Organochlorine pesticides and glyphosate derivatives have been implicated in metabolic disruption through histone acetylation and microRNA modulation.[85] In utero pesticide exposure shifts the chromatin state of adipogenic genes, leading to increased fat deposition.[86] Prospective cohorts show inconsistent associations, partly due to variability in exposure measurement. However, dose–response analyses from agricultural communities indicate that higher maternal organophosphate exposure correlates with increased offspring adiposity.[87] Animal models show clear dose-dependent histone acetylation changes at adipogenic genes, suggesting plausible thresholds for adverse effects, though human translation remains incomplete. Mechanistic studies, however, demonstrate that pesticides can induce histone acetylation and microRNA modulation at adipogenic genes. The disconnect between correlative human evidence and mechanistic plausibility reflects the challenge of exposure assessment in epidemiological settings, where pesticide mixtures and variable timing of exposure complicate interpretation.

Acrylamide and Other Processed Food Contaminants

Acrylamide, formed during high-temperature cooking, has been shown in animal studies to induce fetal DNA methylation changes in pancreatic and hepatic tissues. These epigenetic disruptions compromise insulin secretion and glucose handling, setting the stage for obesity and diabetes.[88] Human data are limited to dietary intake estimates, which are subject to recall bias, and few cohorts have linked acrylamide biomarkers to obesity outcomes. Dietary exposure estimates from the Norwegian Mother and Child Cohort (MoBa) study suggest that higher quartiles of maternal acrylamide intake correlate with lower birth weight and early growth changes, though obesity-specific outcomes remain

uncertain.[89] Rodent models confirm dose-dependent DNA methylation changes in pancreatic tissue at levels comparable to high human dietary intake.[90]

Emerging Toxicants: PFAS, Microplastics, and the Expanding Maternal Exposome

In addition to conventional obesogens such as phthalates, and BPA, a growing set of emerging contaminants is now recognized within the maternal exposome. Per- and polyfluoroalkyl substances (PFAS) are environmentally persistent and bioaccumulative compounds can cross the placenta and they have been linked in epidemiological studies to altered birth weight trajectories, adiposity, and dyslipidemia in offspring.[91,92] Experimental data suggest that PFAS can modulate nuclear receptor signaling and induce persistent changes in DNA methylation and histone modifications in metabolic tissues.[93,94] Additionally, micro- and nanoplastics which are detectable in human placenta and cord blood, represent another rapidly evolving exposure. These particles and their metabolites may induce oxidative stress, low-grade inflammation, and epigenetic reprogramming in placental and fetal cells.[95] Thus, incorporating PFAS, microplastics, and other emerging contaminants into DOHaD frameworks is important to embrace the full spectrum of real-world maternal exposures that may converge on shared epigenetic pathways governing energy equilibrium and adiposity.

Translational Evidence from Human Cohorts

Longitudinal studies provide compelling evidence linking maternal toxicant exposure to epigenetic reprogramming and obesity risk. The Dutch Hunger Winter cohort revealed that famine-exposed individuals exhibited altered methylation at IGF2, compounded by exposure to environmental pollutants postnatally.[12] Historically, placental epigenomics has moved from candidate loci toward integrative, multi-omics frameworks. Large-scale studies now combine placental DNA methylation, gene expression, and genetic variation to map regulatory circuits linking birthweight loci to placental transcriptional programs, thereby grounding DOHaD concepts in specific molecular pathways.[96] Complementary work integrates placental epigenomic profiles with maternal diet, microbiota and metabolite signatures, suggesting that maternal nutritional and microbial milieus can remodel placental chromatin and transcriptomes with consequences for fetal growth and later metabolic risk.[97] These placental multi-omics studies accentuate the placenta as a central hub where nutritional and toxicant signals converge on shared regulatory networks, rather than acting solely through cord blood or peripheral tissues.

The emergence of exposome-wide association studies (ExWAS) has been an important methodological development that scientifically test large panels of environmental exposures against obesity-related phenotypes, and it is analogous to genome-wide association studies.[98] Early-life exposome projects such as HELIX and related cohorts have applied ExWAS frameworks to prenatal and childhood exposure data, revealing clusters of air pollutants, metals, and lifestyle factors associated with childhood BMI and waist circumference, often with modest but reproducible effect sizes.[99–101] Large exposome and omics consortia such as the Pregnancy and Childhood Epigenetics (PACE) consortium and European early-life exposome initiatives (eg, HELIX) now combine high-dimensional exposure assessment with epigenomic, metabolomic, and microbiomic profiling to identify molecular signatures linking complex maternal exposomes to childhood overweight and metabolic traits. These projects illustrate both the promise and the controversy of exposome-wide approaches. PACE consortium pools epigenome-wide methylation data from multiple birth cohorts to perform meta-analyses of maternal characteristics and early-life exposures in relation to offspring CpG methylation and downstream cardiometabolic phenotypes, using harmonized pipelines and causal-inference extensions.[102] Furthermore, the Western Australian Pregnancy Cohort (Raine) Study provides multigenerational life-course data that have been used to evaluate how early-life growth, adiposity and cardiometabolic traits track into adolescence and adulthood.[103] In the United States, the Environmental influences on Child Health Outcomes (ECHO) Program unites loads of cohorts to evaluate how preconception-to-childhood environments shape obesity and related health outcomes, contributing to unique sample size and exposure diversity.[104] While they reveal coherent exposure clusters and candidate molecular pathways, reported effect sizes are often modest, signatures can vary across cohorts and tissues, and results are sensitive to analytical choices in mixture modelling and multiple-testing correction.

Recent birth cohort studies (ALSPAC, Generation R, CHAMACOS) demonstrate associations between prenatal BPA, phthalate, and heavy metal exposures with differential DNA methylation patterns in cord blood, correlating with higher

BMI and adiposity in childhood and adolescence.[23,105] While DNA methylation remains the most extensively characterized mechanism, these findings likely represent only one layer of a broader epigenetic landscape that also includes histone lactylation, chromatin accessibility, and 3D genome organization, all of which may be sensitive to maternal nutritional and toxicant cues. These findings underscore the clinical relevance of maternal toxicant exposures in shaping the obesity epidemic. However, most of these findings remain associative and are limited by confounding and the difficulty of separating toxicant effects from nutritional or socioeconomic variables. By contrast, animal and in vitro models provide causal evidence of specific epigenetic mechanisms but may not fully capture human pregnancy physiology. Remarkably, not all human studies report positive associations between maternal toxicant exposure and offspring adiposity. Several birth cohorts have observed weak, null, or even inverse associations for specific compounds or time windows, particularly when exposure is assessed using single spot urine samples or limited biomarkers. For instance, while some analyses in ALSPAC, Generation R, and CHAMACOS cohorts link higher prenatal BPA, phthalate, or pesticide levels to increased childhood BMI, other analyses within the same or similar cohorts report no clear dose–response relationship, sex-restricted effects, or outcomes that attenuate after adjustment for socioeconomic and lifestyle confounders.[70,106] Inconsistencies are also evident for heavy metals, where associations with adiposity often depend on exposure level, co-exposures, and child age at follow-up. These divergent findings underscore that obesogenic effects of toxicants are not universal; rather, they are contingent on exposure timing, dose, and mixture, underlying nutritional status, epigenetic susceptibility, and residual confounding.

To clarify how different classes of maternal toxicants exert their effects on the fetal epigenome, Table 2 summarizes representative compounds, their primary epigenetic targets, supporting evidence, and the downstream obesity-related outcomes.

As shown in Table 2, a consistent theme emerges: endocrine disruptors (BPA, phthalates) and heavy metals (arsenic, cadmium, lead) have the strongest translational evidence, with human cohort associations reinforced by mechanistic studies demonstrating epigenetic reprogramming of adipogenic and insulin signaling pathways. By contrast, food-borne toxins and agricultural chemicals show clear mechanistic plausibility in animal models but remain underexplored in human populations, where exposure assessment and co-exposure confounding limit causal inference. Across toxicant classes, DNA methylation appears to be the most frequently disrupted mechanism, although histone modifications and noncoding RNAs are increasingly recognized as critical mediators. The convergence of multiple epigenetic marks across different compounds suggests shared obesogenic pathways, underscoring the importance of integrating multi-omics approaches in future studies.

Nutrition–Toxicant Interactions: Synergy or Antagonism?

The risk of obesity programmed in utero rarely arises from maternal nutrition or toxic exposures in isolation. Instead, these factors frequently intersect, particularly in vulnerable populations, creating a complex exposome where nutritional status can either exacerbate or buffer toxicant-induced epigenetic disruptions. Comprehending this interplay is critical for elucidating mechanisms of metabolic programming and for designing targeted interventions. More so, human cohort studies increasingly highlight the translational relevance of these interactions.

Dual Burden in Low-Resource Settings

In low- and middle-income countries, pregnant women are often simultaneously exposed to nutritional deficiencies (protein, micronutrients, methyl donors) and high levels of environmental pollutants (air pollution, pesticides, heavy metals). This "dual burden" magnifies epigenetic instability during fetal development.[107] Chronic deficiencies in protein, folate, vitamin B_{12}, and micronutrients often coexist with elevated exposures to arsenic-contaminated groundwater, pesticide residues in food, and indoor air pollution from biomass fuels. These overlapping stressors magnify epigenetic instability during fetal development, predisposing offspring to obesity and metabolic disease later in life.[108]

Human Evidence

In Bangladesh, arsenic exposure combined with low folate status has been associated with global DNA hypomethylation in cord blood and higher childhood adiposity compared with either exposure alone.[109]

Table 2 Maternal Toxicant Classes, Primary Epigenetic Targets, and Offspring Obesity Outcomes

Toxicant Class	Representative Compounds	Epigenetic Targets	Key Genes/ Pathways Affected	Evidence Base	Obesity-Related Outcomes
Endocrine disruptors	BPA, BPS, BPF	DNA methylation ↓ (PPARγ, LEP, ADIPOQ), histone acetylation ↑ at estrogen receptor loci, altered miRNAs (miR-146, miR-21)	Adipogenesis, estrogen signaling	Human cohorts (ALSPAC, CHAMACOS), animal models[65,66]	↑ Childhood BMI, enhanced adipocyte differentiation
Phthalates	DEHP, DBP, DEP	Hypomethylation at adipogenic genes, histone modification at lipid metabolism loci, altered miRNAs (miR-27, miR-143)	PPARγ, lipid metabolism pathways	Birth cohorts (Project Viva, CHAMACOS), mechanistic rodent studies[23,72,105]	↑ Adiposity, impaired lipid handling
Heavy metals	Arsenic, cadmium, lead	Global DNA hypomethylation, locus-specific hypermethylation (GLUT4, IRS2), histone acetylation changes, disrupted ncRNA profiles	Insulin signaling, mitochondrial metabolism	EWAS in exposed populations, mechanistic rodent studies[73,74,82]	↑ Insulin resistance, early weight gain, metabolic dysfunction
Food-borne toxins	Aflatoxins, acrylamide	DNA methylation changes in hepatic and pancreatic tissues, altered histone acetylation	Lipid metabolism, insulin secretion	Limited human cohorts, strong rodent evidence[83,84]	Impaired glucose handling, obesity predisposition
Agricultural chemicals	Organochlorines, glyphosate, organophosphates	Histone acetylation ↑ at adipogenic loci, altered microRNA expression	Adipogenesis, inflammatory pathways	Human cohort associations inconsistent, strong mechanistic evidence[86,87]	↑ Fat deposition, chronic low-grade inflammation

Notes: This table summarizes representative maternal toxicants, their major epigenetic targets, and downstream effects on metabolic pathways relevant to obesity. Arrows indicate directionality of epigenetic change: ↓ = decrease or reduction (eg, DNA hypomethylation, reduced enzyme activity). ↑ = increase or elevation (eg, histone acetylation, higher risk of adiposity). Evidence is drawn from both human cohorts and mechanistic animal studies, with stronger translational relevance noted where findings converge across models.

https://doi.org/10.2147/DMSO.S579409

A Chinese famine follow-up study found that individuals prenatally exposed to both famine and industrial pollutants had more pronounced hypomethylation of *INSR* and *IGF2* compared to famine exposure alone, translating into higher rates of adult obesity.[110]

The INfancia y Medio Ambiente (INMA, Spain) cohorts demonstrated that maternal smoking and cadmium exposure had stronger associations with offspring body weight.[111] A similar study reported significant increased anogenital index in male offspring, suggesting altered androgenic signaling.[112] According to Chen et al[113] in their seven European birth cohorts study, an inflammatory, suboptimal maternal prenatal diet may negatively affect offspring body composition and increase the risk of overweight and obesity, particularly in late childhood. Thus, promoting the use of nutritious, anti-inflammatory maternal prenatal diet may aid in the prevention of childhood obesity. These findings suggest that nutritional deprivation reduces epigenetic resilience, making the developing fetus more vulnerable to obesogen-induced reprogramming.

Mechanistic Evidence

Malnutrition reduces epigenetic resilience by limiting one-carbon metabolites such as folate, methionine, and choline, thereby lowering S-adenosylmethionine (SAM) pools. When coupled with pollutant exposure, DNA methylation fidelity is impaired, leading to stochastic epimutations in metabolic genes (IGF2, PPARγ, LEP).[114]

Evidence from rat and goat studies reported that protein-energy restriction during gestation alters chromatin remodeling complexes, leaving fetal tissues more vulnerable to obesogen-induced histone modifications.[115,116]

Pollutant co-exposure (eg, arsenic in drinking water + poor folate intake) further drives global hypomethylation and specific hypermethylation of metabolic genes, compounding obesity risk postnatally.[117,118] Thus, in low-resource settings, the interaction of malnutrition and pollutants generates a compounding epigenetic burden, locking offspring into obesogenic trajectories even before birth.

Policy Implications

The dual burden has profound equity dimensions. Nutritional supplementation programs (like folate and iron fortification) are rarely paired with environmental health policies in LMICs, leaving vulnerable populations without integrated protection. Moreover, weak regulatory systems mean that pesticide residues and heavy metals often exceed international safety thresholds, while poor populations are the least able to afford safe food or water alternatives. Without interventions, LMICs risk a "double epidemic" of persistent undernutrition and rising obesity, widening health disparities relative to high-income countries.

Protective Role of Nutrients Against Toxicant-Induced Epimutations

Adequate maternal nutrition can buffer against toxicant-induced epigenetic insults, highlighting a protective antagonism between nutrients and pollutants. In high-income countries, access to balanced diets may mitigate pollutant effects, while in LMICs, nutritional inadequacy limits this resilience. For example, a recent randomized control trials in Bangladesh found that folate supplementation reduced arsenic-induced hypomethylation, yet supplementation coverage remains uneven globally, particularly in rural and low-resource settings.[119]

Antioxidants

Nutrients such as vitamins C and E, polyphenols, and carotenoids reduce reactive oxygen species (ROS) generated by pollutants. This limits oxidative DNA damage and prevents ROS-driven activation of histone-modifying enzymes (HDACs, HATs) that promote pro-adipogenic chromatin states.[120] Polyphenols like resveratrol and EGCG activate SIRT1, a histone deacetylase that suppresses inflammatory and adipogenic gene expression, counteracting BPA- and phthalate-induced chromatin activation.[121]

Methyl Donors (Folate, Choline, B12, Methionine)

Adequate intake of methyl donors maintains SAM-dependent methylation reactions, stabilizing DNA methylation and preventing pollutant-induced hypomethylation at key metabolic loci. For example, folate supplementation mitigates arsenic-induced global hypomethylation and prevents obesity-related gene dysregulation in animal models.[119,122]

Trace Elements (Zinc, Selenium)

Zinc as cofactors for epigenetic enzymes (DNMTs, TETs, HDACs), maintaining balanced activity in the presence of toxicant stress.[123] Selenium in particular counteracts cadmium-induced epigenetic dysregulation in hepatic metabolic pathways.[124] Collectively, these findings suggest that nutritional adequacy functions as an epigenetic shield, buffering fetal development against obesogen-induced programming.

Human Evidence

In Project Viva (USA), higher maternal folate intake attenuated the association between prenatal polyfluoroalkyl substances (PFAS) exposure and adverse birth outcomes, with protective effects persisting into early childhood BMI trajectories.[125]

Solomon et al[23] found that prenatal phthalate exposure altered DNA methylation patterns in Mexican-American neonates' cord blood, highlighting the impact of environmental exposures on their health and development. This corroborates an earlier research by Huen et al[126] concerning Mexican-American infants from the longitudinal birth cohort CHAMACOS. However, experimental and human research indicate that maternal consumption of diets high in antioxidants and polyphenols can affect DNA methylation and other epigenetic mechanisms, implying a possible nutritional route to alleviate environmental impacts.[127–129]

In prospective cohorts, prenatal mercury exposure correlates with variations in cord-blood DNA methylation; concurrently, omega-3 consumption has been associated with methylation alterations near pro-inflammatory genes (such as TNF and IL6), indicating that nutrition may influence epigenetic inflammatory pathways, although this interaction has not been documented in Generation R.[130,131]

Together, these findings provide compelling evidence that maternal diet quality can mitigate toxicant-induced epimutations, offering a feasible prevention strategy.

Policy Implications

Embedding environmental exposure reduction into existing maternal nutrition programs could be highly cost-effective. For example, combining folate supplementation with arsenic-free water initiatives in South Asia could address both nutritional and toxicological drivers of epigenetic disruption simultaneously.

More Case Studies in Human Cohorts

Historical famine studies and modern cohort evidence (eg, Dutch Hunger Winter, Chinese Famine, Project Viva, CHAMACOS, and INMA) underscore that maternal nutrition modifies the effects of toxicant exposures on offspring obesity risk. While high-income settings demonstrate protective effects of antioxidants and omega-3s against pollutants, LMIC settings reveal a compounding risk where undernutrition exacerbates pollutant-induced epimutations. The following human cohort studies provide real-world evidence of the nutrition–toxicant interplay in shaping obesity risk through epigenetic pathways:

i. Dutch Hunger Winter (1944–1945): Individuals exposed to famine in utero displayed persistent hypomethylation at the IGF2 gene six decades later. Subsequent analyses revealed that those exposed to higher environmental pollutants postnatally had exacerbated obesity risk, highlighting a cumulative effect.[23,132]
ii. Chinese Famine (1959–1961): Prenatal undernutrition was associated with altered DNA methylation at INSR (insulin receptor) and higher risk of obesity in adulthood. These effects were stronger in regions with higher environmental pollutant exposure, underscoring the synergistic burden of famine and toxicants.[110]
iii. Project Viva (USA): This prospective birth cohort demonstrated that prenatal phthalate and BPA exposure correlated with altered DNA methylation in cord blood, predicting increased adiposity in childhood. Interestingly, maternal diets richer in folate and antioxidants attenuated these associations, supporting a protective nutrient–toxicant antagonism.[33,125]
iv. Exposome–Nutrition Interactions in Recent Cohorts: Multi-omics approaches in European and North American cohorts reveal that maternal diet quality modifies the relationship between air pollution exposure and methylation changes at obesity-related loci, further linking nutrition and toxicant exposures in real-world settings.[101,133] These findings emphasize the necessity of integrating nutrition and toxicology in exposome research.

Policy Implications

Global maternal health strategies must address the structural inequities that sustain this dual burden. This includes strengthening food safety regulations to reduce pesticide and aflatoxin exposure, scaling up micronutrient supplementation and food fortification, and integrating environmental monitoring into antenatal care. Without coordinated policy action, intergenerational obesity risks will remain disproportionately higher in LMICs, reinforcing cycles of health inequity.

To illustrate how maternal diet can exacerbate or buffer toxicant-induced epigenetic alterations, Table 3 compiles evidence from key human cohorts and famine studies that highlight the interactive effects of nutrition and environmental exposures on obesity risk.

As summarized in Table 3, evidence from diverse human cohorts demonstrates that maternal nutrition significantly modifies the impact of toxicant exposures on offspring obesity risk through epigenetic mechanisms. Cohorts from famine-exposed populations (Dutch Hunger Winter, Chinese Famine) highlight how undernutrition amplifies pollutant-induced epimutations with long-lasting metabolic consequences, while more studies (Project Viva, CHAMACOS, INMA/HELIX) reveal that adequate folate, antioxidants, and omega-3 fatty acids can attenuate or even neutralize the obesogenic effects of phthalates, pesticides, and heavy metals. These findings underscore the translational importance of maternal diet quality in shaping the fetal exposome, suggesting that nutritional interventions may offer a practical and scalable means of mitigating toxicant-driven obesity programming.

Microbiome–Epigenome Crosstalk in Maternal Programming of Obesity

The maternal gut microbiome is increasingly recognized as a key intermediary linking diet, environmental exposures, and fetal development. Microbial communities metabolize nutrients and xenobiotics into bioactive compounds that cross the placenta or are delivered via breastmilk, directly influencing the fetal and neonatal epigenome. These interactions operate through short-chain fatty acids (SCFAs), bile acids, tryptophan metabolites, and microbial toxins, which serve as substrates or inhibitors of chromatin-modifying enzymes.[135] Perturbations in maternal diet or toxicant exposure can shift microbial composition, thereby altering the epigenetic landscape of developing metabolic tissues and programming offspring obesity risk.[23] While rodent studies provide direct causal data, human findings are predominantly associative, and distinguishing correlation from causation remains a critical challenge.

Maternal Diet Shapes Gut Microbiota and Epigenetic Signaling

Maternal nutritional status directly modulates the composition and function of the gut microbiota, which in turn generates metabolites with epigenetic activity. For instance, SCFAs produced from dietary fiber fermentation, cross the placenta and act as histone deacetylase (HDAC) inhibitors, enhancing histone acetylation at genes regulating lipid oxidation and insulin sensitivity.[136] Butyrate also promotes DNA demethylation by serving as a substrate for α-ketoglutarate–dependent dioxygenases (TET enzymes), facilitating chromatin remodeling toward metabolic flexibility.[137]

Maternal diets rich in fats alter gut microbiota-derived bile acid pools, which engage nuclear receptors (FXR, TGR5) and modulate histone acetylation in fetal liver. Dysregulated bile acid signaling predisposes offspring to hepatic steatosis and obesity.[138] Similarly, indole derivatives produced by microbial metabolism of tryptophan influence aryl hydrocarbon receptor (AhR) activity, which regulates histone acetylation and noncoding RNAs in immune–metabolic pathways.[139] Maternal tryptophan availability, therefore, indirectly programs offspring immunity and adiposity via microbiome–epigenome signaling. Thus, maternal diet establishes a microbiota–metabolite–epigenome axis that can either protect against or promote obesity, depending on nutrient quality.

In sum, rodent studies provide strong causal evidence: SCFAs such as butyrate cross the placenta, act as HDAC inhibitors, and directly increase histone acetylation at genes regulating lipid oxidation and insulin sensitivity.[140] Supplementation experiments confirm that maternal butyrate administration alters fetal chromatin states and reduces obesity risk.[23,141]

https://doi.org/10.2147/DMSO.S579409

Table 3 Human Evidence of Nutrition–Toxicant Interactions in Epigenetic Programming of Obesity

Cohort/Study	Nutritional Context	Toxicant Exposure	Epigenetic Targets	Observed Outcomes	Key Insights
Bangladesh Birth Cohorts[119]	Low folate and methyl donor deficiency	Arsenic in drinking water	Global DNA hypomethylation; hypermethylation of metabolic loci (IGF2, PPARγ)	Higher childhood adiposity, insulin resistance	Nutrient deficiency amplifies arsenic-induced epigenetic drift
Chinese Famine (1959–1961)[110]	Severe prenatal undernutrition	Industrial pollutants (regional variation)	Hypomethylation of INSR and IGF2	Higher obesity risk in adulthood, modified by pollution levels	Combined burden of famine + pollutants worsens metabolic outcomes
Dutch Hunger Winter (1944–1945)[23,132]	Prenatal famine exposure	Postnatal environmental pollutants	Persistent hypomethylation at IGF2	Increased obesity and diabetes risk across generations	Nutritional deprivation sensitizes epigenome to later pollutant exposure
Project Viva (USA)[33,125]	Higher folate and antioxidant intake	BPA, phthalates	Cord blood methylation changes at metabolic genes (LEP, IRS1)	Childhood adiposity attenuated in high-folate/antioxidant groups	Nutrients buffer toxicant-induced epimutations
CHAMACOS (California, USA)[126]	Maternal diet rich in antioxidants and polyphenols	Pesticides, phthalates	DNA methylation at stress and metabolic genes	Reduced adiposity risk in offspring despite high toxicant exposure	Antioxidants protect against pesticide-induced epigenetic disruption
INMA & HELIX (Europe)[100,134]	Variable maternal diet quality	Air pollution, multi-pollutant mixtures	Epigenome-wide methylation at obesity-related loci	Stronger adiposity effects when poor diet coexisted with high pollution	Multi-cohort exposome studies confirm interactive risk effects

Notes: This table summarizes findings from major human cohorts and historical famine studies examining how maternal nutrition modifies the impact of toxicant exposures on offspring obesity risk through epigenetic mechanisms. Arrows denote directionality where applicable: ↓ = reduction or hypomethylation (loss of epigenetic mark). ↑ = increase or hypermethylation (gain of epigenetic mark) or greater phenotypic risk. Cohorts are listed with their nutritional context, major toxicant exposures, identified epigenetic targets, and observed outcomes, with key insights emphasizing synergistic or protective effects.

Longitudinal Human Evidence

Human evidence, however, is largely associative. A prospective cohort study conducted by Fu et al[142] aimed to assess the correlation between dietary fibre consumption and short-chain fatty acid-producing bacteria during critical illness, involving 129 patients in the intensive care unit. The main outcome was the relative abundance of SCFA-producing bacteria after 72 hours in the ICU, determined by 16S rRNA gene sequencing of the rectal swab taken at 72 hours. The group with elevated fibre consumption had reduced stomach distension, with no rise in diarrhoea or other negative outcomes.

Emerging evidence challenges the once-held paradigm of a sterile intrauterine environment, underscoring that SCFAs, products of maternal fiber fermentation can reach the fetal compartment and potentially modulate DNA methylation landscapes.[143]

Epidemiological and mechanistic data suggest that maternal consumption of dietary fiber promotes an increase in SCFA-producing gut microbes, which may in turn influence the fetal epigenome via altered DNA methylation patterns in cord blood.[144]

The above studies report correlations between maternal fiber intake, increased abundance of SCFA-producing microbes, and differential DNA methylation in cord blood. Yet, direct causal pathways are difficult to establish because SCFA levels are typically inferred from diet or microbiome composition, rather than measured in maternal or cord blood. Thus, while human studies support plausibility, causality remains to be proven.

In analyses within the KOALA Birth Cohort (Netherlands), maternal probiotic use during the last month of pregnancy was included as a confounder when examining how early infant gut microbiota composition related to atopic outcomes.-[145] Additionally, the INFANTMET study (Ireland) followed maternal–infant dyads and demonstrated that infant gut microbiota development during the first six months of life is strongly influenced by delivery mode and feeding method, with associated changes in urinary metabolite profiles.[146] These findings support the hypothesis that maternal diet can shape the maternal–infant microbiome axis, which in turn modulates epigenetic programming of energy balance.

Toxicants Disrupt Microbiota and Epigenetic Pathways

Environmental toxicants disrupt maternal microbial ecology, thereby reprogramming epigenetic signaling in offspring. Mechanistic studies in animals show causality: exposure to BPA, arsenic, or glyphosate reduces microbial diversity and SCFA production, which in turn weakens HDAC inhibition, leading to tighter chromatin states at insulin sensitivity genes. Experimental microbiota transfer studies confirm that maternal toxicant-induced microbiome alterations can be sufficient to reprogram offspring metabolism. Endocrine Disruptors (BPA, Phthalates) reduce microbial diversity and favor pro-inflammatory taxa (like *Proteobacteria*), leading to increased production of lipopolysaccharide (LPS).[147] LPS induces chronic low-grade inflammation and alters histone acetylation in fetal immune cells, predisposing to metabolic dysfunction.[148,149]

Heavy Metals (Arsenic, Cadmium, Lead) alter gut microbial composition, reducing SCFA producers (eg, *Faecalibacterium*) while enhancing toxin-producing strains.[150] Loss of SCFAs weakens HDAC inhibition, resulting in tighter chromatin states at genes regulating insulin sensitivity.[151] Glyphosate and organophosphates disrupt microbial aromatic amino acid metabolism, reducing indole derivatives that regulate AhR-mediated epigenetic signaling. This fosters pro-adipogenic chromatin states in fetal tissues.[85]

Overall, toxicant-induced microbiome dysbiosis translates into epigenetic silencing of protective metabolic pathways and activation of obesogenic programs, amplifying obesity risk.

Longitudinal Human Evidence

In humans, findings remain associative. For example, the Lifelines NEXT cohort (Netherlands) found that prenatal exposure to air pollution was associated with altered maternal and infant gut microbiota diversity, which correlated with methylation changes at metabolic genes in cord blood.[152] However, it cannot definitively prove that microbial shifts mediated the epigenetic changes.

In the CHAMACOS cohort (USA), prenatal exposure to DDT and DDE was associated with increased risk of overweight or obesity by age 9 in male children.[153,154] Separately, analyses of prenatal exposure to mixtures of phthalates

and phenols revealed epigenetic alterations such as gestational-age acceleration that are linked to increased obesity risk.[23,155] Maternal pesticide exposure no doubt is linked to reduced abundance of beneficial SCFA-producing microbes, and these microbial shifts could be associated with epigenetic marks in offspring linked to obesity risk. Nevertheless, confounding by direct toxicant effects cannot be ruled out.

These studies strengthen translational relevance by demonstrating real-world links between environmental toxicants, microbiome shifts, and epigenetic regulation in humans.

Transplacental and Breastmilk-Mediated Microbial–Epigenetic Interactions

Maternal microbiome-derived metabolites reach the fetus not only via the placenta but also through breastmilk, shaping early postnatal epigenetic trajectories. SCFAs, bile acids, and indoles cross the placenta and act directly on fetal hepatocytes, adipocytes, and hypothalamic neurons, establishing chromatin marks that regulate energy balance.[156] For example, butyrate-mediated HDAC inhibition in fetal liver promotes histone acetylation at lipid oxidation genes, improving metabolic efficiency.[157]

Breastmilk contains microbial metabolites (such as SCFAs), immunomodulatory microRNAs, and microbial extracellular vesicles that shape infant gut colonization and epigenetic regulation.[158] Epigenetic modifications induced by breastmilk-derived miRNAs (miR-148a, which regulates DNMT1) persist into childhood, influencing adiposity and metabolic health.[159] Critically, the prenatal–neonatal transition is a sensitive period in which maternal microbiome-derived signals leave lasting epigenetic imprints. Disruption during this window (eg, maternal antibiotic use, pollutant exposure, or poor diet) has disproportionate long-term effects on offspring obesity risk.[160]

Longitudinal Human Evidence

While rodent experiments demonstrate causality, human evidence is suggestive but not causal. A study by Fehr et al[161] examined mother–infant pairs from the Canadian Healthy Infant Longitudinal Development (CHILD) cohort, showing that bacteria present in breastmilk co-occur with those found in infant stool, suggesting that breastmilk may seed the infant gut microbiome, especially influenced by breastfeeding practices such as exclusivity and pumping.

Similarly, the Finnish HELMi cohort reported that maternal antibiotic use altered breastmilk microbiota and metabolites, which were associated with differences in DNA methylation patterns in infants, correlating with adiposity outcomes at age 3.

Evidence from CHILD birth cohorts indicates that maternal antibiotic exposure and breastfeeding can influence breastmilk and infant microbiota composition,[162] while breastfeeding has also been associated with DNA methylation differences in Avon Longitudinal Study of Parents and Children (ALSPAC) cohort in infants.[163] Moreover, the result of the Pregnancy and Childhood Epigenetics (PACE) Consortium established an association between pre-pregnancy maternal BMI and methylation in newborn blood DNA which has been linked to later adiposity outcomes.[27] The Finnish Health and Early Life Microbiota (HELMi) cohort, with its integrated collection of breastmilk, infant microbiota, and DNA samples, is well positioned to investigate these interrelated mechanisms.[164]

These longitudinal data confirm that maternal microbiome–epigenome interactions are not transient but persist into early childhood, influencing obesity trajectories. However, causality remains unresolved because breastmilk metabolites coexist with maternal nutrients, hormones, and toxicants, all of which could contribute to epigenetic regulation.

Transgenerational Epigenetic Inheritance

The concept that maternal nutrition and toxicant exposures can influence not only the immediate offspring but also subsequent generations represents one of the most profound implications of the DOHaD framework. Unlike genetic mutations, which are fixed, epigenetic modifications are dynamic and reversible, yet certain marks established in germ cells can escape epigenetic reprogramming during gametogenesis and early embryogenesis. This raises the possibility of germline epimutations that transmit altered metabolic phenotypes including obesity susceptibility across multiple generations.[165]

Germline Epimutations Induced by Maternal Diet and Toxins

Nutritional perturbations during pregnancy can induce persistent epimutations in germline DNA of the developing fetus. Maternal overnutrition like high-fat diets during gestation alter DNA methylation and histone modifications in fetal oocytes and spermatogonia, particularly at genes controlling adipogenesis (PPARγ, C/EBPβ). These germline changes are propagated into the next generation, predisposing to increased adiposity even in the absence of continued maternal overnutrition.[23] Folate or methyl-donor deficiency reduces SAM availability, leading to global DNA hypomethylation.[166] In primordial germ cells where genome-wide demethylation and remethylation occur, this can disrupt the fidelity of imprinting marks.[167,168] Indeed, paternal folic acid deficiency in mice has been shown to alter imprinted gene methylation (including *H19, Snrpn, Peg3*) and increase adverse outcomes in F_2 offspring[169] while recent work indicates that such methylation changes can persist into F_3 progeny.[170]

Toxicant exposures including obesogens such as bisphenols and phthalates, as well as heavy metals like cadmium, induce heritable epigenetic reprogramming in germline cells. For example, Manikkam et al,[171] showed that gestating (F_0) rats exposed to a mixture of plastic-derived endocrine disruptors including BPA) during fetal gonadal sex determination produced F_3-generation offspring exhibiting increased obesity (adiposity), in conjunction with sperm epimutations involving promoter-region DNA methylation changes. Thus, both diet and toxins act as epigenetic architects of germline memory, encoding metabolic vulnerability that extends beyond direct exposure. These findings support the concept of true epigenetic inheritance beyond direct exposure.

Imprinting Errors and Obesity Inheritance

Genomic imprinting, monoallelic gene expression regulated by parent-of-origin-specific DNA methylation, is particularly vulnerable to nutritional and toxicant perturbations. Disruptions in imprinted loci contribute to obesity and metabolic dysfunction across generations.[172,173]

Imprinted genes, such as *IGF2* and *H19*, are unusually vulnerable to nutritional and toxicant perturbations because their parent-of-origin–specific methylation states are normally preserved through embryonic reprogramming.[174] Altered imprinting at these loci has been linked to obesity risk in both rodent and human studies, supporting their role as potential mediators of multigenerational inheritance. A study by Wu et al[175] using mice demonstrated that paternal exposure to a high-fat diet leads to altered methylation of the Igf2/H19 imprinting control region (ICR) in germ cells. This epigenetic change perturbs hepatic glucose metabolism in the offspring, implicating transmission of impaired metabolic health across generations.

Periconceptual exposure of individuals to the Dutch famine was associated with DNA hypomethylation in the differentially methylated region (DMR) that regulates the imprinted gene insulin-like growth factor-2 (IGF2), as assessed in the peripheral blood later in life.[176] This hypomethylation has been proposed as a plausible mechanism linking low birth weight to higher risk of later-life metabolic conditions, such as adiposity, insulin resistance, diabetes, and hypertension.[177] Animal models further indicate that similar epigenetic changes can persist across multiple generations (for instance, maternal protein-restriction causing promoter hypomethylation and metabolic dysfunction in F1 and F2).[178,179]

H19 is a long noncoding RNA co-regulated with IGF2 at the imprinted IGF2/H19 locus. H19 exhibits hypermethylation following maternal undernutrition and toxicant exposure, leading to dysregulated growth signaling and enhanced obesity susceptibility in offspring.[180] Altered methylation at IGF2/H19 around birth/childhood is associated with greater adiposity/overweight risk in offspring.[181,182]

Furthermore, altered methylation at imprinted loci such as MEG3, PLAGL1, and PEG3 has been observed in offspring of obese parents, with maternal obesity associated with decreased methylation at MEG3 and increased methylation at PLAGL1, and paternal obesity linked to decreased methylation at PEG3.[183] Additionally, epigenetic dysregulation of these loci has been associated with disrupted energy metabolism and transgenerational obesity phenotypes in animal models.[184] Imprinting errors are particularly consequential because they bypass the genome-wide epigenetic reprogramming events that typically reset the epigenome during early embryogenesis, ensuring that these obesity-related epimutations persist.

Mechanistic Gaps: How Do Marks Escape Reprogramming?

Despite compelling findings, the mechanisms by which epigenetic marks escape the two major waves of reprogramming in mammals remain poorly understood:

i. Germline Reprogramming: During gametogenesis, most DNA methylation marks are erased to reset developmental potential. However, some imprinted regions and transposable element–associated loci resist erasure.[185] How diet- or toxin-induced epimutations persist at non-imprinted loci (eg, metabolic genes) is unclear.
ii. Early Embryonic Reprogramming: After fertilization, the zygote undergoes a second round of genome-wide demethylation, followed by de novo methylation. Certain regions, such as repetitive elements and imprinted loci, retain partial methylation.[186] It remains uncertain how environmental exposures introduce "protected" epimutations that can evade this process.
iii. Histone Modifications and Retained Nucleosomes: In sperm, most histones are replaced by protamines during maturation, but a small fraction of nucleosomes are retained at developmental genes. Animal studies suggest that exposure-induced histone modifications at these sites may be inherited, but direct evidence in humans is lacking.[187]
iv. Small Noncoding RNAs: Germline transmission of altered microRNAs and tRNA fragments has been implicated in rodent models of diet- and toxin-induced obesity, but whether these molecules persist long enough to influence human embryogenesis is debated.[188]

These unresolved mechanisms highlight a major knowledge gap: while rodent studies demonstrate plausible escape routes, the molecular basis for true transgenerational inheritance in humans remains speculative.

Evidence from Rodent and Human Cohorts

Rodent models provide robust mechanistic evidence, while human famine and exposure cohorts demonstrate transgenerational effects in real-world populations. These findings highlight the urgent need for preventive maternal interventions, not only to protect immediate offspring but also to break cycles of obesity inheritance spanning generations.

Rodent Models

Numerous studies confirm true transgenerational inheritance, with obesity phenotypes persisting into the F3 generation despite the absence of continued exposure. These models provide compelling proof-of-principle for germline transmission of epimutations.

i. Maternal High-Fat Diets: Multiple studies show that offspring of high-fat-fed animals exhibit obesity and insulin resistance, which persist into F2 and F3 generations despite return to a normal diet. These phenotypes are associated with persistent methylation changes at PPARγ and leptin signaling genes in sperm and oocytes.[23,189,190]
ii. Toxicant Models: Prenatal exposure to a mixture of BPA and phthalates induces transgenerational obesity in rodents, with F3-generation animals displaying increased adiposity and associated sperm DNA methylation epimutations, implicating germline epigenetic alterations.[171] Additionally, multiple reviews summarize that epigenetic mechanisms, including DNA methylation and histone modifications, underlie the transgenerational inheritance of obesogenic effects following early-life exposure to EDCs like BPA.[59] In contrast, while chronic arsenic exposure has been shown to drive transgenerational genotoxicity and global DNA methylation changes into the F3 generation (eg, in rat models), true evidence for F3-generation obesity via hepatic or adipose-specific epigenomic alterations remains to be demonstrated.[191,192]

Human Evidence

Human evidence is more controversial. Historical famine studies (Dutch Hunger Winter, Chinese Famine) show persistent DNA methylation differences at metabolic loci such as *IGF2* in exposed individuals, with some reports suggesting effects in grandchildren. Studies have also identified methylation differences in other metabolic gene loci such as IL10, INSIGF, LEP,

ABCA1, MEG3, and GNASAS in individuals exposed to the Dutch famine.[41,193] The Överkalix cohort linked paternal prepubertal nutrition to altered health outcomes in grandchildren, suggesting possible germline-mediated effects.[194] However, these findings remain associative rather than causal and are subject to major methodological challenges, including small sample sizes, confounding by shared environments, and the inability to disentangle multigenerational exposure (F0, F1, F2) from true transgenerational inheritance (effects in F3 and beyond without direct exposure).

Together, rodent and human evidence underscore that maternal nutrition and toxicant exposures can leave epigenetic "scars" in germline cells, perpetuating obesity risk across generations even in the absence of direct exposure.

Ongoing Controversy and Research Needs

The notion of transgenerational inheritance in humans remains highly debated. Some researchers argue that persistent multigenerational effects may reflect shared social, cultural, and nutritional environments rather than stable germline epimutations. Others point to limited but intriguing evidence from famine and epidemiological cohorts as suggestive of transgenerational epigenetic memory. There is therefore need for cautious framing: while rodent data support causality, human evidence should be described as preliminary, associative, and not yet definitive.

Future research will require large, multi-generational cohorts with detailed exposure, genetic, and epigenetic data, coupled with advanced statistical models that can disentangle shared environment from true inheritance. Until then, the idea of transgenerational epigenetic inheritance in humans should be regarded as a promising but unproven hypothesis.

Sex-Specific Epigenetic Vulnerability

One of the most intriguing and underexplored aspects of developmental programming of obesity is the sex-specific nature of epigenetic responses to maternal nutrition and toxicant exposures. Male and female offspring often exhibit divergent metabolic trajectories following identical in utero exposures, reflecting differences in placental function, sex hormone signaling, and chromatin dynamics. These differences are not merely quantitative but involve qualitatively distinct epigenetic reprogramming events, suggesting that sex-specific epigenetic vulnerability is a critical determinant of obesity risk.

Male vs Female Offspring Differences in Metabolic Programming

Epidemiological and experimental studies consistently demonstrate that males are often more vulnerable to maternal overnutrition, while females may show heightened sensitivity to maternal undernutrition or toxicant exposures.

Earlier findings indicate that maternal high-fat feeding throughout pregnancy and lactation predisposes offspring to molecular insulin resistance and fatty liver in mouse models.[195] Male offspring exposed to maternal high-fat diets tend to develop greater adiposity, insulin resistance, and fatty liver compared to female offspring. A 2025 study demonstrated that male offspring of high-fat diet–fed dams exhibited greater weight gain, increased adiposity, and impaired glucose homeostasis compared to female offspring, along with elevated serum insulin, leptin, and cholesterol levels.[196] Mechanistically, males exhibit greater DNA hypomethylation at certain liver metabolic gene promoters (for example, *Cytochrome P450 2d9*), which may contribute to diminished mitochondrial oxidative capabilities.[197] Females, by contrast, often maintain metabolic resilience, in part due to activation of oxidative pathways by ERRα, a key regulator of mitochondrial biogenesis and fatty acid metabolism.[198]

Christians et al[199] conducted a systematic review and meta-analysis on prenatal food or protein restriction in rats and mice, looking specifically for sex-dependent effects in offspring physiology. They concluded that majority of studies found no consistent sex-dependent effects.

Rodent offspring exposed to maternal high-fat diet (HFD) often show altered epigenetic regulation in appetite- and metabolism-related genes (like leptin receptor, POMC, NPY, dopamine/opioid genes) in the hypothalamus, which can affect appetite and energy balance.[200] In male offspring, maternal HFD has been shown to induce epigenetic modifications in adipose tissue, such as hypomethylation of adipogenic regulators (such as Zfp423) and alterations in PPARγ promoter methylation, contributing to enhanced adipogenesis in offspring.[201]

Prenatal exposure to endocrine disruptors such as BPA and phthalates often yields sex-specific outcomes: male offspring exhibit pronounced weight gain, while female offspring experience more subtle but enduring alterations in adiposity and inflammatory profiles.[202,203] These differences reflect sex-dependent chromatin remodeling at estrogen

receptor (ER) and androgen receptor (AR) response elements. Together, these findings emphasize that sex is a biological variable in DOHaD research and must be integrated into epigenetic models of obesity risk.

Human cohort evidence adds important nuance:

i. ALSPAC (UK): In ALSPAC, prenatal maternal diets high in fat and sugar were associated with lower IGF2 methylation in male offspring cord blood; this association has been linked to behavioral outcomes, though links to childhood BMI trajectories remain unexplored.[204] An epigenome-wide study (NEST), with attempted replication in ALSPAC, identified sex-specific differential DNA methylation associated with maternal pre-pregnancy obesity, which was further linked to offspring BMI and blood pressure in early childhood.[205]
ii. Generation R (Netherlands): In the Generation R Study, continued maternal smoking during pregnancy was associated with lower IGF2DMR methylation in newborns, an effect that was more pronounced in girls ($\beta = -1.38$) than in boys ($\beta = -0.72$).[206] Prenatal cadmium exposure has been shown in population studies to produce sex-specific DNA methylation changes, female-predominant hypomethylation and male-predominant hypermethylation.[207]
iii. CHAMACOS (USA): Prenatal exposure to certain phthalates and parabens was associated with increased BMI z-score and overweight/obesity status in children at age 5.[155] In another study, prenatal phthalate exposure was linked to higher adiposity in boys at age 12, mediated by altered methylation at adipogenic genes, while girls showed weaker associations.[153]
iv. Project Viva (USA): In some pregnancy cohorts, sex-stratified analyses suggest that maternal dietary sugar intake may differentially influence offspring epigenetic marks at insulin signaling loci (IRS1), with stronger effects observed in boys than girls.[23] Recent human studies corroborate this result. For instance, ex-differentiated DNA methylation patterns in the placenta have also been observed, including male-biased hypermethylation at the ZNF300 locus in first-trimester placenta,[23] and widespread sex-dependent methylation regulation across the autosomal genome.[208]
v. HELIX Consortium (Europe): In the HELIX Consortium, a multi-cohort EWAS meta-analysis found that prenatal NO_2 exposure was associated with DNA methylation at loci related to mitochondrial metabolism (including *LONP1, HIBADH, SLC25A28*).[209] A related multi-cohort analysis of placentas reported sex-specific DNAm responses to prenatal air-pollution exposure, with several associations stronger in female placentas.[210] Another study identified significant sex-specific DNA methylation differences in first-trimester human placentas, notably at the transcription factor ZNF300: hypermethylated in males, with correspondingly lower expression.[23]

These findings align with rodent studies, showing that males often exhibit greater epigenetic susceptibility to obesogenic diets, while females may display heightened vulnerability to toxicants and stress-related exposures.

Epigenetic Regulation of Sex Hormone Receptors and Adiposity

Sex-specific epigenetic vulnerability arises in part from differential regulation of sex hormone receptors and downstream adipogenic networks.

In females, estrogen receptor α (ERα) promotes lipid oxidation and insulin sensitivity. Dudley et al[211] found that maternal high-fat nutrition led to increased methylation of the ERα-1b promoter and reduced ERα expression in the medial preoptic area of female rat offspring. Maternal high-fat diet induces epigenetic changes in metabolic genes (eg, PGC-1α promoter methylation in skeletal muscle, MEF2A promoter hypermethylation in liver), thereby diminishing estrogen's protective metabolic effects.[212] ER-regulated microRNAs are also epigenetically altered in maternal obesogenic environments, modulating adipocyte differentiation.[213]

In males, androgen receptor (AR) signaling is tightly linked to visceral adiposity and hepatic lipid metabolism.[214] Sol et al[23] in their Generation R data showed that maternal exposure to endocrine disruptors such as BPA or phthalates may lead to epigenetic changes (especially DNA methylation).[23] Mechanistic studies indicate that maternal exposure to endocrine disruptors such as bisphenols or phthalates can perturb AR signaling by altering AR–coregulator interactions, and because AR-driven

transcription requires p300/CBP-mediated histone acetylation at AR-binding sites, such disruptions are expected to modify local chromatin acetylation and downstream gene expression at androgen-responsive loci.[215,216]

Research has shown that obesity in male rats results in altered methylation of epididymal sperm, with differentially methylated regions identified between high-fat diet–fed rats and controls, suggesting potential involvement in obesity transmission across generations.[217] Another rodent model highlighted diet-induced alterations in sperm methylome linked to paternal obesity, implicating epigenetic inheritance in offspring's metabolic health.[218] In rats with diet-induced obesity, hypermethylation of the pro-opiomelanocortin (Pomc) gene promoter was observed in sperm and in the hypothalamic arcuate nucleus of their offspring. This epigenetic change correlated with metabolic dysregulation and supports the concept of paternal epigenetic influence on obesity predisposition.[219]

Although related to environmental toxins rather than obesity, arsenic exposure during gestation in mice induced hypomethylation in F1 sperm, particularly at retrotransposon elements (LINEs and LTRs). These methylation features were seen to re-establish in F2 embryos, suggesting a mechanism for intergenerational epigenetic transmission of disease risk including obesity.[220]

Importantly, there is sex chromosome–linked epigenetic regulation. Differences in X-chromosome inactivation in females vs Y-linked gene expression in males introduce additional layers of epigenetic complexity.[221] For example, a recent study by Lin et al[222] demonstrates that KDM6A escapes X-chromosome inactivation, enabling female-biased expression of a histone-demethylase that actively regulates Xist via H3K27 demethylation, promoting effective X–inactivation and potentially endowing females with enhanced chromatin-remodeling adaptability. In sum, histone-demethylase activity confers female-specific flexibility in chromatin remodeling, potentially explaining resilience to certain obesogenic exposures.[222]

These mechanisms highlight that sex hormone receptor epigenetics acts as a molecular switchboard, modulating how male and female offspring translate maternal exposures into metabolic outcomes. Recognition of these sex-dependent epigenetic landscapes is essential for developing precision maternal interventions and for ensuring that obesity prevention strategies are tailored to both male and female offspring.

Future Directions: Toward Sex-Stratified Interventions and Clinical Monitoring

Recognizing sex-specific vulnerability opens new avenues for precision prevention:

i. Sex-Stratified Interventions: Nutritional supplementation interventions could be tailored by sex. For example, ensuring adequate methyl donor and antioxidant intake in pregnancies with male fetuses to buffer obesogenic diet exposures, while prioritizing protein sufficiency and stress-reducing nutrients (like omega-3s) in pregnancies with female fetuses more sensitive to undernutrition and toxicants.[223,224] For environmental risk reduction, regulatory policies and clinical guidance may need to account for sex differences, targeting higher-risk exposures (for instance, endocrine disruptors for boys, heavy metals for girls).
ii. Clinical Monitoring: Development of sex-specific cord blood or placental epigenetic biomarkers stratified could allow early identification of high-risk infants. Again, pediatric follow-up programs may benefit from sex-specific cutoffs and trajectories, recognizing that male and female children exhibit distinct metabolic responses to early-life exposures. Because placental adaptations differ between male and female fetuses, placental epigenetic profiling could inform personalized monitoring strategies during pregnancy.[225]
iii. Research Priorities: There is need to expand sex-stratified analyses in ongoing birth cohorts (ALSPAC, Generation R, HELIX) to validate findings across populations. Furthermore, intervention trials that evaluate whether nutritional or exposure-reduction strategies have differential effects in male vs female offspring is necessary. Incorporating sex as a biological variable in epigenome-wide association studies (EWAS) and multi-omics research to avoid obscuring critical differences is essential.

Clinical and Translational Perspectives

The convergence of maternal nutrition, toxic exposures, and epigenetic programming in shaping obesity risk provides not only mechanistic insight but also translational opportunities. Advances in biomarker discovery, nutritional interventions,

and exposure-reduction interventions offer realistic near-term opportunities for improving maternal–fetal health, whereas genome- and epigenome-editing technologies are still confined to experimental models offering new avenues for prediction, prevention, and precision healthcare. Integrating these strategies into maternal and public health frameworks has the potential (if supported by robust interventional evidence) to substantially reduce the intergenerational burden of obesity and metabolic disease. Yet, enthusiasm must be tempered by recognition that current evidence is largely observational, effect sizes are modest, and major ethical, safety, and implementation challenges remain. To balance enthusiasm with critical realism, Table 4 contrasts the promises of epigenetic translation in maternal–fetal health with the key pitfalls and challenges that must be addressed before clinical implementation.

As summarized in Table 4, epigenetic translation offers powerful opportunities for improving maternal–fetal health, yet significant barriers remain. Biomarkers show potential for early risk prediction but face reproducibility and cost challenges. Nutritional interventions are safe and scalable but require sex- and context-specific tailoring, especially in low-resource settings. Policy-driven toxicant reduction has proven effectiveness in high-income countries, yet enforcement gaps leave LMIC populations disproportionately exposed. Epigenome editing represents an exciting frontier, but unresolved safety, ethical, and equity concerns currently preclude clinical use. Addressing these barriers will be critical to move from promising proof-of-concept to equitable and effective implementation in public health and clinical practice.

Epigenetic Biomarkers of Maternal Exposures

Epigenetic modifications serve as molecular archives of intrauterine exposures, making them powerful biomarkers for predicting metabolic risk. The development of epigenetic biomarker panels combining cord blood, placental marks, and circulating ncRNAs could enable stratification of pregnancies at high risk for programming obesity. While promising, these biomarkers require validation across larger and more diverse cohorts before clinical adoption.

Table 4 Promise vs Pitfalls of Epigenetic Translation in Maternal–Fetal Health

Domain	Promise (Opportunities)	Pitfalls (Challenges & Limitations)
Epigenetic Biomarkers	• Cord blood methylation and placental marks as early predictors of obesity risk • Circulating ncRNAs as minimally invasive biomarkers • Potential for risk stratification in prenatal care	• Poor reproducibility across cohorts/tissues • Limited predictive power for complex traits • High cost of multi-omics assays • Ethical concerns (stigmatization, misuse of risk data)
Precision Maternal Nutrition	• Methyl donor and antioxidant supplementation buffers epigenetic disruption • Omega-3 fatty acids and bioactives modulate inflammatory gene expression • Nutritional interventions are low-risk and scalable	• Heterogeneity of response (sex, population differences) • Limited evidence from long-term RCTs • Structural barriers in LMICs (food insecurity, regulation gaps)
Toxicant Reduction Policies	• Phasing out obesogenic chemicals (BPA, phthalates, pesticides) reduces exposure burden • Integration of environmental monitoring in antenatal care • Synergy when combined with nutritional strategies	• Weak enforcement in many LMICs • Persistent legacy pollutants with long half-lives • Difficulty translating population-level policy into individual-level benefit
Epigenome Editing	• CRISPR/dCas9-based editing shows proof-of-concept for reversing epimutations • Potential to restore metabolic flexibility in developmental windows • Opens frontier for preventive medicine	• Safety concerns: off-target effects, unintended chromatin changes • Profound ethical debates (germline editing, consent, enhancement vs therapy) • High cost and inequitable access, likely widening global health disparities

i. Cord Blood DNA Methylation: Differential methylation at loci such as LEP, IGF2, and *PPARγ* in cord blood has been associated with maternal high-fat diet, undernutrition, and exposure to BPA and phthalates. Differential methylation at loci such as *IGF2* (hypomethylated following prenatal undernutrition during the Dutch Hunger Winter), *LEP* (induced by maternal high-fat diet in animal models and associated with methylation changes in human cord blood in the context of maternal obesity), and *PPARγ* (epigenetically altered by maternal protein restriction in animal studies) has been linked to maternal nutrition.[226,227] Similarly, exposure to environmental endocrine disruptors like BPA and phthalates during gestation has been associated with DNA methylation changes observed in cord blood.[23,228] Epigenome-wide association studies (EWAS) have revealed methylation signatures that correlate with childhood BMI, suggesting cord blood methylation can function as an early-warning system for obesity risk.[229]
ii. Placental Epigenome: The placenta is highly sensitive to maternal environment and acts as a critical interface between mother and fetus. Altered methylation at genes involved in nutrient transport, stress responses (NR3C1), and growth regulation (IGF2) reflects both maternal nutritional and toxicant exposures.[230] A review by Green and Marsit[231] discusses how maternal environmental exposures including both nutritional factors (eg, diet) and toxicants (including heavy metals, endocrine disruptors, smoking) are linked to alterations in gene-specific DNA methylation in fetal tissues. It emphasizes that such epigenetic programming may involve key pathways including nutrient transport, stress response, and growth regulation—highlighting genes like IGF2, NR3C1, and others.[231] Placental histone modifications and imprinted gene regulation further predict offspring adiposity, making placental epigenomics a promising diagnostic tool. Placental epigenomic signatures, particularly DNA methylation at specific CpG sites, predict childhood adiposity, suggesting that placental epigenomics is a promising tool for early diagnostic applications.[232] Placental histone modifications and imprinted gene regulation also play critical roles in fetal development, underpinning the mechanistic foundation for this predictive potential.[233]
iii. Circulating Noncoding RNAs: MicroRNAs (miRNAs) such as miR-21, miR-29, and miR-148a in maternal plasma have been linked to gestational obesity, insulin resistance, and pollutant exposures. Circulating miRNAs including miR-21 and the miR-29 family are altered in the context of maternal metabolic dysregulation such as obesity and insulin resistance.[234,235] Additionally, miR-148a-3p has been found to be downregulated in plasma exosomes of women with gestational diabetes mellitus (GDM), linking it to impaired metabolic regulation during pregnancy.[236] In parallel, miRNAs such as miR-21 have been shown to respond to environmental pollutant exposures, especially air pollution, acting as epigenetic markers of maternal environmental quality.[237] These circulating miRNAs can traffic across the placenta, impact fetal gene expression (as suggested by their presence in fetal and placental tissues and exosomal transfer), and serve as minimally invasive biomarkers that reflect the maternal–fetal environment.

Challenges

i. Validation: Epigenetic signatures often lack reproducibility across cohorts and populations due to differences in tissue specificity, measurement techniques, and confounding exposures.
ii. Predictive value: Many signals explain only a small proportion of obesity variance, limiting their utility as standalone diagnostic tools.
iii. Feasibility and cost: Multi-omics profiling (EWAS, ncRNA panels) is expensive and not yet feasible for routine clinical screening, particularly in low-resource settings where the dual burden of malnutrition and toxicants is greatest.
iv. Ethical considerations: The potential use of biomarkers for prenatal risk stratification raises concerns about stigmatization, insurance discrimination, and how to manage high-risk pregnancies when effective interventions remain limited.

Intervention Strategies

Precision Maternal Nutrition

Methyl donor supplementation (folate, choline, B_{12}, methionine) supports one-carbon metabolism and stabilizes DNA methylation patterns during fetal development, reducing the risk of obesogen-induced epimutations. In the Southampton

Women's Survey, poorer maternal and early childhood diet quality across preconception to childhood was associated with higher offspring adiposity at age 6, measured by DXA-assessed fat mass and BMI z-score.[238] Periconceptional folic acid exposure and maternal one-carbon status have been linked to altered IGF2 methylation at birth,[239] and imbalance of maternal folate and vitamin B_{12} during pregnancy (high folate with low B_{12}) has been associated with greater childhood adiposity and insulin resistance in the Pune cohort.[240] Similarly, supplementation trials in the Pune Rural Intervention in Young Adolescents (PRIYA) study showed that maternal vitamin B_{12} supplementation during pregnancy improved offspring insulin sensitivity and reduced adiposity at 6 years.[241]

Randomized trials in Bangladesh show that folic acid supplementation enhances arsenic methylation and lowers blood arsenic.[242] Another Bangladeshi birth-cohort data link prenatal arsenic exposure to altered global DNA methylation in cord blood.[243] A recent systematic review and meta-analysis reports that folic acid fortification is projected to be the most effective strategy to ameliorate arsenic exposure and neural tube defects (NTDs) risk in Bangladesh, where arsenic exposures are high.[244] Together, these studies illustrate protective nutrient–toxicant antagonism.

The Supplementation with Multiple Micronutrients Intervention Trials (SUMMIT, Indonesia) found that maternal multiple micronutrient supplementation improved infant survival and growth outcomes, with follow-up studies suggesting epigenetic effects on growth-regulatory pathways.[245,246] Zinc and selenium supplementation studies, though limited, suggest potential benefits for stabilizing DNA methylation and reducing oxidative stress–related epimutations.[247,248]

More so, antioxidants (vitamin C, vitamin E, polyphenols) neutralize toxicant-induced ROS, preventing oxidative activation of histone-modifying enzymes. For instance, resveratrol activates SIRT1, counteracting obesogen-driven chromatin activation.[249] Furthermore, bioactive supplementation (omega-3 fatty acids, sulforaphane, EGCG) modulate histone acetylation and DNA methylation in metabolic pathways, buffering the fetal epigenome against obesogenic programming.[250] The ROLO trial (Ireland) reported that maternal low-glycemic diets during pregnancy reduced offspring birth weight and cord blood insulin resistance markers, with preliminary evidence of DNA methylation changes in metabolic genes.[251–253]

In the European Nutraceuticals for a Healthier Life (NUHEAL) trial, pregnant women received long-term effects of n-3 (omega-3) LC-PUFA and/or 5-methyltetrahydrofolate report no consistent cognitive benefit, but maternal dietary status may be related to later cognitive function in children.[254] However, a follow up study reports that maternal fish oil supplementation during pregnancy could shape resting-state network functioning in their offspring at school age, thus producing long-term effects on children´s cognitive processing.[255] Separately, a randomized trial of third-trimester choline supplementation altered methylation of CRH/NR3C1 in placenta and cord and improved early information-processing in infants.[256] Another double-blind randomized controlled trial at Oslo University Hospital reports that supplementation of arachidonic acid and docosahexaenoic acid has the potential to improve brain maturation and reduce inflammation related diseases in infants.[257] These interventions underscore the potential for targeted maternal dietary strategies to mitigate epigenetic disruptions.

Reducing Toxicant Exposure During Pregnancy

Phasing out obesogenic chemicals such as BPA and certain phthalates from food packaging; stricter regulation of pesticide residues and heavy metals in food and water are correct policy measures. Public health interventions such as education programs promoting safer food storage practices, avoidance of contaminated water sources, and use of toxin-free cosmetics and household products are critical. Incorporating environmental exposure assessments into prenatal care, enabling early risk identification and intervention, are good clinical integration approaches.

Together, precision nutrition and toxicant reduction represent complementary strategies to reshape the maternal exposome toward healthier developmental outcomes.

Challenges

i. Heterogeneity of response: Nutritional interventions may have sex-specific or population-specific effects, requiring stratified recommendations rather than one-size-fits-all guidelines.
ii. Implementation barriers: In many LMICs, structural issues such as food insecurity and weak regulatory oversight limit the impact of individual-level interventions.

iii. Long-term follow-up: Few trials have tracked whether maternal dietary interventions translate into reduced obesity risk in offspring, making clinical translation premature.

Practical Implications for Clinical Care and Public Health

From a clinical perspective, one of the closely actionable indicators evolving from this study relate to established maternal-health priorities rather than novel strategies. Recent evidence consistently supports optimizing preconception and antenatal nutrition (via sufficient micronutrients intake, evading of extreme energy restriction or highly obesogenic diets), managing maternal BMI and gestational weight gain within guideline ranges, and reducing avoidable exposure to known obesogens (such as tobacco smoke, excessive air pollution, some job-related chemicals) using existing public-health and regulatory frameworks. These recommendations are already endorsed for other maternal–fetal outcomes; the epigenetic and DOHaD data reviewed here mainly strengthen the rationale and help refine sensitive windows and potentially vulnerable subgroups. In contrast, more speculative applications like epigenetic biomarker panels for routine risk prediction or targeted epigenome-modifying interventions remain at a preclinical or proof-of-concept stage and should not yet inform decision-making in clinical setting. Thus, the evidence is promising but unproven, and the experimental strategies may help clinicians, policymakers, and patients navigate the growing but heterogeneous epigenetic literature.

Future of Epigenome Editing and Preventive Medicine

Looking forward, epigenome editing tools and maternal epigenetic counseling hold promise for personalized preventive medicine. Together, these innovations establish the foundation for a translational epigenetic framework to combat intergenerational obesity.

CRISPR/dCas9-Based Epigenome Editing

Emerging technologies such as CRISPR/dCas9 fused to epigenetic modifiers (including DNMT3A, TET1, histone acetyltransferases) allow targeted editing of DNA methylation and histone states without altering DNA sequence. These tools are being applied in experimental DOHaD models to reverse obesogen-induced epimutations.[258] For example, targeted demethylation of PPARα in animal models restored metabolic flexibility, suggesting a potential therapeutic role in correcting developmental epimutations.[259] Although not yet clinically feasible, this approach represents a proof-of-principle concept that some developmental epimutations are reversible in animal models, but it remains unknown whether similar approaches will be safe, effective, or acceptable in humans.

Maternal Epigenetic Counseling

Epigenetic biomarker screening has been proposed as a route to more personalized risk assessment for pregnant women. By integrating dietary intake, toxicant exposure profiles, and epigenetic readouts (cord blood methylation, placental marks, circulating ncRNAs), clinicians could provide epigenetic counseling tailored recommendations for nutrition, lifestyle, and environmental exposure management to optimize fetal metabolic programming.[260] Such approaches would represent a paradigm shift from treating obesity to preventing it before birth, transforming prenatal care into a cornerstone of metabolic disease prevention. At present, however, such approaches remain speculative as limited trials have demonstrated that epigenetic risk stratification and counselling improve obesity outcomes. Moreover, substantial ethical, logistical, and equity concerns would need to be resolved before clinical implementation.

Challenges

i. Safety and off-target effects: Epigenome editing is still in its infancy, with significant risk of unintended chromatin changes that could have unpredictable developmental effects.
ii. Ethical concerns: Editing the fetal or germline epigenome raises profound ethical questions about consent, intergenerational consequences, and the boundary between therapy and enhancement.
iii. Equity and cost: Cutting-edge technologies are likely to be prohibitively expensive and available only in high-income settings, risking further widening of global health inequities.

AI and Multi-Omics Approaches to Obesity Risk Prediction

Advances in data science are promising in the translation of DOHaD concepts into predictive tools. Recent reviews and proof-of-concept studies show that machine-learning models can leverage routinely collected clinical information and environmental data to predict pediatric obesity risk with higher accuracy than traditional regression alone, and some groups have developed interoperable pipelines designed for integration with electronic health records.[261,262] In the multi-omics space, integrative frameworks combining genomics, epigenomics, metabolomics, and microbiomics have identified multi-omics clusters that stratify children into distinct adiposity and metabolic risk profiles and link these to specific prenatal exposures such as maternal BMI and persistent pollutants.[263] While these AI-driven, multi-omics risk models may not be yet ready for routine prenatal or pediatric use, they provide cues for how maternal nutrition and toxicant data could eventually be integrated into personalized early-life risk stratification.

Unresolved Debates in Epigenetic Interpretation

Despite rapid progress, several fundamental debates complicate the interpretation of epigenetic data in the context of maternal nutrition, toxicants, and obesity. The first question is whether observed epigenetic changes are causal mediators of disease or primarily biomarkers of underlying exposures and physiological states. Most human epigenome–phenotype associations arise from observational cohort studies that are vulnerable to confounding, reverse causation, cell-type heterogeneity, and technical artefacts. While experimental animal work and in vitro models support the plausibility of causal pathways, in humans epigenetic marks are better regarded as mechanistic candidates and exposure–response indicators rather than established drivers of obesity risk, awaiting stronger evidence from longitudinal designs, and causal inference frameworks. Results from PACE, HELIX, Raine, ECHO and related consortia highlight both the promise and the limitations of current exposome and omics science. Many reported associations between early-life exposures, epigenetic marks, obesity or adiposity are statistically robust at the consortium level yet modest in magnitude, sensitive to analytic decisions (eg, cell-type adjustment, multiple-testing control, mixture modelling strategy), and sometimes heterogeneous across cohorts, tissues and developmental windows.[100,102–104] These patterns fuel debate about how strongly such results should be interpreted as causal, which epigenetic or multi-omics markers will ultimately prove reproducible and clinically relevant, and how best to balance discovery-oriented exposome scans with hypothesis-driven mechanistic work.

The second debate relates to how reversible developmentally induced epimutations are, and over what time windows. Many experimental models signify that some marks established during sensitive periods can be diminished or relayed by enhancing maternal diet, normalizing postnatal nutrition, or modifying obesogenic environments, whereas others show relative stability once key developmental programs are set.[264–266] Human trials are still scarce and often limited to a few tissues and time points. Moreover, it is unclear which obesity-related epigenetic changes are truly “hard wired”, which are conditionally plastic, and to what extent postnatal interventions can compensate for suboptimal intrauterine environments. This uncertainty cautions against both overly deterministic narratives and overly optimistic assumptions about complete reversibility.

Another debate comprises the difference between intergenerational and transgenerational inheritance. In mammalian systems, in utero exposure of a pregnant female (F0) directly affects not only the fetus (F1) but also the developing germ cells within that fetus (F2). Accordingly, phenotypes observed in F1 and F2 generations may mirror direct exposure rather than true transmission of epigenetic information through the germline.[267] Conventionally, evidence for transgenerational inheritance via epigenetic mechanisms would require effects in the F3 generation (for maternal exposures) or the F2 generation (for paternal preconception exposures), after excluding persistent environmental and social transmission. In humans, long generation times, pervasive confounding across generations, and extensive epigenetic reprogramming during gametogenesis and early embryogenesis make such demonstrations extremely challenging.[268] As a result, claims of robust transgenerational epigenetic inheritance of obesity in humans should be viewed as intriguing but provisional. Thus, our review focuses primarily on intergenerational effects that are biologically plausible and empirically supported.

Conclusions and Future Directions

Key Insights

Maternal nutrition and environmental toxicant exposures act, both independently and in combination, as epigenetic architects of obesity risk across the life course. Mechanisms include: DNA methylation, histone modifications, and noncoding RNAs. These processes link maternal macronutrient and micronutrient status, one-carbon metabolism, and obesogenic diets to persistent changes in gene networks controlling adipogenesis, insulin signalling, appetite regulation and energy expenditure. Obesogenic toxicants, including endocrine disruptors, heavy metals, food-borne and agricultural contaminants, appear to converge on overlapping pathways, sometimes amplifying the effects of nutritional imbalance. The evidence reviewed here highlights how nutrient excesses, deficiencies, and environmental pollutants converge on the fetal epigenome to establish enduring "metabolic memories" that predispose offspring to obesity and related disorders. Importantly, these effects are not confined to the immediate generation but may propagate across lineages, raising intergenerational stakes for maternal health. Recent studies demonstrate that non-canonical mechanisms such histone lactylation, chromatin accessibility, and 3D genome architecture, as well as placental multi-omics, give the placenta an important location for turning nutritional and toxicant signals into foetal epigenomic states. Nonetheless, results from extensive consortia and exposome-wide studies indicate that effect sizes are typically modest, heterogeneous, and contingent upon context. This suggests that epigenetic marks ought to be regarded as potential mechanistic candidates and exposure-response indicators, rather than conclusive causal determinants.

Outstanding Gaps and Conceptual Challenges

While substantial progress has been made, significant knowledge gaps remain. Much of the mechanistic understanding derives from animal studies, whereas human evidence is primarily associative and limited by confounding, single-exposure assessments. Moreover, human evidence is dominated by observational cohorts from high-income settings, with limited representation of low- and middle-income populations that bear a disproportionate dual burden of undernutrition and environmental pollution. Clarifying causality, integrating multi-omics approaches, and embedding sex-specific analyses are necessary next steps. Beyond issues of causality, the epidemiological literature on toxicants and obesity is characterized by substantial heterogeneity. Effect estimates frequently vary by sex, developmental window, and analytic approach, and many studies report wide confidence intervals or null associations despite plausible mechanistic data. Publication bias toward positive findings and under-reporting of null results likely further distort the apparent strength of evidence. Together, these limitations indicate that current toxicant–obesity associations should be interpreted as suggestive rather than definitive and highlight the need for large, harmonized multi-cohort analyses with repeated exposure measures and robust mixture modelling.

Future Research Agenda

To fully maximize maternal nutrition–toxicant–epigenetic interactions translational potential, it is necessary to transition from association to intervention. This involves integrating mechanistic endpoints into pragmatic trials, evaluating scalable nutrition and exposure-reduction strategies across varied contexts, and perpetually reassessing epigenetic and multi-omics signatures for their robustness and clinical significance. Only via this kind of iterative, cross-disciplinary work can epigenetic insights be used in an accountable manner to break, rather than just describe, cycles of metabolic disease that pass from one generation to the next. Future research should focus on:

i. Integrative multi-omics: Combine epigenomics, transcriptomics, metabolomics, microbiomics, and exposomics to improve predictive accuracy and mechanistic understanding.
ii. Biomarker development: Conduct large, multi-ethnic, longitudinal cohorts to validate epigenetic signatures (DNA methylation, ncRNAs, histone marks) as robust predictors of obesity risk.
iii. Sex-specific studies: Incorporate sex as a biological variable in cohort analyses and intervention trials to tailor prevention strategies.

iv. Intervention studies: Test whether targeted nutritional supplementation and exposure reduction strategies can prevent obesogenic epimutations in randomized controlled trials.
v. Transgenerational tracking: Design multi-generational human studies to resolve the controversy around true epigenetic inheritance.
vi. Ethics and equity focus: Establish global guidelines for safe, equitable, and ethical applications of epigenome editing, ensuring benefits are not restricted to high-income settings.

Translational Outlook

Early-life prevention is widely regarded as a critical leverage point for curbing the obesity epidemic. Optimizing maternal nutrition and minimizing toxicant exposure are plausible and increasingly evidence-supported strategies to improve metabolic programming, although definitive proof that they prevent obesity across the life course is still limited. Moving forward, integration of epigenetic risk assessment into prenatal care, coupled with structural policy interventions (nutrient fortification, environmental regulation, public health campaigns), may contribute to interrupting the intergenerational cycle of obesity. This study highlights a set of promising, but yet incompletely validated, opportunities that will require rigorous evaluation in diverse settings. Policymakers, clinicians, and nutrition scientists must converge on strategies grounded in epigenetic evidence to prevent obesity before it takes root in fetal development. By aligning scientific discovery with public health policy and maternal care, it is possible to interrupt the intergenerational cycle of metabolic disease. In doing so, we may redefine obesity prevention, not as an individual lifestyle challenge, but as a societal commitment to safeguarding the epigenetic foundations of health across generations.

Strengths and Limitations of the Current Evidence Base

Although this study converges data from animal models, human cohorts, and emerging multi-omics studies, the overall evidence base still has important limitations that temper clinical translation. Most human findings rely on observational designs with modest effect sizes, limited tissue analysis, and potential residual confounding and reverse causation. Epigenetic modifications linked with maternal nutrition or toxicant exposures may act as causal mediators, but they may also function as correlated biomarkers of underlying physiological states. Results are often heterogeneous across cohorts, developmental windows, and null or contradictory findings are imminent. Large consortia and exposome-wide approaches improve power and generalizability but also highlight issues of multiple testing, mixture modelling, and reproducibility. Recognizing these constraints is important. Currently, epigenetic evidence should be regarded as strengthening the biological plausibility of established maternal-health interventions and generating hypotheses for targeted trials, rather than providing definitive, stand-alone grounds for new screening programmes or advanced therapies.

Data Sharing Statement

All data generated during this study are included in the manuscript.

Author Contributions

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Funding

No funding was received.

Disclosure

The authors declare no competing interests.

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