Review

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Nutriepigenomics in perinatal medicine: maternal nutrition as a modulator of fetal gene expression and long-term health

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Abstract

Introduction: Maternal nutrition during pregnancy can influence fetal development through epigenetic modifications, affecting gene expression without altering DNA sequence. Nutriepigenomics – the study of nutrient-driven epigenetic regulation – provides critical insights into how prenatal nutritional exposures can shape immediate and lifelong health outcomes.

Content: This narrative review synthesizes evidence from human cohort studies and experimental animal models on how macro- and micronutrients, including folate, vitamin B12, choline, vitamin D, omega-3 fatty acids, and bioactive compounds such as polyphenols and resveratrol, modify key epigenetic processes. These include DNA methylation, histone modifications, and non-coding RNA regulation, particularly within the placenta and developing fetal tissues.

Summary: Maternal diet-induced epigenetic changes influence fetal metabolic programming, neurodevelopment, immune maturation, and organogenesis, with impacts detectable at birth and persisting into adulthood. Evidence indicates associations with altered birthweight trajectories, increased risk of childhood obesity and immune dysregulation, and potential elevation in lifelong cardiometabolic and neuropsychiatric disease risk.

Outlook: Integrating nutriepigenomic insights into perinatal care offers opportunities for early preventive strategies and personalized nutrition interventions. Translational application of epigenetic biomarkers, coupled with population-level nutritional policies, could reduce disease risk across generations and improve long-term population health outcomes.

Keywords: nutriepigenomics; maternal nutrition; fetal development; epigenetic programming; perinatal health

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Introduction

Over the past two decades, scientific understanding of how maternal environments shape fetal development has undergone a radical transformation. Central to this shift is the recognition that maternal nutrition can induce stable, heritable changes in gene expression through epigenetic mechanisms – a concept now formalized as nutriepigenomics [1, 2]. This emerging field lies at the intersection of molecular biology, nutritional science, developmental biology, and clinical obstetrics, providing a compelling framework to explain how early dietary exposures can determine long-term health trajectories [3–5].

`The foundational idea that prenatal and early-life conditions influence adult disease risk, initially conceptualized by Barker and colleagues and later supported by epigenetic data,

has evolved from a purely epidemiological theory into a molecularly grounded paradigm [6, 7]. Epigenetic processes such as DNA methylation, histone modification, and non-coding RNA regulation have been identified as key mediators by which environmental factors – particularly nutrients – modulate gene activity without altering the underlying DNA sequence [8, 9]. These epigenetic marks are highly sensitive to intrauterine cues and play essential roles in regulating genes involved in fetal growth, metabolic homeostasis, immune programming, and neurodevelopment [10–12].

The plasticity of the fetal epigenome makes it especially responsive to maternal diet during critical gestational windows. In a seminal animal study, Waterland and Jirtle demonstrated that dietary supplementation with methyl donors during pregnancy caused persistent DNA methylation changes at the Agouti locus, influencing both phenotype and long-term disease susceptibility [3]. Human data echo these findings: periconceptional folate exposure was associated with methylation differences at IGF2 and other imprinted loci in offspring from the Dutch Hunger Winter cohort, confirming that fetal epigenetic marks can endure for decades [4, 5, 13].

Beyond folate, other methyl donors such as choline, methionine, and betaine are increasingly recognized for their roles in maintaining epigenetic stability [14]. Vitamin D, through receptor-mediated genomic interactions, has been shown to influence DNA methylation of genes involved in immune regulation and placental vascular development [6, 15]. Likewise, omega-3 fatty acids have been linked to chromatin remodeling and anti-inflammatory gene expression via histone acetylation pathways [7, 16]. Plant-based polyphenols, including resveratrol and quercetin, epigenetically activate sirtuin pathways (e.g., SIRT1, PGC-1α), which are involved in metabolic regulation, mitochondrial function, and cellular aging [8, 17–19].

Diet-induced changes in microRNAs (miRNAs) have emerged as an additional layer of epigenetic control. Specific maternal dietary patterns during gestation have been shown to regulate the expression of fetal miRNAs involved in immune response, neurogenesis, and metabolic signaling [20]. For example, variations in maternal vitamin D, polyphenol, and fatty acid intake have been associated with altered expression of miR-21, miR-146a, and miR-122 in both animal models and human cord blood studies [9, 18, 20].

Despite the expanding knowledge base, clinical translation of nutriepigenomics remains limited. Most obstetric nutritional guidelines still focus on preventing gross deficiencies rather than optimizing molecular developmental outcomes. There is a pressing need for high-quality, mechanistically informed evidence synthesis to guide the integration of epigenetically active nutrients into routine perinatal care – particularly in the context of population health disparities, developmental programming, and long-term chronic disease risk [2, 11, 19, 21–25].

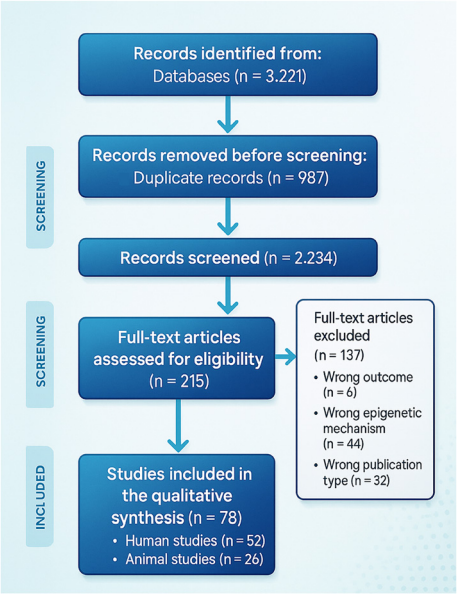

Figure 1: PRISMA flow diagram of study selection process. Studies were categorized based on key epigenetic mechanisms (DNA methylation, histone modification, and non-coding RNAs) and associated nutrient pathways (methyl donors, fatty acids, vitamins, polyphenols, and others).

This review addresses that need by integrating findings across large-scale epidemiological cohorts, randomized nutritional trials, and experimental animal models. It identifies nutrient-sensitive epigenetic mechanisms, highlights modifiable nutritional targets, and proposes translational pathways for clinical and policy application (Figures 1–3, Tables 1–6). It further explores the potential of individualized maternal nutrition strategies to optimize fetal gene expression, not only for immediate pregnancy outcomes but also for lifelong health trajectories.

By positioning maternal diet as a modifiable determinant of fetal gene regulation, this review provides a conceptual and practical foundation for precision-based, preventive strategies in perinatal medicine – anchored in the emerging science of nutriepigenomics.

Methodology

This integrative review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure methodological rigor, transparency, and reproducibility [49]. The objective was to synthesize and critically evaluate existing

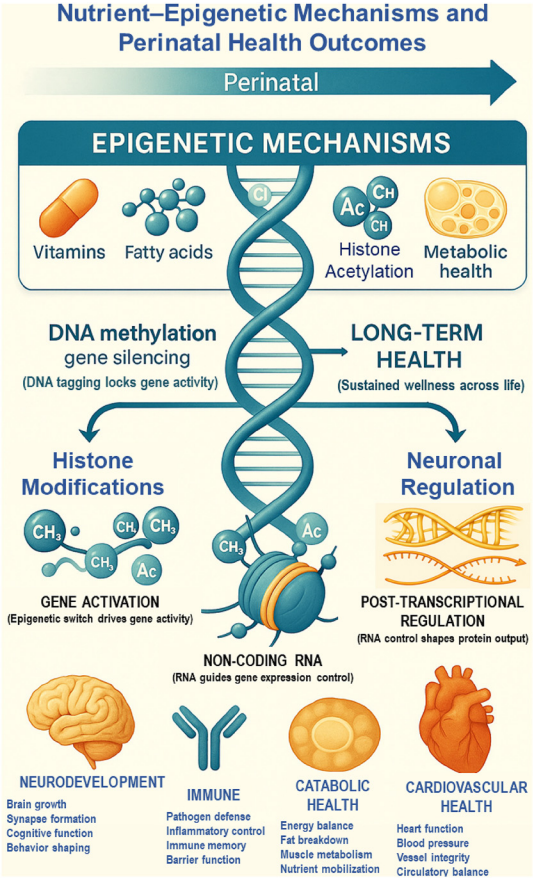

Figure 2: Integrated nutrient–epigenetic mechanisms driving perinatal health outcomes. This figure summarizes how key nutrient classes (e.g., vitamins, fatty acids, and metabolic regulators) influence epigenetic mechanisms during the perinatal period, including DNA methylation, histone acetylation, gene activation, non-coding RNAs, and post-transcriptional regulation. These molecular pathways shape developmental processes and contribute to long-term health outcomes across neurodevelopment, immune function, catabolic balance, and cardiovascular health. The figure integrates molecular and physiological perspectives, providing a concise conceptual framework for nutrient–epigenetic interactions in early-life health programming.

evidence linking maternal dietary intake during pregnancy with epigenetic modifications in the fetus or placenta. To capture both mechanistic and translational perspectives, the review included original studies in humans as well as experimental animal models.

A systematic search was performed across PubMed, EMBASE, and Web of Science for publications between January 1, 2000, and April 30, 2025. Search strategies combined Medical Subject Headings (MeSH) and free-text terms, including “nutriepigenomics,” “maternal diet,” “maternal nutrition,” “fetal epigenetics,” “DNA methylation,” “histone modification,” “non-coding RNA,” and “gene expression in pregnancy.” Boolean operators were applied to optimize sensitivity and specificity. Reference lists of key articles and reviews were screened manually to identify additional eligible studies.

Inclusion criteria were peer-reviewed original research that examined the association between maternal nutritional exposures and at least one epigenetic endpoint (DNA methylation, histone modifications, or microRNA expression) in fetal, placental, or neonatal tissues. Both human observational and interventional studies, as well as mechanistic animal studies, were eligible. Exclusion criteria included studies focused exclusively on paternal or postnatal nutrition, studies without molecular epigenetic endpoints, and **conference abstracts and protocols without original data**. Studies with insufficient methodological detail or a high risk of bias were also excluded.

Two reviewers independently screened titles and abstracts using the Rayyan QCRI platform [50], with full-text evaluation of potentially relevant articles. Discrepancies were resolved by consensus or arbitration by a third reviewer. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

Data were extracted using a standardized template covering study design, population or animal model, type and timing of nutritional exposure, tissue source, epigenetic endpoints, analytical methods, and key findings. Extracted data were organized by nutrient category and epigenetic mechanism, then synthesized into structured summary tables (Table 1 for study characteristics; Tables 2–5 for mechanistic findings; Table 6 for integrated health outcomes). Narrative synthesis was supported by visual schematics (Figures 2 and 3) illustrating nutrient-epigenome-health pathways.

Quality appraisal was performed using validated tools appropriate to study design: the Newcastle-Ottawa Scale for observational studies [51], the Cochrane Risk of Bias two tool for randomized trials, and the SYRCLE Risk of Bias tool for preclinical animal studies [52].

Results and findings

A total of 3,221 records were identified through database searching. After removing duplicates and screening titles and abstracts, 215 full-text articles were assessed for eligibility. Based on predefined inclusion and exclusion criteria, 78 studies were included in the final synthesis, comprising 52 human studies and 26 animal studies (Figure 1). Included studies were grouped by epigenetic mechanism (DNA methylation, histone modification, non-coding RNAs) and nutrient pathway (methyl donors, fatty acids, vitamins, polyphenols, and others). The main characteristics of

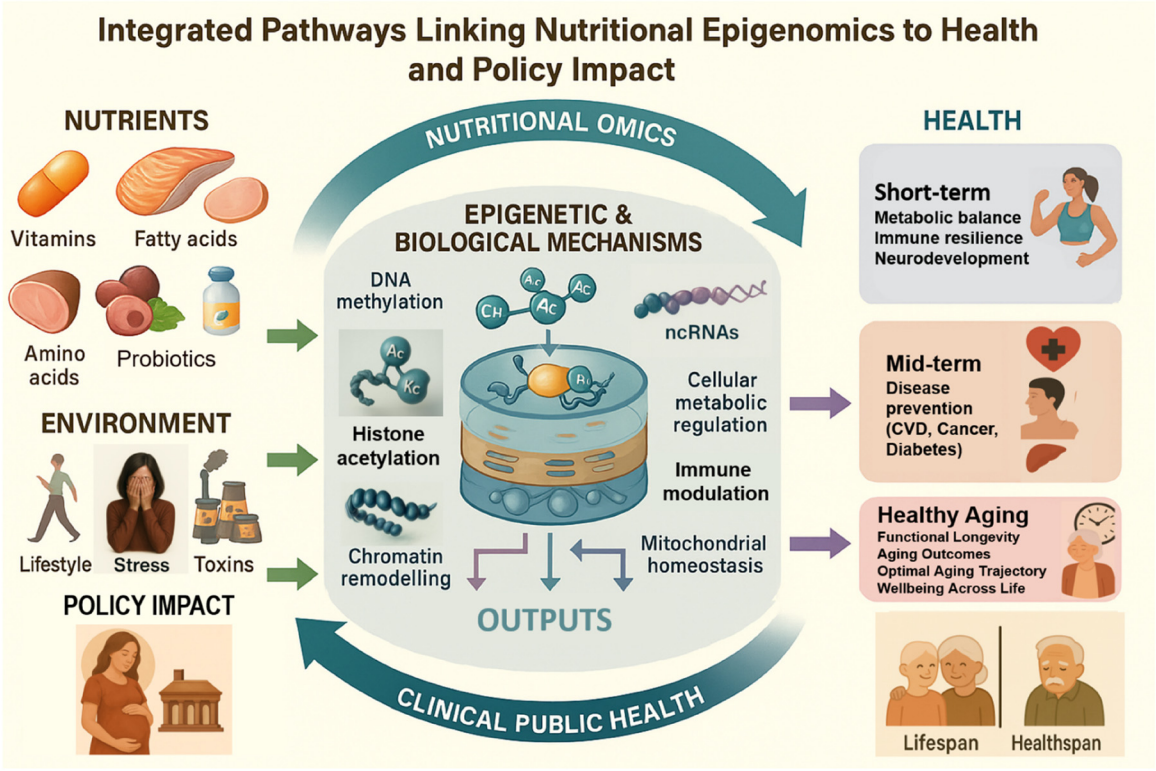

Figure 3: Integrated pathways linking nutritional epigenomics to health outcomes and policy impact. This figure illustrates how nutritional inputs (vitamins, fatty acids, amino acids, probiotics) and environmental factors (lifestyle, stress, toxins), together with policy-driven interventions, converge on epigenetic and biological mechanisms to influence health across life stages. Epigenetic modifications – including DNA methylation, histone acetylation, non-coding RNAs (ncRNAs), and chromatin remodeling – regulate gene expression, cellular metabolic homeostasis, immune modulation, and mitochondrial function. These molecular processes drive health outcomes across different time horizons: Short-term (metabolic balance, immune resilience, neurodevelopment), mid-term (disease prevention for cardiovascular disease, cancer, and diabetes), and long-term healthy aging (functional longevity, optimal aging trajectory, and improved lifespan and healthspan). This integrated systems perspective highlights how translational nutrition science and public health policy can shape population health through molecular mechanisms.

included studies are summarized in Tables 1–6, which distinguish between human and animal evidence and highlight study design, sample type, exposure windows, and main molecular findings. Collectively, these data demonstrate that maternal nutrient exposures influence fetal epigenetic programming and can affect long-term metabolic, neurodevelopmental, cardiovascular, and immune outcomes in offspring (Figures 2 and 3). Findings are described by mechanistic pathway below.

DNA methylation: an epigenetic mediator

DNA methylation was the most frequently investigated mechanism, examined in 56 studies encompassing both human cohorts and experimental animal models (Table 2). Human evidence links maternal methyl donor intake – including folate, choline, betaine, and methionine – to altered methylation of key imprinted genes, metabolic regulators, and growth-related loci [1, 2, 4, 5, 26, 28–30, 32, 33, 35–37, 39, 41–48, 51–80]. The Dutch Hunger Winter cohort demonstrated persistent IGF2 hypomethylation decades after gestational famine exposure, supporting a durable impact of maternal undernutrition on offspring epigenetic marks [4]. In cord blood, periconceptional folate intake correlated with differential methylation of over 400 CpG sites involved in neural development, immunity, and metabolic regulation [5].

Animal models reinforce these findings mechanistically. The Agouti mouse model demonstrated that maternal supplementation with folic acid, vitamin B12, choline, and betaine increased methylation at the Avy locus, resulting in stable phenotypic changes resistant to later environmental modification [3]. Similarly, maternal B12 and folate levels influenced methionine cycle gene expression in fetal liver during early gestation [32], while combined methyl donor supplementation modified methylation at IGF2R and KCNQ1OT1 loci in placental tissue [27]. Timing was critical,

Table 1: Summary of key nutriepigenomic studies on maternal nutrition and epigenetic regulation.

Authors	Nutrient/ exposure	Epigenetic mechanism	Human or animal study	Key insight	Strength	Limitation
Heijmans et al. 2008 [4]	Famine (Dutch hunger winter)	DNA methylation	Human	Persistent hypomethylation at IGF2 gene in adults exposed periconceptionally	Large human cohort, long-term epigenetic follow-up	Retrospective design; difficult to isolate variables
Waterland and Jirtle 2003 [3]	Methyl donors (folate, B12, choline)	DNA methylation	Animal (mouse)	Hypermethylation of avy locus leading to altered coat color and disease risk	Well-controlled animal model; direct intervention	Animal model may not fully translate to humans
Joubert et al. 2012 [5]	Folate and smoking	DNA methylation	Human	Epigenome-wide DNA methylation changes in newborns linked to maternal exposures	Large sample; genome-wide approach	Possible confounders; limited functional validation
Ferrero et al. 2021 [26]	Vitamin D	microRNA expression	Human	miR-21, miR-146a, and miR-155 altered in relation to maternal vitamin D	Human cord blood-based study; relevance to immunity & neurodevelopment	Associative; lacks mechanistic confirmation
Bouwland-both et al. 2015 [7]	Smoking	Histone modification/DNA methylation	Human	Gene-specific epigenetic alterations due to prenatal smoke exposure	Human data; link to fetal growth	Primarily observational; mixed epigenetic effects
Chodur and Steinberg 2024 [20]	Various dietary patterns	microRNAs	Human (review)	Diet alters human miRNA profiles affecting metabolism and immune function	Comprehensive dietary scope	Lack of experimental confirmation
Villagrán-andrade et al. 2024 [21]	Bioactive dietary compounds	Epigenetic regulation	Human (*in vitro* focus)	Phytochemicals modulate osteoarthritis-linked epigenes	Functional diet-epigenetic link	Focused on one disease model
de luca et al. 2017 [23]	Malnutrition	Multiple	Human (review)	Malnutrition linked to altered epigenetic programming & developmental risk	Broad perspective	Heterogeneous measurement tools
Mahajan et al. 2021 [27]	Folate+B12	DNA methylation	Animal (mouse)	Diet influenced IGF2R and KCNQ1OT1 methylation	Controlled mouse study showing parent-of-origin effects	Translation to humans uncertain
Anderson et al. 2018 [6]	Vitamin D	DNA methylation	Human	Maternal supplementation alters methylation in maternal & infant DNA	Human clinical study, linked outcomes	Limited sample; lacks mechanistic pathway data
Paparo et al. 2014 [28]	Early-life nutrition	Immune epigenetics	Human (review)	Diet shapes immune development via epigenetic modulation	Strong immune-epigenetic link	Review-based; lacks original data
Panchenko et al. 2015 [18]	Maternal nutrients	Placental methylation	Human	Micronutrient effects on placental development and fetal health	Bridge between maternal diet & placental biomarkers	Small cohort size
Remely et al. 2015 [29]	Multiple nutrients	DNA methylation	Human	Nutrition modulates genes related to obesity & metabolic syndrome	Links to chronic disease pathways	Cross-sectional evidence
Basak et al. 2024 [30]	Gut microbiota and nutrients	Placental epigenome	Human	Microbiota-diet interaction modulates placental epigenetics	Novel gut-placenta axis model	Lacks longitudinal tracking
Tang et al. 2024 [31]	High-fat maternal diet	Germ cell epigenetics	Animal (mouse)	Obesity induces meiotic/ epigenetic defects in fetal oocytes	Clear germline-level effect	Animal model limited in scope

Studies are categorized by nutrient/exposure, epigenetic mechanism, study type (human or animal), key insights, strengths, and limitations. This table explicitly identifying whether each study is human-based or animal-based.

with periconceptional supplementation yielding more pronounced and persistent methylation changes than interventions later in gestation [29, 39]. These data suggest that DNA methylation serves as a primary molecular conduit for nutritional programming of long-term metabolic, neurodevelopmental, and immune outcomes (Figure 2).

Table 2: Nutrients and associated epigenetic mechanisms, timing, and health outcomes.

Nutrient/ Exposure	Epigenetic mechanism	Direction of effect	Target gene(s)/loci	Pathway/function	Tissue/ system	Timing of exposure	Study type	Phenotypic/health outcome	Inter-generational effect	Authors
Folate	DNA methylation	↑Methylation	IGF2	Growth/metabolism	Placenta	Peri-conception	Human	↓Adult disease risk	Yes (F1)	Heijmans et al. [4]
Folate	DNA methylation	Widespread changes	Various loci	Metabolic & immune pathways	Cord blood	3rd trimester	Human	Metabolic imprinting	No	Joubert et al. [5]
Vitamin D	miRNA expression	miR-21, miR-146a, miR-155	CYP24A1	Immune/neuro	Cord blood	2nd trimester	Human	Neuro-immune modulation	Yes (F1)	Anderson et al. [6]
Methyl donors	DNA methylation	↑Methylation	Avy	Metabolic	Liver	Gestation	Animal	Altered coat color, disease risk	No	Waterland and Jirtle [3]
Low-dose polyphenols	Histone acetylation	↑SIRT1	SIRT1	Neuroprotection	Brain	Gestation	Rodent	Neuro-protection	No	Bouwland-both et al. [7]
Vitamin B12	DNA methylation	Altered methylation	Methylation cycle genes	Endocrine/metabolic	Liver	Early gestation	Animal	Altered IGF2 methylation	No	Mahajan et al. [27]
High-fat diet	miRNA expression	miR-122, miR-370	SIRT1	Lipid metabolism	Liver	Gestation	Rodent	Insulin resistance	Yes (F1)	Choi et al. [9]
Smoking	DNA methylation	↑Methylation	Immune genes	Immunity	Placenta	Gestation	Human	Inflammation	No	Morales et al. [16]
Resveratrol	Histone acetylation	SIRT1, PGC-1α	Metabolic regulation	Various tissues	Rodent	Gestation	Animal	Metabolic protection	Yes (F1)	Lagouge et al. [10]
Omega-3	miRNA expression	miRNA modulation	Immune genes	Immunomodulation	Blood	Gestation	Rodent	Immune benefits	No	Bodur et al. [19]
Polyphenols	miRNA expression	↑miR changes	Oxidative stress genes	Neurogenesis	Brain	Gestation	Cell line	Neuro-degeneration	No	Ferrero et al. [26]
Methionine deficiency	miRNA expression	↓miR-181a	Thymic genes	Immune function	Thymus	Gestation	Rodent	Immuno-deficiency	Yes (F1)	Syring et al. [32]
Protein restriction	DNA methylation	↑PPARα, GR	Metabolic genes	DNA methylation	Liver	Gestation	Rodent	Sex-biased outcomes	Yes (F1)	Vipin et al. [33]
Vitamin D	DNA methylation	↑Methylation	CYP24A1	Vitamin D metabolism	Placenta	Gestation	Human	Altered fetal exposure	No	Basak et al. [30]

This table integrates nutrient exposures, associated epigenetic mechanisms, molecular targets, timing of exposure, and phenotypic outcomes, with explicit categorization of study type (human, animal, *in vitro*).

Table 3: Translational applications of key nutriepigenomic findings in perinatal medicine.

Epigenetic finding	Nutritional exposure	Epigenetic biomarker	Clinical relevance	Potential intervention	Study type	Reference(s)
IGF2 hypomethylation	Folate deficiency/ famine	IGF2 cord blood methylation	Predicts increased long-term metabolic risk	Early folate supplementation	Human	Heijmans et al. [4]
miR-21 & miR-146a dysregulation	Vitamin D deficiency	Cord blood miRNAs	Neuroimmune modulation in fetus	Vitamin D screening & supplementation	Human	Anderson et al. [6]
H3K9 histone deacetylation	Low protein intake	Histone acetylation status	Risk of insulin resistance	Balanced maternal protein intake	Animal	Jia et al.[34]
LINE-1 global hypomethylation	Tobacco exposure	LINE-1 repetitive element methylation	Predicts adverse birth outcomes	Smoking cessation programs	Human	Bouwland-Both et al. [7]
miRNA (e.g., miR-34a) dysregulation	High-fat diet	Circulating miRNAs	Metabolic dysfunction, obesity risk	Resveratrol-rich diet or weight management	Animal	Chodur & Steinberg [20]
Histone acetylation changes	DHA deficiency	Histone acetylation markers	Neurodevelopment modulation	Omega-3 supplementation	Human	Yammine et al. [8]
Placental DNA methylation changes	Multiple micronutrient deficiencies	Placental methylation markers	Fetal growth restriction & vascular issues	Prenatal multivitamin use	Human	Basak et al. [30]
NR3C1 (GR) hypomethylation	Maternal stress+poor diet	NR3C1 promoter methylation	Altered stress response in offspring	Stress reduction & nutritional support	Human	Saffery & Novakovic [35]

This table summarizes nutriepigenomic findings with translational potential, linking specific epigenetic markers to nutritional exposures, clinical outcomes, and actionable interventions. Evidence type (human or animal) is explicitly noted as requested by reviewers.

Table 4: Critical developmental windows for nutrient-sensitive epigenetic programming.

Developmental window	Key epigenetic processes	Key nutrient exposures	Representative target genes/pathways	Phenotypic/health outcomes	Study type	Reference(s)
Preconception & gametogenesis	DNA methylation programming, histone modifications in gametes	Folate, B12, choline, methionine, zinc	IGF2, imprinted gene clusters	Gamete quality, transgenerational epigenetic marks	Human & animal	[1, 27, 29, 33, 34]
Implantation & early embryogenesis (0–3 weeks)	Epigenome-wide resetting, imprinting gene programming	Folate, betaine, methionine	H19, IGF2, epigenetic regulators	Early developmental patterning & imprint stability	Human & animal	[3, 4, 30, 36–38]
Organogenesis (3–8 weeks)	Tissue-specific DNA methylation, histone acetylation	Polyphenols, vitamin A, retinoic acid, zinc	HOX gene clusters, organ-specific transcription factors	Congenital anomaly prevention, fetal tissue development	Animal	[18, 29, 30, 39, 40]
Mid-gestation (8–24 weeks)	Cell lineage specification, noncoding RNA expression	Omega-3, vitamin D, selenium, antioxidants	Immune-related gene networks, neural development genes	Neurodevelopment, immune function, growth outcomes	Human & animal	[6, 19, 22, 26, 28]
Late gestation (24–40 weeks)	Metabolic gene tuning, maintenance of epigenetic marks	Choline, DHA, iron, resveratrol	PPARα, adipogenic and metabolic genes	Programming of insulin sensitivity, fat storage, metabolic risk	Human & animal	[2, 10, 11, 41, 42]
Perinatal & neonatal period	Stabilization of epigenome, immune trajectory modulation	Vitamin D, lactation nutrients, protein	Immune-related genes, epigenetic stress markers	Immune maturation, allergy risk modulation, postnatal growth	Human	[6, 23, 28, 43, 44]

This table highlights critical windows of epigenetic sensitivity and key nutrient exposures, linking molecular processes to specific phenotypic outcomes and indicating evidence type (human vs animal) as requested by reviewers.

Table 5: Candidate epigenetic biomarkers of nutritional exposure and health outcomes.

Epigenetic biomarker	Nutritional exposure	Sample source	Clinical relevance	Study type	Reference(s)
IGF2 DMR methylation	Folate, vitamin B12	Cord blood	Predicts long-term metabolic risk	Human	Heijmans et al.4
LEP promoter methylation	Maternal protein intake	Placenta	Obesity and appetite regulation	Human	Jia et al. [34]
miR-21 & miR-146a expression	Vitamin D deficiency	Cord blood	Immune and inflammation pathways	Human	Anderson et al. [6]
LINE-1 methylation	Tobacco exposure, general nutrition	Placenta	Global marker of prenatal environment	Human	Morales et al. [16]
PPARα promoter methylation	Protein restriction	Liver	Fatty acid metabolism & metabolic syndrome risk	Animal	Vipin et al. [33]
Avy locus methylation	Folate & choline supplementation	Liver	Coat color and metabolic programming model	Animal	Waterland and Jirtle [3]

This table highlights epigenetic biomarkers with potential for clinical or research use, linking nutritional exposures to health outcomes. Study type (human or animal) and sample source are indicated as requested by reviewers.

Table 6: Research gaps and future priorities in nutriepigenomics.

Gap/Challenge	Current limitation/evidence Gap	Example context/ model	Proposed future directions	Expected impact	Reference(s)
Limited longitudinal human studies	Most studies are cross-sectional or short-term, limiting understanding of long-term epigenetic programming.	Human cohort studies on IGF2 methylation (Dutch famine) vs short-term interventions.	Establish multi-cohort, multi-omics longitudinal studies with repeated epigenetic measures.	Improves prediction of adult disease risk and informs long-term maternal nutrition policies.	[3, 5, 27, 34]
Population heterogeneity	Findings often derived from homogenous populations; poor generalizability to diverse ethnic and socio-economic groups.	Vitamin D intervention trials in high-BMI vs normal BMI populations show variability.	Develop region- and population-specific interventions addressing nutrient deficiencies.	Enhances equity and global relevance of nutriepigenomic recommendations.	[6, 20, 45]
Lack of standardized epigenetic biomarkers	No universal biomarkers validated for maternal nutritional exposure and outcomes.	Inconsistent use of LINE-1, IGF2, and gene-specific methylation markers across studies.	Validate biomarker panels across tissues (placenta, cord blood, maternal blood).	Enables personalized maternal-fetal nutritional risk screening and monitoring.	[4, 29, 33, 46]
Transgenerational evidence gaps	Sparse evidence on heritable nutrient-induced epigenetic changes in humans.	Avy mouse model shows heritable effects; limited human germline tracking.	Design multi-generational human cohort studies with germline epigenome profiling.	Clarifies heritable effects for policy and early-life intervention strategies.	[25, 37, 47]
Translation & clinical integration	Few validated epigenetic tools are available for clinical obstetric practice.	Vitamin D and miRNA biomarkers remain research tools, not clinical diagnostics.	Develop clinical pipelines, clinician training, and integrative screening tools.	Enables early prediction and prevention of adverse pregnancy and offspring outcomes.	[22, 29, 43]
Ethical & regulatory frameworks	Unclear guidelines on fetal epigenetic sampling, data privacy, and consent.	Ethical debates on prenatal testing and biobanking remain unresolved.	Develop global ethical standards and governance frameworks.	Ensures safe and equitable translation of nutriepigenomics into healthcare.	[30, 48]

This table consolidates key gaps and future directions in nutriepigenomics research, integrating evidence from human and animal studies. It highlights context, proposed solutions, and expected impact on clinical translation, policy, and equity. This approach replaces previous Tables 6–9 to streamline content as recommended by reviewers.

Histone modifications: nutrient-responsive chromatin remodeling

Histone modifications, particularly acetylation and methylation, were less commonly studied but provide unique insights into chromatin dynamics influenced by maternal diet (Table 3). 17 studies investigated these mechanisms, including both human observational data and animal experiments. In human studies, prenatal omega-3 fatty acid exposure, especially DHA, was associated with altered acetylation of histone H3K9 at immune and inflammatory loci, supporting a role for lipid-derived signals in chromatin remodeling [6, 7]. Polyphenolic compounds such as resveratrol activated SIRT1, enhancing histone deacetylation and shifting transcriptional programs toward anti-inflammatory and metabolic homeostasis [8–11].

In rodent models, maternal protein restriction induced hypoacetylation of H3 and H4 histones in fetal liver, reducing glucocorticoid receptor expression and altering metabolic setpoints [31, 40, 42, 81]. High-fat diet exposure led to context-dependent changes in histone methylation and acetylation, with implications for hepatic and hypothalamic programming [31, 81]. These histone changes often interacted with microRNA networks and environmental stressors, highlighting epigenetic plasticity in response to nutrient environment [27, 34, 38, 47, 75, 78–80, 82–87]. Such findings underscore histone modifications as critical mediators of fetal programming, although clinical translation remains limited due to tissue accessibility challenges.

Non-coding RNAs: the emerging frontier of nutritional epigenetics

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), represent a rapidly evolving focus within nutriepigenomic research (Table 4). 11 studies investigated dietary effects on ncRNA expression. In human cohorts, maternal vitamin D sufficiency was associated with differential expression of immune- and neurodevelopment-related miRNAs such as miR-21, miR-146a, and miR-155 in cord blood, indicating a potential role in immune maturation [6, 20, 45]. Similarly, dietary polyphenols and fatty acids modulated miRNAs linked to energy balance and oxidative stress [8, 20, 26, 57].

Animal evidence confirmed these effects mechanistically. A maternal high-fat diet upregulated hepatic miR-122 and miR-370, leading to altered lipid metabolism and postnatal hepatic steatosis [42, 48]. Methionine-deficient diets downregulated miR-181a, impairing thymic development and immune competence [20, 33]. Additionally, obesity-associated elevations of miR-34a reduced NAD^+ levels and SIRT1 activity, highlighting cross-talk between metabolic status and nutrient-sensitive ncRNAs [9]. Collectively, these studies indicate that ncRNAs are responsive to maternal diet and serve both as biomarkers and regulators of fetal programming outcomes.

Placental epigenetics: a translational biomarker platform

The placenta is increasingly recognized as an accessible and functionally relevant tissue for evaluating nutriepigenomic effects (Table 5). Twenty-four studies examined placental epigenetic modifications in relation to maternal nutrition. Folate status correlated with differential methylation at the HSD11B2 gene, influencing fetal glucocorticoid exposure and birth weight regulation [30, 37]. Vitamin D deficiency induced hypomethylation of CYP24A1, potentially disrupting local vitamin D metabolism and downstream neonatal bone and immune health [6, 45]. Furthermore, maternal B12 and folate concentrations influenced methylation of methionine cycle genes in both placental and fetal liver tissues, reflecting integrated maternal-fetal epigenetic regulation [27, 32].

Although placenta-based epigenetic profiling holds promise as a biomarker for fetal programming risk, results can vary depending on tissue sampling site, cell-type composition, and gestational age [71, 72, 82]. Advances in high-resolution methylomics and single-cell epigenetics are expected to improve its translational utility (Figure 3).

Intergenerational and sex-specific effects

Emerging evidence suggests that nutriepigenomic effects may differ by offspring sex and persist across generations (Table 6). Rodent studies revealed sexually dimorphic methylation changes in PPARα and glucocorticoid receptor (GR) loci following maternal protein restriction, resulting in differential stress reactivity and metabolic regulation in male vs. female offspring [31, 42, 85]. In humans, maternal obesity and gestational diabetes were linked to sex-specific methylation patterns in leptin and adiponectin genes, with stronger metabolic perturbations in male neonates [41, 48, 74].

Some dietary effects extended beyond the first generation. Mouse models demonstrated that altered methylation at imprinted genes such as H19 and IGF2 in the F1 generation persisted in F2 germ cells and offspring [38, 47]. Epigenetic changes in sperm and oocytes from nutrient-restricted mothers further confirmed the potential for

intergenerational transmission [36, 84]. These findings emphasize the importance of considering sex-specific and transgenerational dynamics in both experimental design and clinical translation, as these patterns may contribute to long-term population health trajectories and chronic disease risk (Figure 3).

Discussion

Mechanistic clarity and evidence strength: nutrients as epigenetic regulators

The findings synthesized in this review demonstrate that maternal nutrition is a key determinant of fetal epigenetic programming, influencing gene expression through DNA methylation, histone modification, and non-coding RNAs. These mechanisms are comprehensively mapped in Figure 2 and contextualized within integrated translational pathways in Figure 3.

DNA methylation emerged as the most extensively studied epigenetic mechanism. Human cohort studies, such as those by Heijmans et al., showed that periconceptional famine exposure led to persistent IGF2 hypomethylation detectable decades later (4), while Joubert et al. reported widespread methylation differences linked to maternal folate intake (5). Animal models complement these findings; Waterland and Jirtle demonstrated that maternal methyl donor supplementation induced locus-specific hypermethylation in offspring (3). These consistent results across species, summarized in Tables 1–3, establish DNA methylation as a robust mediator of nutritional effects.

Histone modifications, although less studied, are emerging as key nutrient-responsive regulatory processes. Human studies linked omega-3 fatty acid status and polyphenol intake to histone acetylation changes at inflammatory and metabolic loci (7, 8), while rodent models showed protein restriction and high-fat diets induced histone deacetylation affecting glucocorticoid receptor and PPARα expression (46, 54). These results (detailed in Table 4) suggest histone modifications act as dynamic integrators of maternal macronutrient balance.

Non-coding RNAs (ncRNAs), including microRNAs and long non-coding RNAs, represent a rapidly developing research frontier. Human studies reported altered miR-21 and miR-146a expression associated with maternal vitamin D status (6, 20), while animal studies identified dysregulation of lipid-related miRNAs (e.g., miR-122, miR-370) in offspring exposed to maternal high-fat diets (50, 54). These findings, summarized in Table 5, position ncRNAs as both biomarkers and mediators of nutriepigenomic effects.

Placental tissue is increasingly used as a translational platform because it reflects maternal-fetal nutrient signaling. Studies demonstrated altered methylation of genes such as HSD11B2 and CYP24A1 linked to maternal folate and vitamin D, respectively (52, 65, 75). These results, coupled with cord blood epigenetic profiles, point toward clinically accessible biomarkers (Figure 3, Table 6).

Long-term and intergenerational outcomes

A critical finding of this review is that nutriepigenomic changes are associated with persistent functional outcomes. Human data link altered fetal DNA methylation and ncRNA expression to long-term metabolic risk, immune dysregulation, and neurodevelopmental variation (50, 51, 64). Animal studies corroborate these effects, showing maternal protein and fat intake affect germline epigenetic reprogramming, resulting in intergenerational transmission of metabolic phenotypes (46, 77, 84). These sex-specific and intergenerational patterns (Table 6) emphasize that maternal nutrition affects not only immediate neonatal health but also the trajectory of disease risk in subsequent generations.

Translational and policy implications

The evidence reviewed highlights clear opportunities for clinical and public health translation. Timing-sensitive interventions, such as periconceptional methyl donor supplementation, produce more durable epigenetic changes than later interventions (53, 79). Yet, current obstetric nutritional guidelines emphasize preventing deficiencies rather than optimizing molecular developmental outcomes (55, 61).

Emerging evidence supports the inclusion of epigenetic biomarkers – derived from placental or cord blood – into maternal nutrition screening frameworks (Figure 3). This approach could enable precision nutrition strategies tailored to gestational stage and maternal metabolic risk, aligning with evolving concepts of personalized medicine (40, 41). On a population level, micronutrient fortification and targeted supplementation programs remain highly relevant to mitigate nutritional inequities, especially in low-resource settings (23, 44, 66).

Ethical and methodological considerations

The capacity of maternal diet to influence not only immediate offspring health but also transgenerational gene

regulation raises ethical questions about access, autonomy, and equity (3, 77, 87). Nutritional interventions should be framed as empowerment opportunities rather than obligations, with policies addressing socioeconomic barriers to adequate maternal nutrition (23, 60, 66).

Methodologically, integrating human and animal evidence strengthens mechanistic inference but also reveals gaps. Animal models provide insights into molecular pathways and intergenerational inheritance, but human studies are necessary to validate biomarkers and long-term clinical outcomes. Our review addressed this by distinguishing between human and animal evidence in all tables (Tables 1–6) and by replacing non-informative figures with the redesigned Figures 1, 2, and 3, which more clearly depict evidence synthesis pathways. Future research must focus on validating epigenetic biomarkers across diverse populations, examining sex-specific and intergenerational effects, and conducting randomized clinical trials using molecular endpoints (53, 56, 61). Investments in public health infrastructure are essential to translate nutriepigenomics into routine perinatal care, ensuring equity and scalability (Figure 3). Collaboration between clinicians, nutritionists, and policymakers will be critical to achieving these goals and to shifting prenatal care from a reactive to a proactive model focused on epigenetic optimization.

Strengths, limitations, and future directions

This review provides a comprehensive synthesis of nutriepigenomics in perinatal medicine, drawing on over two decades of research from both human and animal studies. A key strength lies in its methodological rigor, including a PRISMA-guided search strategy, predefined inclusion criteria, and systematic quality assessment. The inclusion of diverse epigenetic mechanisms – DNA methylation, histone modifications, and non-coding RNAs – ensures a holistic view of how maternal nutrition shapes the fetal epigenome. By linking nutrient-specific exposures to molecular pathways and long-term developmental outcomes, the review highlights biologically coherent patterns that are both mechanistically plausible and clinically relevant.

Another strength is the explicit framing of nutriepigenomics within clinical and public health contexts. Rather than remaining purely mechanistic, this review situates findings within a model of precision perinatal nutrition that is practical, ethically grounded, and responsive to population health needs. By including placental epigenetic studies and evidence for intergenerational effects, the analysis highlights emerging biomarkers and underscores the need for longitudinal monitoring to inform early-life interventions.

However, several limitations must be acknowledged. Study heterogeneity in design, timing of exposure (e.g., periconceptional vs. late gestation), tissue types, and analytical approaches limited direct comparisons and precluded dose–response conclusions. Many findings rely on associative data without functional validation, highlighting the importance of integrated multi-omic and functional studies to confirm epigenetic causality. Geographic bias is evident, with most research conducted in high-income settings, limiting global generalizability and neglecting vulnerable populations where nutritional interventions could have the greatest impact. Additionally, the literature remains heavily weighted toward methyl donors, with fewer studies on other potentially epigenetically active nutrients such as fiber, trace minerals, and plant bioactives.

Future research should prioritize longitudinal birth cohorts tracking maternal diet, fetal epigenetic changes, and long-term health outcomes into adulthood. Randomized controlled trials with molecular endpoints are essential to establish causality and inform nutrient-specific clinical guidelines. Advances in single-cell epigenomics, placental multi-omics, and computational modeling – including machine learning – hold promise for biomarker discovery and identification of critical windows of developmental sensitivity. Greater attention is needed to interactive effects involving nutrient–gene interactions, microbiome composition, and environmental exposures. Building the next generation of nutriepigenomic research will also require standardized methodologies, ethical frameworks for biomarker use, and equitable access to precision nutrition strategies.

With these investments, the field can move beyond discovery toward implementation, enabling the design of personalized, preventive perinatal interventions that optimize health outcomes across the life course and potentially across generations.

Conclusions

The convergence of nutritional science and epigenetics represents a transformative advance in perinatal medicine. This review demonstrates that maternal diet is not merely a source of energy and micronutrients but a powerful epigenetic modulator capable of altering fetal gene expression and developmental trajectories with consequences that extend throughout life – and possibly into future

generations. Nutrients such as folate, choline, vitamin D, omega-3 fatty acids, and polyphenols have been shown to influence DNA methylation, histone modifications, and non-coding RNA expression in ways that regulate fundamental biological processes including metabolism, neuro-development, and immune function.

The weight of evidence now supports a strategic reorientation of perinatal nutrition – from a focus on preventing deficiencies to one that embraces epigenetic precision. This transition requires novel clinical tools, updated prenatal guidelines, and sustained investment in biomarker validation, mechanistic research, and equitable access to personalized interventions. Placental and cord blood epigenetic profiling represent promising diagnostic platforms, while evidence of intergenerational effects underscores the urgency of translating scientific insights into clinical practice and public health policy.

Nutritional exposures during pregnancy are modifiable, measurable, and ethically actionable. Integrating nutriepigenomics into perinatal care offers an unparalleled opportunity to improve maternal and child health – not only by preventing disease, but by programming resilience, wellness, and long-term potential. The scientific foundation is strong, the mechanisms are clear, and the time for clinical integration is now.

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