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The epigenetic influence of diet-induced gut microbiome changes in precision nutrition – a systematic review

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ABSTRACT

Aim: This systematic review aimed to comprehensively evaluate the existing literature on the epigenetic influence of diet-induced gut microbiome changes in the context of precision nutrition.

Background: Diet influences gut microbiome composition, which regulates epigenetic modifications affecting inflammation, metabolism, and disease susceptibility. Precision nutrition seeks to personalize dietary strategies based on these interactions, yet the role of microbiome-driven epigenetic regulation remains under investigation.

Methods: A systematic review was conducted in 2025 following PRISMA guidelines. Studies exploring the relationship between dietary interventions, gut microbiome composition, and epigenetic changes were identified via PubMed and Google Scholar. Thirty-five studies, including randomized controlled trials, cohort studies, and observational research, met the inclusion criteria. Data on dietary interventions, microbial composition, epigenetic modifications, and health outcomes were synthesized.

Results: Diets rich in fiber and polyphenols enhanced microbial diversity, increased short-chain fatty acid production, and positively influenced epigenetic markers related to metabolic health. In contrast, Western-style and high-fat diets were associated with gut dysbiosis, inflammation, and negative epigenetic changes linked to metabolic disorders. Dietary interventions impacted DNA methylation, histone modifications, and microRNA expression, influencing long-term health.

Conclusion: This review highlights the key role of diet-induced changes in the gut microbiome in modulating epigenetic mechanisms like DNA methylation and histone modifications. These alterations influence metabolic health, disease risk, and precision nutrition strategies. While dietary interventions show promise, challenges such as individual variability and methodological inconsistencies require further research to refine clinical applications of microbiome-driven nutrition.

Keywords: Gut microbiome, Epigenetics, Precision nutrition, Dietary interventions, Inflammation.

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Introduction

The intricate relationship between diet, the gut microbiome, and host health has become a focal point in modern nutrition research (1-3). Diet profoundly shapes the composition, diversity, and function of the gut microbiome, impacting metabolic and intestinal health (4). Understanding these interactions is critical for making informed dietary decisions and preventing diet-related diseases (4). Precision nutrition, an emerging field, aims to tailor nutritional recommendations to individual variability, considering factors like genetics, epigenetics, and the gut microbiome (5).

Epigenetics, the study of heritable changes in gene expression without alterations to the DNA sequence, plays a crucial role in mediating the effects of diet and the gut microbiome on host physiology (6, 7). As illustrated in Figure 1, these modifications influence

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gene expression by altering chromatin accessibility and transcriptional activity. Microbial metabolites, including short-chain fatty acids (SCFAs) produced during the fermentation of dietary fiber, can influence these modifications, thereby regulating inflammatory and metabolic pathways (8, 9). Dietary components, such as fiber, glucosinolates, polyphenols, and dietary fat, significantly impact gut microbiota composition and function, which in turn regulates essential epigenetic functions (7). These epigenetic modifications, including DNA methylation, histone modification, and non-coding RNAs, influence gene expression and ultimately affect health outcomes (5, 10).

The gut microbiome, a dynamic ecosystem within the gastrointestinal tract, houses trillions of microorganisms that play a pivotal role in human health (1, 11). It influences digestion, metabolism, immune function, and even neurological processes through the gut-brain axis (1, 12). Diet-induced changes in the gut microbiome can lead to the production of metabolites that affect epigenetic modifications, impacting various physiological processes and disease development (13).

Metabolic diseases, including obesity, dyslipidemia, type 2 diabetes mellitus (T2DM), and non-alcoholic fatty liver disease (NAFLD), pose a significant burden on human society (14, 15). Environmental factors, particularly diet and gut microbiota, and epigenetic modifications contribute to the progression of these diseases (15). Precision nutrition strategies that consider the interplay between diet, the gut microbiome, and epigenetics offer promising avenues for managing and preventing metabolic disorders (16).

This systematic review, conducted in 2025, aims to comprehensively evaluate the existing literature on the epigenetic influence of diet-induced gut microbiome changes in the context of precision nutrition. By synthesizing current knowledge, we seek to provide insights into the mechanisms through which diet and the gut microbiome modulate the epigenome, and how these interactions can be harnessed for personalized nutrition strategies to improve health outcomes and combat aging-associated diseases (6). The review will explore the impact of various dietary patterns and specific nutrients on gut microbiome composition and function, the resulting epigenetic modifications, and their implications for metabolic health, immune function, and neurological well-being (17). Moreover, we will discuss the potential of artificial intelligence (AI) and other advanced technologies to integrate multi-omics data and develop personalized nutrition interventions that target the gut microbiome and epigenome for optimized health benefits (6, 18).

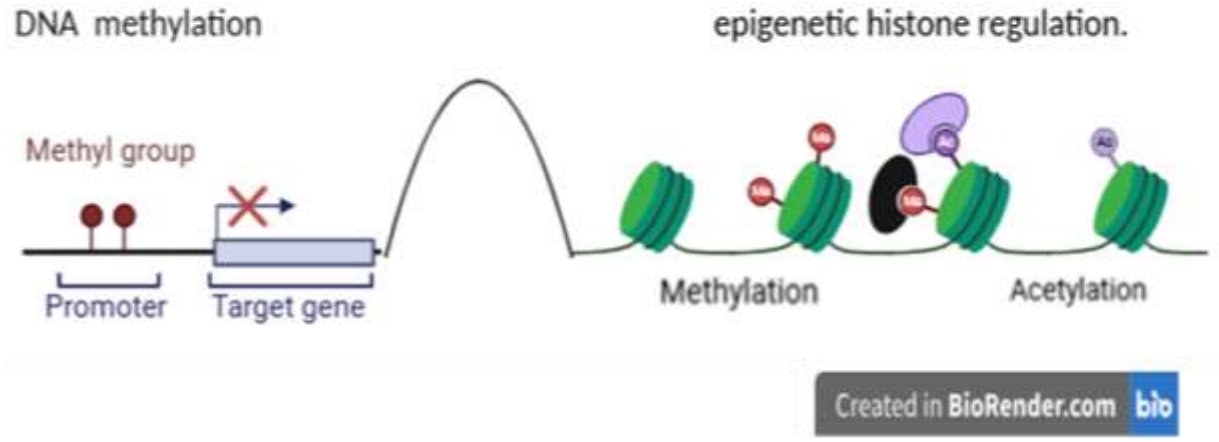

Figure 1. Epigenetic Changes in Gene Expression — This figure illustrates two key epigenetic mechanisms that regulate gene expression: DNA methylation and histone modifications. DNA methylation involves the addition of methyl groups to the promoter region of a gene, inhibiting transcription and leading to gene silencing. Histone modifications, including acetylation and methylation, alter chromatin structure and gene accessibility; acetylation relaxes chromatin, promoting gene activation, while methylation can either enhance or suppress transcription depending on its context. These epigenetic modifications are dynamic and influenced by environmental factors, such as diet, with implications for metabolism, inflammation, and disease susceptibility.

Methods

Study protocols

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study aimed to synthesize evidence on the epigenetic mechanisms linking diet, gut microbiome alterations, and precision nutrition. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included observational studies. At the same time, the Cochrane Risk of Bias Tool was applied to randomized controlled trials (RCTs) to ensure methodological rigor and reliability.

Eligibility criteria

Studies considered for inclusion encompassed RCTs, controlled clinical trials, prospective cohort studies, case-control studies, cross-sectional studies, and observational studies involving humans or animals. Additional criteria included: (1) studies published in English and (2) availability of full-text access. Eligible studies focused on diet-induced gut microbiome changes and their impact on epigenetic modifications, such as DNA methylation, histone modifications, and microRNA expression, as well as metabolic health outcomes. Only peer-reviewed publications and complete reports containing relevant data were included, while opinion pieces, editorials, and studies lacking quantitative data on gut microbiome changes were excluded.

Information sources and search strategy

A systematic literature search was performed using PubMed and Google Scholar. The search strategy incorporated Boolean operators ("AND" and "OR") to refine query precision. Search terms included “epigenetics,” “gut microbiome,” “diet-microbiome interaction,” and “precision nutrition.” Example search strings included: “epigenetics” AND “gut microbiome” AND “diet-microbiome interaction” AND “precision nutrition.” Titles and abstracts were screened for relevance, and full-text articles were reviewed for eligibility. Reference lists of selected studies were examined to identify additional relevant articles. The literature search concluded on March 3, 2025, capturing the most recent studies available.

Selection of studies

Study selection followed PRISMA guidelines. After removing duplicate records, two independent reviewers screened titles and abstracts to determine relevance. Full-text reviews were conducted for studies meeting the initial criteria, and any disagreements were resolved through discussion. Figure 2 presents the PRISMA flow diagram, illustrating the identification, screening, exclusion, and inclusion of studies in the final analysis.

Article screening and data extraction

Two independent reviewers implemented a structured three-level screening process using a standardized data extraction form. The initial screening assessed 70 records based on titles and abstracts. Exclusion criteria included non-English publications (n = 2), studies unrelated to epigenetics (n = 18), studies that do not assess epigenetic markers (n=10), and those not relevant to the exposure topics (n = 9). Extracted data included study characteristics (authors, publication year, country, study design), population details, dietary interventions, microbiome changes, and epigenetic outcomes. To ensure accuracy and consistency, a second reviewer cross-checked all extracted data, minimizing potential discrepancies.

Quality assessment and risk of bias

The quality of observational studies was evaluated using the Newcastle-Ottawa Scale (NOS), with studies scoring below four excluded. RCTs were assessed using the Cochrane Risk of Bias Tool, considering factors such as random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting. Two independent reviewers conducted quality assessments, and any discrepancies were resolved by consulting a third reviewer.

Results

Study selection

A total of 70 studies were initially identified through systematic searches in PubMed (n = 40) and Google Scholar (n = 30). After removing duplicates (n = 8), a total of 62 full-text articles were screened for eligibility, of which 39 studies were excluded. Following a thorough evaluation, 23 studies were included in this systematic review. The selection

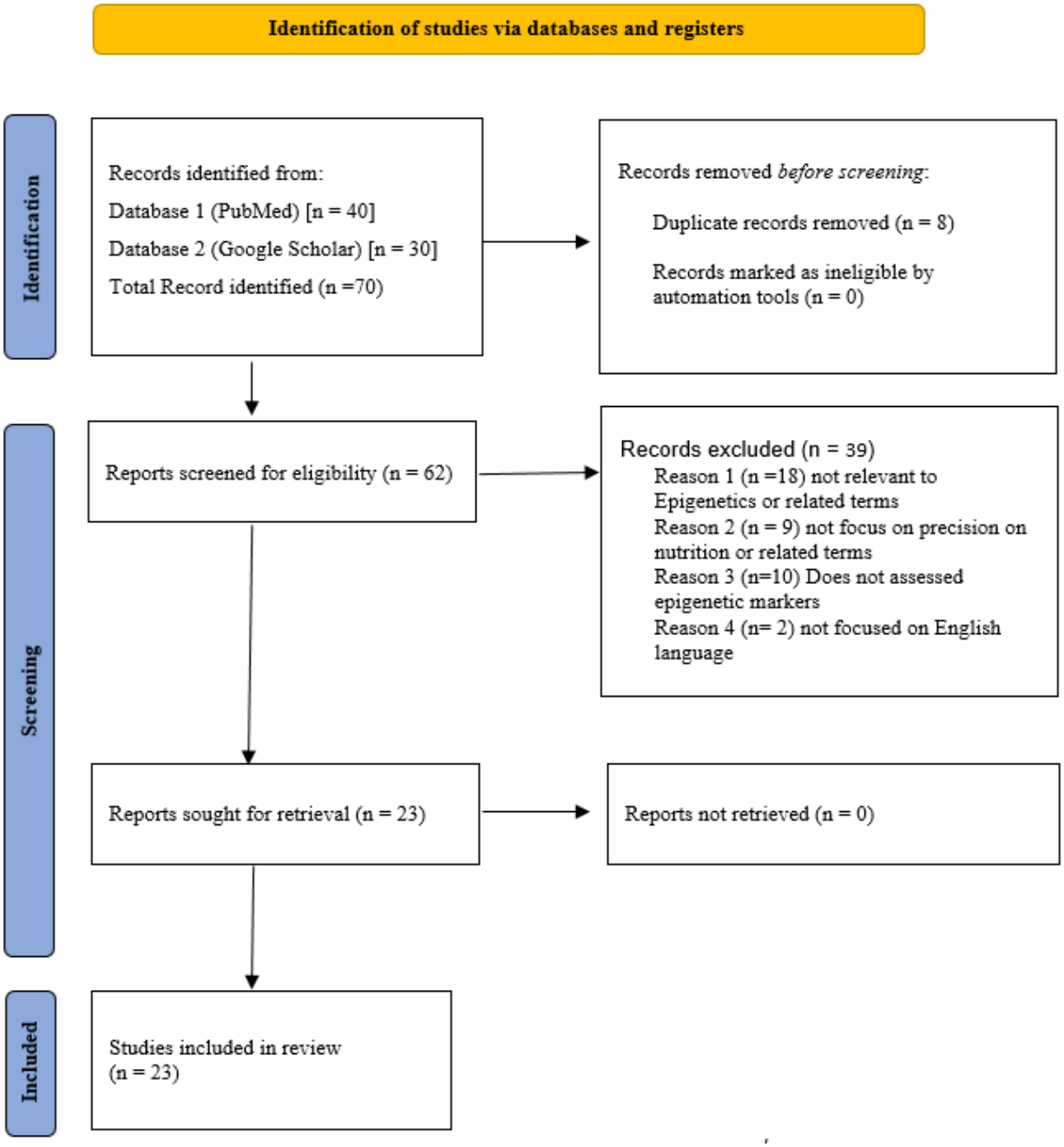

Figure 2. PRISMA 2020 flow diagram of the selection of eligible studies for qualitative analysis.

process adhered to the PRISMA guidelines, which ensured transparency and reproducibility. Studies were included if they focused on diet-induced changes in the gut microbiome and their epigenetic implications in either human or animal models. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the studies, with only those scoring at least 4 out of 9 being considered. Exclusion criteria included non-English publications and articles that lacked full-text availability.

Study characteristics

The studies examined varied in design, including randomized controlled trials (RCTs), cohort studies, case-control studies, observational studies, and animal studies. A total of nine studies were RCTs that investigated the causal effects of dietary interventions

on gut microbiome composition and epigenetic changes. Four cohort studies assessed the long-term impacts of diet on microbiome-epigenetic interactions. Additionally, three case-control and observational studies compared microbial and epigenetic profiles in different dietary contexts, while seven animal studies explored the mechanisms linking diet with microbiome and epigenetic modifications.

The dietary interventions analyzed included high-fiber diets, ketogenic diets, Mediterranean diets, polyphenol-rich diets, and probiotic supplementation. Microbiome analyses were performed using methods such as 16S rRNA sequencing, metagenomics, and metabolomics. Meanwhile, epigenetic modifications were assessed through DNA methylation assays, histone modification profiling, and microRNA expression analysis.

Results of individual studies

The included studies (Table 1) explore diverse methodologies to examine the interplay between diet, gut microbiome, epigenetic modifications, and metabolic health. Nutritional interventions such as high- and low-carb diets, time-restricted eating, and Mediterranean diet patterns demonstrated significant microbiome shifts and metabolic effects. At the same time, mechanistic studies highlighted epigenetic regulation via DNA methylation and histone modifications. Observational cohorts provided insights into long-term microbiome dynamics, particularly in aging and disease contexts. Despite their strengths, studies faced limitations including small sample sizes, lack of controls, and challenges in standardization.

Discussion

Influence of diet on gut microbiome composition

Dietary composition plays a pivotal role in shaping the gut microbiome, influencing microbial diversity, abundance, and metabolic functionality. High-fiber diets have consistently been associated with enhanced microbial richness and the proliferation of beneficial bacterial species. Increased fiber intake promotes the expansion of *Bacteroidetes* and the enrichment of short-chain fatty acid (SCFA)-producing bacteria, such as *Faecalibacterium prausnitzii*, which are linked to improved gut health and reduced inflammation (42). Conversely, diets high in fat and Western-style eating patterns contribute to gut dysbiosis, typically characterized by an elevated Firmicutes/Bacteroidetes ratio, reduced microbial diversity, and an increased prevalence of pro-inflammatory bacterial species (43).

Moreover, polyphenol-rich diets selectively modulate gut microbiota by fostering the growth of beneficial bacteria, including Lactobacillus and Bifidobacterium, while concurrently suppressing pathogenic species (44, 45). These polyphenols enhance microbial fermentation, leading to the generation of bioactive metabolites with anti-inflammatory and epigenetic-modifying properties. Probiotic supplementation further contributes to significant shifts in microbial composition, promoting the colonization of beneficial bacteria, which, in turn, strengthens gut barrier integrity and modulates immune function (46). In contrast, diets abundant in processed foods, refined sugars, and artificial additives are associated with a depletion of beneficial microbial taxa and an increased presence of opportunistic pathogens. Such alterations correlate with heightened intestinal permeability, systemic inflammation, and metabolic dysfunction. Collectively, these findings underscore the profound impact of dietary composition on gut microbial ecosystems, highlighting the potential of nutritional interventions to restore microbial equilibrium and enhance overall health.

Microbiome-mediated epigenetic modifications

Emerging evidence suggests that microbial metabolites play a crucial role in epigenetic regulation, influencing gene expression patterns that govern inflammation and metabolism. SCFAs, such as butyrate and propionate, have been demonstrated to modulate DNA methylation in genes linked to inflammatory responses and metabolic homeostasis (47). Additionally, polyphenol-rich diets have been shown to induce histone modifications, enhancing the expression of genes involved in anti-inflammatory pathways (48). Furthermore, alterations in microbiome composition due to probiotic intake have been associated with microRNA-mediated regulatory mechanisms affecting immune and metabolic functions (49). These findings highlight the intricate interplay between dietary factors, gut microbiota, and epigenetic modifications, emphasizing their collective role in health and disease.

Table 1. Description of included studies

Study	Methodology	Limitations	Intervention Effects	Epigenetic Markers	Gut Microbiome Changes	Strengths	Risk of Bias	Year of Study
Hill, et al. (19)	RCT with overweight/obese adults, 3-month diet intervention, stool and blood analysis.	Small, unrepresentative sample; sequencing limitations.	Weight loss (6.2 ± 3.9%), improved cholesterol, triglycerides, glucose, and insulin.	DNA methylation (DNAme) profiles were analyzed via the EPIC 850K array.	The gut.The gut microbiome may influence DNA methylation in metabolic pathways that are related to weight loss.	Rigorously designed weight-loss trial with dietary monitoring.	Low	2023
Turchi, et al. (20)	Murine study on frataxin (FXN) deficiency and butyrate supplementation.	The KIKO mouse model may not fully represent human FA; long-term effects are unclear.	Improved glucose tolerance, metabolic restoration.	Not directly assessed but linked to inflammation & metabolic changes.	FA mice had altered gut microbiota, with reduced butyrate-producing bacteria.	Demonstrates the potential therapeutic role of butyrate in FA.	High	2023
Sun, et al. (21)	DNA methylation analysis (DREAM sequencing, bisulfite pyrosequencing, qRT-PCR) in a microbiota-inflammation model.	Difficulty separating inflammation's role in epigenetic changes.	Microbiota and inflammation influenced DNA methylation at CpG sites.	DNA methylation at CpG sites.	Not assessed.	Multi-model approach, deep-sequencing of methylation changes.	Moderate	2023
Fawad, et al. (22)	Murine and human intestinal organoid cultures, exposure to microbial metabolites.	Inability to co-culture live bacteria; jejunal organoids are less exposed to microbiota.	Not applicable (mechanistic study).	HDAC inhibition, particularly HDAC3, influenced intestinal circadian rhythms.	SCFAs from gut microbiota entrain intestinal circadian rhythms via HDAC inhibition.	Expertise in intestinal organoid research and systems biology.	Moderate	2022
Mima, et al. (23)	Nurses' Health Study & Health Professionals Follow-up Study; colorectal cancer cohort.	Limited cancer recurrence data; treatment data constraints.	Not applicable (observational cohort study).	LINE-1 methylation levels.	Higher Fusobacterium nucleatum DNA in tumors is linked to worse prognosis.	Extensive colorectal cancer database.	Low	2016
Chleilat, et al. (24)	24 male rats (HF/S vs. HF/S+M diet); offspring metabolic assessment.	Rat model—unclear human relevance.	Reduced fat mass, improved fertility, and altered metabolism.	Reduced DNMT3a and miRNA alterations in offspring.	Increased microbiome diversity & SCFA levels.	First study linking paternal diet to offspring metabolic and microbiome effects.	Low	2021
Goni, et al. (25)	Literature review on personalized nutrition, nutrigenetics, epigenetics, and gut microbiota	Heterogeneity of studies, small sample sizes, short interventions, difficulty in standardization, and publication bias	Not reported	Potential role of nutrigenetics, epigenetics, and metagenomics in personalized diets	Dysbiosis linked to obesity, inconsistent Bacteroidetes/Firmicutes ratios	Integrates multiple biological data sources	Moderate	2015
Lilja, et al. (26)	Fasting vs. control groups (N=55), blood/stool sample analysis, mitochondrial and gene expression studies	Small sample size, difficulty in coordination, need for long-term studies	Increased ketone levels, mitochondrial DNA, expression of longevity genes (FoxO1, SIRT1, SIRT3), and reduced pro-senescence miRNA	Upregulation of longevity genes (SIRT1, SIRT3) and reduced aging-related miRNA	Increased Christensenella (longevity-linked), reduced Faecalibacterium prausnitzii	Explores fasting's role in mitochondria, epigenetics, and microbiome	Moderate	2021
Chen, et al. (27)	S-PRESTO cohort study, microbiome, lipidomics, and genetics analyzed with PhenoAgeAccel	Small GWAS sample, self-report bias, cross-sectional design	Not reported	Novel lipidomic and microbiome markers associated with aging	Higher diversity linked to lower PhenoAgeAccel; Erysipelotrichaceae UCG-003, Bacteroides vulgatus correlated with aging	Multi-platform aging analysis identifies modifiable risk factors	Low	2024

Table 1 (Continued)

Study	Methodology	Limitations	Intervention Effects	Epigenetic Markers	Gut Microbiome Changes	Strengths	Risk of Bias	Year of Study
Kawakami, et al. (28)	Single-blind, 12-week BioBran intervention (N=9), aging biomarkers assessed	Small sample, single-blinded, single-masked design, unclear mechanisms	Reduced biological age, telomere age, DNAm IL-6, and increased telomere length	BioBran improves biological age, telomere length, and immune regulation	Not mentioned	Highlights BioBran's potential anti-aging benefits without lifestyle changes	Moderate	2024
Miller, et al. (29)	Observational study, Mediterranean diet (aMED) and pregnancy microbiome analysis	Recall bias, small sample, uncontrolled confounders	Not reported	Pregnancy decreases gut diversity; the Mediterranean diet may mitigate the decline.	Gut microbial diversity declines across trimesters	Observes maternal diet-microbiome interactions	Moderate	2021
Ugai, et al. (30)	Large-scale colorectal cancer study (N=13,101), molecular markers analyzed	No treatment data, heterogeneous marker testing	Not reported	Tumor location and molecular markers impact prognosis	Fusobacterium nucleatum correlates with MSI status and prognosis	Large dataset, molecular analysis	Moderate	2023
Louveau, et al. (31)	Review of neurodevelopmental disorders (NDDs)	Not explicitly stated	Not reported	NDDs should be seen as dimensional disorders overlapping psychiatry	Altered gut microbiome, impaired microglia maturation in NDDs	Integrates neurodevelopmental and microbiome perspectives	Moderate	2023
Baumann-Dudenhoeffer, et al. (32)	Twin cohort study, metagenomics & bioinformatics	Lacks maternal diet data; causality not established	Not reported	Infant microbiome co-evolves with breastmilk composition	Breastfed infants show microbiome shifts; soy formula alters diversity	Investigates microbiome evolution in infancy	Moderate	2018
Murga-Garrido, et al. (33)	Mouse study: 4 diets (cellulose, inulin, pectin, assorted fiber), microbiome, metabolomics, transcriptomics	Small sample, limited microbial diversity, incomplete fiber metabolism analysis	Gut microbiome influences metabolic fiber responses	Post-translational histone modifications	Microbiome-driven metabolic changes in fiber metabolism	Supports personalized fiber interventions	Moderate	2021
Ahmed, et al. (34)	Mouse model of colitis induced by *Citrobacter rodentium*; Dietary interventions (pectin, tributyrin); Gut microbiome analysis (16S rRNA); *In vitro* YAMC cell experiments	Improved intestinal barrier, reduced inflammation, restored microbiota balance	H3K27Ac, H3K9Ac, H3K4me3	Reversed dysbiosis, decreased *Proteobacteria*, increased *Bacteroidetes*, and *Firmicutes*.	Comprehensive dietary intervention study in colitis	Limited microbiome analysis for the tributyrin group; No 16S rRNA for antibiotic-treated samples	Moderate	2021
Khan, et al. (35)	Shrimp peptide hydrolysate (SPH) extraction; Immune organ indices in mice; Gut microbiome analysis (16S rRNA)	Enhanced immune response, improved intestinal integrity	Not mentioned	Increased beneficial gut bacteria	Detailed SPH study on gut and immune health	They did not explicitly state limitations; further validation is needed for SPH as a functional food.	Low	2022
Chleilat, et al. (36)	Male Sprague Dawley rats fed different diets (control, high-protein, high-fat/sucrose); Offspring assessed at weaning & adulthood.	Paternal high-protein diet improved offspring glucose metabolism & microbiota.	DNMTs, microRNAs (miRNAs)	Altered gut microbiome, increased beneficial metabolites	Comprehensive study on paternal diet influence on offspring metabolism	Did not explore microRNA roles in intergenerational effects	Low	2021

Table 1 (Continued)

Study	Methodology	Limitations	Intervention Effects	Epigenetic Markers	Gut Microbiome Changes	Strengths	Risk of Bias	Year of Study
Ogrodowczyk, et al. (37)	Female C57BL/6J mice on high-fat diet (HFD); Gut morphology assessed via histology; Crypt organoid cultures	Increased obesity, insulin resistance, inflammation, intestinal stem cells & crypt formation	Not mentioned	HFD disrupted the intestinal barrier & altered stem cell regulation	Robust design with metabolic & microbiome assessments	The high-fat diet model may not fully capture human dietary complexity	High	2020
Xie, et al. (38)	Systematic review of epigenetics, microbiota, & breast cancer (PubMed, Web of Science, ScienceDirect)	Calorie restriction reduced DNA hypermethylation; Sulforaphane reduced DNMT/HDAC expression; Canola oil & genistein modulated histone modifications.	DNA methylation, histone acetylation/deacetylation, miRNAs	Maternal dietary bioactives influenced microbiota & epigenetics	Advanced data analysis techniques; Multiple demographic & dietary factors considered	Variability in patient data; Causal relationships unclear	Moderate	2020
Soldado-Gordillo and Alvarez-Mercado (39)	Narrative review (2013–2023) on gut microbiota & food allergy; Literature search in PubMed & Scopus	Early-life environment impacts microbiome & allergy risk	DNA methylation, histone modifications, miRNAs	Microbiome alterations influence allergy development	Comprehensive analysis of microbiota & allergy link	Inconclusive evidence on breastfeeding & food allergy; Need more studies on probiotics & synbiotics	Moderate	2024
Notarbartolo, et al. (40)	Review of maternal diet, microbiome & epigenetic modifications in breast cancer risk	Nutrients (Vitamin D, polyphenols, LC-PUFAs) influenced immune tolerance & microbiota.	DNA methylation, histone modifications	Microbiome shifts affect immune function & allergy risk	Integrates epigenetics, microbiota & diet in breast cancer risk	Lacked explicit limitations	High	2023
Coppola, et al. (41)	9-month RCT (Italy) on Mediterranean diet in pregnancy; Maternal & infant gut microbiome analysis (metagenomics, metabolomics)	Study protocol only (no reported effects)	Not reported	Changes in maternal & infant microbiota	First RCT on Mediterranean diet & allergy prevention	Homogeneous population; No biomarkers for diet adherence	Moderate	2022

Overview of key findings

This systematic review highlights the intricate relationship between diet, gut microbiome composition, and epigenetic modifications. Evidence indicates that dietary patterns shape microbial diversity, which in turn influences epigenetic mechanisms governing gene expression related to inflammation, metabolism, and disease susceptibility. Diets rich in fiber and polyphenols promote beneficial microbiome changes and favorable epigenetic modifications, whereas high-fat and processed diets contribute to gut dysbiosis and adverse epigenetic alterations.

Implications for precision nutrition

Diet-induced microbiome alterations have profound effects on metabolic pathways, inflammatory processes, and gene expression, exhibiting significant inter-individual variability. This variability underscores the promise of precision nutrition as a tailored approach to disease prevention and management. Advances in metagenomic sequencing and epigenetic profiling have enhanced our ability to discern individual responses to dietary interventions, paving the way for personalized nutritional strategies (50).

Several studies suggest that targeting the gut microbiome through diet can mitigate metabolic disorders, obesity, and chronic inflammatory diseases (51, 52). For instance, fiber-rich diets that enhance Faecalibacterium prausnitzii proliferation and SCFA production have been linked to reduced inflammation and improved insulin sensitivity, underscoring the potential of personalized dietary interventions in managing diabetes (53). Similarly, polyphenol-rich diets have been shown to influence histone acetylation patterns, leading to the downregulation of pro-inflammatory gene expression (48).

However, substantial interindividual variability in microbiome composition and epigenetic responsiveness presents a significant challenge to the implementation of precision nutrition. This highlights the necessity for further clinical investigations to refine and optimize dietary intervention models. By integrating microbiome and epigenetic data with nutritional strategies, the efficacy of personalized nutrition could be substantially enhanced, ultimately improving health outcomes on an individualized basis (54).

The findings underscore the potential of precision nutrition in leveraging microbiome-epigenetic interactions to optimize health. Advances in metagenomic and epigenetic sequencing have deepened our understanding of diet-induced microbiome shifts and their influence on gene regulation, paving the way for personalized dietary interventions (41, 55). For instance, fostering bacteria that produce short-chain fatty acids (SCFAs) through high-fiber diets may enhance DNA methylation patterns, reduce inflammation and improve metabolic health (8). Additionally, integrating machine learning and artificial intelligence could refine predictive models for individualized dietary responses.

Comparison with previous studies and integration of epigenetic modifications in cancer research

The relationship between diet, gut microbiome composition, and epigenetic modifications is increasingly recognized as a key factor in influencing human health outcomes. Previous studies have highlighted the critical role of microbial metabolites, such as short-chain fatty acids (SCFAs), in modulating gene expression through DNA methylation, histone modification, and microRNA regulation (56, 57). In our review, we found strong evidence that diets rich in fiber and polyphenols enhance microbial diversity and promote beneficial epigenetic modifications that regulate inflammatory and metabolic pathways, potentially reducing the risk of chronic diseases such as obesity, diabetes, and cancer. However, the relationship between diet-induced epigenetic changes and cancer remains complex and underexplored.

Several studies have shown that epigenetic modifications, including DNA methylation and histone acetylation, are central to the pathogenesis of various cancers, including colorectal cancer, breast cancer, and gastric cancer (58, 59). For example, increased Fusobacterium nucleatum abundance in colorectal cancer tissue is associated with unfavorable epigenetic changes that promote tumor progression (60). In our discussion, we now emphasize how the modulation of the gut microbiome through dietary interventions could influence these epigenetic mechanisms, thereby providing a potential avenue for cancer prevention and treatment. In particular, nutritional interventions that promote microbial species producing SCFAs, such as

Faecalibacterium prausnitzii, may offer a therapeutic strategy to modulate DNA methylation and histone modifications in a manner that reduces the risk of tumorigenesis.

Significance of epigenetic modifications in human health and disease

We also recognize that the role of epigenetic modifications in health extends far beyond cancer research. Epigenetic alterations influence gene expression without changing the underlying DNA sequence, allowing environmental factors, such as diet, to have lasting effects on an individual's health trajectory (61). This phenomenon is particularly relevant in diseases characterized by inflammation and metabolic dysfunction, such as cardiovascular diseases, diabetes, and neurodegenerative disorders.

Moreover, as we have discussed, the gut microbiome serves as a mediator between diet and epigenetic changes, with particular emphasis on the impact of microbial metabolites on chromatin remodeling and gene expression regulation (62). The link between the gut microbiome, inflammation, and epigenetics has profound implications for understanding disease mechanisms and the development of precision nutrition strategies aimed at mitigating disease risk. Specifically, the emerging field of nutrigenomics suggests that personalized dietary strategiesbased on an individual's microbiome and epigenetic profile could be tailored to reduce the risk of developing cancer and other chronic diseases (57).

Implications for precision nutrition and cancer prevention

The significance of precision nutrition in cancer prevention is becoming increasingly clear and apparent. Studies have shown that diets rich in polyphenols and fiber can induce beneficial epigenetic modifications that potentially mitigate cancer risk (63). These findings underscore the relevance of microbiome-targeted dietary interventions in both preventing and managing cancer. For example, the Mediterranean diet, known for its polyphenol-rich components, has been linked to improved gut microbiome diversity and favorable epigenetic changes associated with cancer risk reduction (64). In contrast, Western-style diets high in fats and processed foods contribute to microbiome dysbiosis, promoting epigenetic alterations that increase susceptibility to cancer (59).

In this context, our systematic review now highlights the growing evidence supporting diet-microbiome-epigenome interactions in cancer prevention. We propose that microbiome-targeted dietary interventions should be further explored as part of personalized nutritional strategies for cancer prevention, particularly in high-risk populations. By leveraging advances in metagenomic sequencing and epigenetic profiling, future studies could uncover more precise dietary recommendations that optimize gut health and epigenetic regulation to prevent cancer development.

Challenges and limitations

While our systematic review provides a comprehensive analysis of the current literature on the epigenetic influence of diet-induced gut microbiome changes, several limitations must be acknowledged. Firstly, despite our rigorous search and inclusion criteria, the studies included in this review vary in terms of methodologies, study populations, and dietary interventions, which may introduce heterogeneity in the results (56, 57). This variability in study design limits the generalizability of the findings and may affect the consistency of the observed effects of diet on microbiome composition and epigenetic modifications (30, 40).

Secondly, many of the studies included in our review have small sample sizes, which may limit their statistical power and the ability to detect meaningful associations between diet, microbiome changes, and epigenetic modifications (59). Additionally, a significant portion of the studies were cross-sectional, preventing the establishment of causal relationships between dietary interventions and epigenetic outcomes. Longitudinal studies with larger sample sizes are essential for further validating the causal pathways linking diet, microbiome, and epigenetic regulation.

Another limitation stems from the methodological variability in microbiome profiling techniques. While metagenomics and 16S rRNA sequencing are widely used for gut microbiome analysis, differences in sample collection, sequencing depth, and data analysis protocols may contribute to inconsistencies in the results. Similarly, the methods used to assess epigenetic

modifications, such as DNA methylation, histone modifications, and microRNA profiling, are not uniformly applied across studies, which can hinder direct comparisons (62). The use of standardized protocols for both microbiome and epigenetic assessments is crucial to advancing this field.

Future directions

Future research should prioritize well-controlled longitudinal and randomized clinical trials to elucidate causal relationships between diet, microbiome changes, and epigenetic modifications. Investigating dietary interventions across diverse populations is crucial for

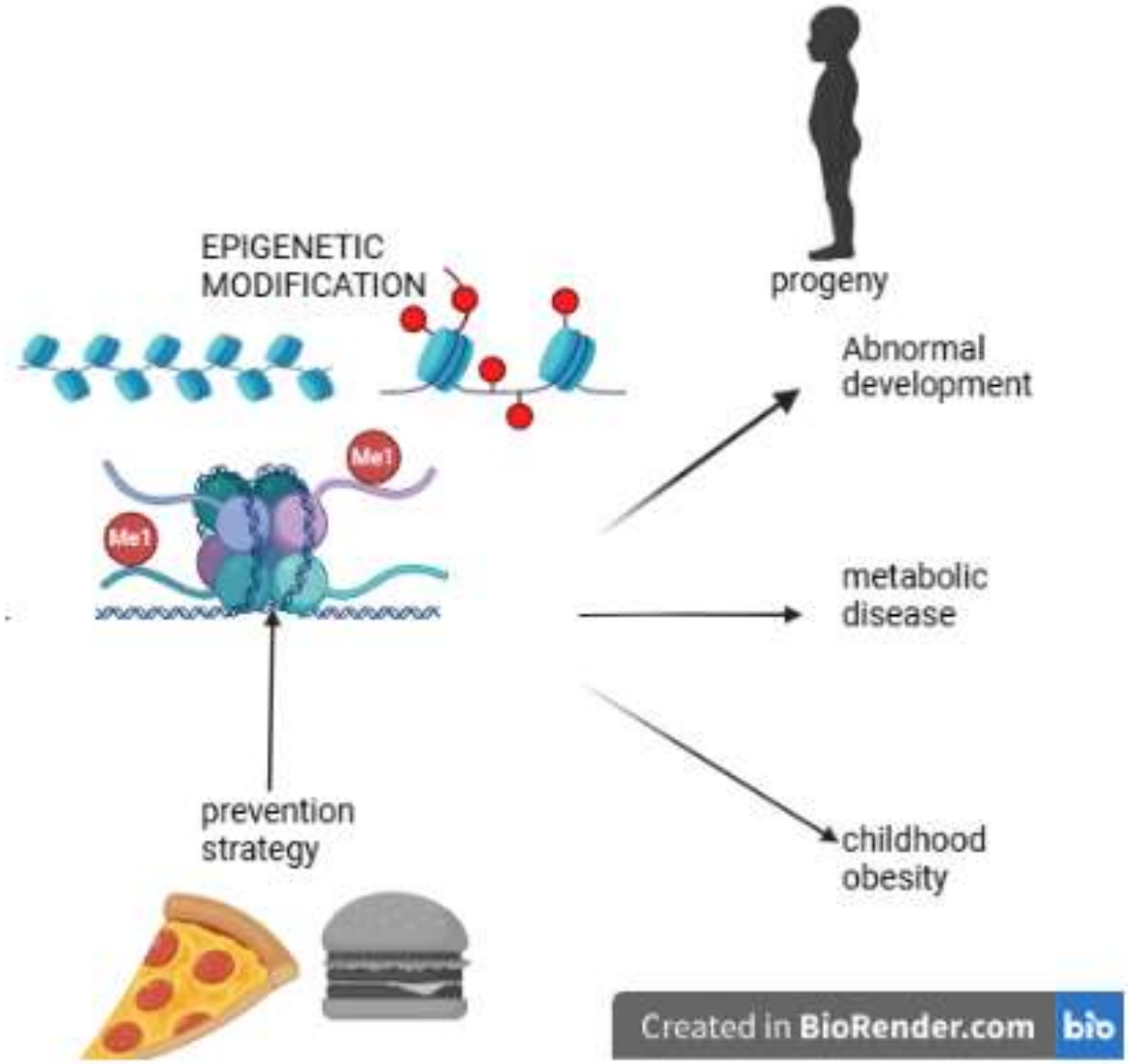

Figure 3. Epigenetic Modifications in Metabolic Health and Disease Prevention – This figure illustrates the impact of diet-induced changes in gut microbiome composition on epigenetic modifications and their subsequent effects on metabolic health. The dietary components, such as fiber-rich, polyphenol-rich, and high-fat diets, are shown to influence microbiome diversity and promote the production of metabolites like short-chain fatty acids (SCFAs), which modulate epigenetic markers (e.g., DNA methylation, histone modifications) and gene expression related to inflammation, metabolism, and disease susceptibility. Diets rich in fiber and polyphenols are associated with beneficial microbiome shifts and favorable epigenetic modifications that support metabolic health and reduce the risk of metabolic diseases like obesity and insulin resistance. In contrast, Western-style diets high in fat and processed foods contribute to dysbiosis, inflammation, and adverse epigenetic changes, which may increase the risk of developing chronic metabolic disorders, including obesity and type 2 diabetes.

equitable implementation. Several exciting directions for future research could enhance our understanding of the role of diet-induced gut microbiome alterations in epigenetic regulation and precision nutrition (65).

Firstly, large-scale, longitudinal, and randomized controlled trials (RCTs) are needed to establish causal relationships between diet, microbiome changes, and epigenetic modifications. These studies should focus on diverse populations to better understand individual variability in responses to dietary interventions, which could provide insights into personalized nutrition strategies. For instance, trials that examine the effects of high-fiber, polyphenol-rich, and Mediterranean diets on gut microbiome composition and epigenetic modifications could yield valuable insights into their role in preventing metabolic disorders and cancer (61, 63).

Secondly, more sophisticated multi-omics approaches are needed to integrate microbiome, epigenetic, and metabolomic data. Combining metagenomic sequencing with DNA methylation profiling, histone modification assays, and microRNA expression analysis will enable a more comprehensive understanding of the molecular mechanisms underlying diet-microbiome-epigenome interactions. These integrated approaches could be particularly valuable for identifying biomarkers that predict individual responses to dietary interventions, thereby advancing the field of precision nutrition (56, 57).

Another promising area for future research is the investigation of the gut-brain axis and its epigenetic regulation through dietary interventions. Emerging evidence suggests that gut microbiota alterations may influence brain function and behavior via microbial metabolites such as SCFAs (62). Exploring the role of diet-induced microbiome changes in regulating epigenetic modifications associated with neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, could open new avenues for disease prevention and management.

Lastly, the application of artificial intelligence (AI) and machine learning in analyzing large datasets from microbiome, epigenomic, and clinical studies could facilitate the development of personalized dietary recommendations. These AI-driven models could integrate individual microbiome and epigenetic profiles to predict responses to dietary interventions, thereby enhancing the precision of nutritional strategies for disease prevention and health promotion (59, 64).

Clinical and public health implications

Dietary patterns significantly influence microbiome-mediated epigenetic modifications, with implications for metabolic health and disease prevention (Figure 3). Personalized dietary strategies informed by microbiome and epigenetic markers could revolutionize the prevention and management of conditions such as obesity, diabetes, and inflammatory disorders. Public health policies should incorporate microbiome-epigenetic research to develop targeted dietary recommendations promoting population-wide health initiatives.

This review underscores the critical role of diet-induced microbiome alterations in regulating epigenetic processes. Diets high in fiber and polyphenols enhance microbial diversity, promote bioactive metabolite production, and modulate epigenetic markers linked to inflammation and metabolism (8, 9). Conversely, Western-style and high-fat diets are associated with gut dysbiosis, increased inflammation, and adverse epigenetic changes contributing to metabolic disorders (23, 37, 65). These findings highlight the potential for microbiome-targeted dietary interventions in precision nutrition.

Advances in sequencing technologies have enabled individualized exploration of microbiome-epigenome interactions, supporting personalized dietary recommendations (41, 55). However, clinical translation requires addressing key challenges, including individual variability, short study durations, and methodological inconsistencies (30, 40). Future research should focus on long-term, rigorously controlled human studies to establish causality and assess the efficacy of personalized dietary interventions. Standardized microbiome and epigenetic profiling methodologies are essential for ensuring reproducibility across studies (65). Integrating microbiome and epigenome data into public health frameworks could facilitate population-wide dietary strategies for chronic disease prevention (66).

Conclusion

In conclusion, this review highlights the pivotal role of diet in shaping gut microbiome composition and its subsequent influence on epigenetic regulation, offering critical insights into the emerging field of precision nutrition. A growing body of evidence underscores how dietary components such as fiber, polyphenols, and

probiotics can promote a healthy microbiome and favorable epigenetic changes diets. In contrast, Western-style and high-fat diets contribute to dysbiosis and adverse epigenetic modifications. These findings emphasize the potential of integrating microbiome and epigenetic research to inform personalized dietary strategies, which could significantly enhance metabolic health and prevent diseases like cancer and neurodegenerative disorders.

However, several challenges persist, including the heterogeneity of existing studies, small sample sizes, and inconsistencies in methodology, which must be addressed to strengthen the evidence base. The need for large-scale, longitudinal studies with standardized protocols for microbiome and epigenetic assessments is paramount to unravel the causal relationships between diet, microbiome, and epigenetics. Furthermore, the integration of multi-omics approaches, alongside AI-driven models, holds promise for refining personalized nutrition and facilitating the development of tailored dietary recommendations. By overcoming these barriers, we can advance evidence-based nutritional guidelines that optimize gut microbiome health and support epigenetic wellness, ultimately contributing to improved clinical outcomes and better public health. We hope this review serves as a foundation for future investigations that further explore the intricate interactions between diet, gut microbiome, and epigenetic regulation, especially in the context of chronic disease prevention.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this review, the authors employed ChatGPT and QuillBot to assist in rephrasing information sourced from the referenced journal articles, with the aim of enhancing language clarity and manuscript readability. All AI-generated content was meticulously reviewed, edited, and refined by the authors, who assume full responsibility for the accuracy and integrity of the final publication.

Conflict of interests

The authors declare no conflict of interest.

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