RESEARCH PAPER

Nutrigenomics and Metabolic Health: A Systematic Review of Biochemical Mechanisms Linking Diet and Disease

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ABSTRACT

Background: The occurrence of metabolic disorders (e.g., obesity, type 2 diabetes, metabolic syndrome) is a result of complex interactions between genetic makeup and the food that one eats. Nutrigenomic science investigates how the nutrient content of foods modulates the expression of genes and the molecular pathways of metabolic health, and explains differences between individuals regarding their risk of metabolic disease.

Objective: This systematic review aimed to synthesize human evidence on the biochemical and molecular mechanisms linking diet, gene regulation, and metabolic health within a nutrigenomic framework.

Methods: Utilizing PRISMA 2020 protocol, the systematic literature review was conducted from January 2000 through December 2024, as identified via website searches (PubMed and Scopus) of the entire literature. The studies identified needed to be original research focused on the nutritional/biological component of the human body, such as human nutrigenomics and/or nutrigenetics, which studied the biochemical, molecular, and/or epigenetic mechanisms that impact an individual's metabo lic health.

Studies meeting both of these factors were then selected according to predetermined eligibility criteria for the study selection process, which outlines answers and qualitative synthesis of data taken from those studies.

Results: Of the total records that were found (740), only 9 studies met our inclusion criteria and were included in the synthesis of qualitative data. The studies examined demonstrated that the components of our diet are signalling molecules (through diet) which can affect gene expression, transcription factor activity and epigenetic regulation, all of which are involved in how the body regulates various processes. The main mechanisms they identified were nutrient-responsive pathways (e.g., regulating lipid metabolism, glucose homeostasis, inflammation) and they highlighted that gene-diet interaction and epigenetic modification resulting from diet significantly contribute towards the variability of susceptibility to metabolic disorders between individuals.

Conclusion: The most recent data shows that the nutrigenomic mechanisms that help maintain the metabolic health of individuals, by directly connecting diets to gene regulation and metabolic pathways, exert a significant influence. To date, there are many examples of integrative human studies that demonstrate the mechanistic detail of how diet influences metabolism and gene regulation; however, there continues to be a significant shortage of primary human studies that also incorporate the molecular endpoints of these interactions. Future research must consider nutritional interventions alongside genomic and epigenetic studies to maximise the potential of precision nutrition strategies to prevent and manage metabolic disease.

Keywords: Nutrigenomics; Metabolic health; Diet–gene interaction; Epigenetics; Metabolic disease; Precision nutrition

How to cite this article: How to cite this article: Chittamuru Maansi Reddy1* Dr. Prabhakar. K2 Dr. Anil Kumar Sakaleecha3. Right liver lobe diameter/albumin ratio and platelet count/spleen diameter ratio as noninvasive predictors of esophageal varices in patients with liver cirr. Nutrigenomics and Metabolic Health: A Systematic Review of Biochemical Mechanisms Linking Diet and Disease. Int J Drug Deliv Technol. 2026;16(76s):2248-2253. DOI: 10.25258/ijddt.16.76s.225.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Obesity, Type 2 Diabetes, and Metabolic Syndrome are major public health concerns worldwide due to their increasing prevalence. These conditions occur in response to a complex interaction between both genetic predisposition and environmental factors, with diet being one of the most important contributors to their development and progression. Traditional nutritional approaches based upon population-level dietary recommendations do not take into account each person's individual differences with respect to metabolic responses and therefore, a more personalised approach to nutrition is necessary (1–3). Nutrigenomics is one aspect of Nutritional Genomics and refers to the study of how different components of the diet affect gene expression and the biochemical pathways involved in metabolism, inflammation and energy homeostasis. In contrast to traditional nutritional research, nutrigenomics specifically focuses on examining how nutrients act as signalling molecules to affect transcription factors, epigenetic modifications and metabolic networks (4–6). The results of these studies provide insight into the variability of human response to similar dietary exposures and the impact of genetic susceptibility on population dietary patterns with respect to increased risk for certain diseases.

The recent development of new research tools has led to several studies indicating that certain nutrients may ultimately modulate key metabolic pathways by regulating

transcriptional regulators such as PPARs, SREBP and NF-kB. The action of nutritional components may also induce epigenetic changes in chromatin structure through: DNA methylation; histone modifications; and deacetylation. These mechanisms could result in long-term changes in regulation of metabolic genes through alteration of gene expression (7–9). By understanding these mechanisms, we will be able to establish the biological basis for the relationships between certain dietary patterns and chronic metabolic disorders.

The interplay between genes and diets also further influences metabolic heterogeneity due to the existence of differences between individuals in the way that macronutrients and bioactive food compounds affect lipids, insulin, and inflammation. Genetic variations in genes responsible for lipid transport, lipid metabolism and glucose homeostasis have been associated with higher risk of obesity and Type 2 Diabetes (10–13). Understanding how these gene-nutritional interactions occur is essential for developing an effective precision nutrition approach to prevention of metabolic disorders.

Although significant progress has been made in nutrigenomics research over the past several years, the link between diet, gene regulation and metabolic disease is still not well understood in many aspects of human nutrition research (5,13–15). Therefore, a thorough synthesis and review of the existing literature is required in order to clarify how different dietary components influence the molecular pathways that regulate metabolic health. Hence, the purpose of this systematic review is to provide a critical appraisal of the existing literature on human studies that investigate how nutrigenomics interactions can affect metabolic health and therefore risk for disease.

2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency and methodological rigor.

2.1 Literature Search Strategy

Two digital libraries were used to carry out an article database search: Scopus and PubMed. The purpose of selecting both of these databases was to provide a wider range of access to the biomedical, nutritional, and molecular research article databases. The search strategy was designed to identify research articles that studied the bio-chemical pathways that nutrigenomic interactions have resulted in the metabolic health of humans.

The primary search terms that were used to perform the article search were as follows: "nutrigenomics," "nutritional genomics," "diet-gene interaction," "metabolic health," "metabolic syndrome," "obesity," "diabetes," "epigenetics," and "biochemical pathways." The search was conducted according to the specific syntax of each database, wherever there were differences.

The articles reviewed during this search were in the English language and were published between January 1, 2000, and December 1, 2024. The reference lists of eligible articles were also included as part of the search effort to identify additional eligible articles for review.

2.2 Eligibility Criteria

The following criteria must be met for a study to be included in this review: (i) the study used human participants; (ii) there was a consideration of nutrigenomic and/or nutrigenetic interaction; (iii) a comparison between nutritional elements to metabolic health / disease was made using biochemically/molecularly/epigenetically based explanations; (iv) the study was an original research article, a narrative review, or systematic review of the literature. The metabolic outcomes (i.e. obesity, insulin resistance, type 2 diabetes, metabolic syndrome) will be prioritized over other outcomes in this review. Studies that were conducted on animals or cell cultures (in vitro) only, studies that did not provide mechanistic information related to nutrition-to-health/disease considerations and studies that did not consider health outcome measures were not included. Conference abstracts, editorial comments and opinion pieces will be eliminated from consideration.

2.3 Study Selection

The reference management system (RMS) was used to store all records retrieved from database searches. All duplicate records were removed from the RMS before each title and abstract was screened by at least two independent reviewers per eligibility criteria. Full-text articles were obtained for each study that met the inclusion criteria, and those articles were reviewed to determine whether they would ultimately be included in the review. Differences between independent reviewers were resolved through discussion and consensus. Figure 1 graphically displays PRISMA Flowchart for the Current Study.

2.4 Data Extraction and Synthesis

The standardised extraction process was used to obtain data for each of the included articles, and data extracted during the data extraction phase consist of the following items: The year the publication of each article was published; The type of study; The characteristics of the population being studied; The dietary factors examined; The genetic and/or epigenetic targets for the dietary factors studied; Metabolic outcomes resulting from the dietary factors studied; Proposed biochemical mechanisms for the metabolic effects of the dietary factors studied. The heterogeneity of study designs, outcomes and their combination made performing a meta-analysis impossible; therefore, the authors of this research performed a qualitative narrative synthesis of the data to identify common molecular pathways and mechanistic themes through which diet, gene regulation, and metabolic health are linked.

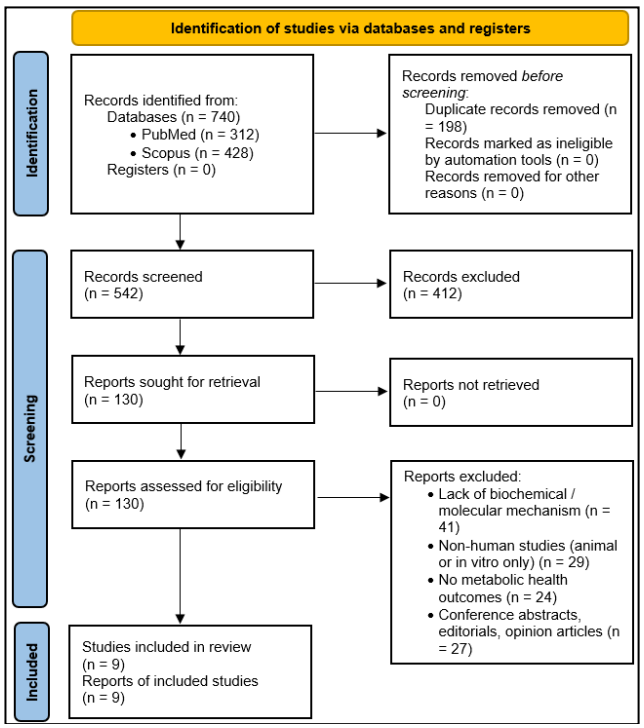

Figure 1. PRISMA Flow Chart

3. Results

3.1 Study Selection

A database search of both PubMed and Scopus yielded a cumulative total of 740 articles. After removing any duplicates, 542 articles remained for screening based on titles and abstracts. During that initial screening process, 130 articles were reviewed for full-text eligibility. At that point, 121 of those articles were excluded because they did not provide mechanistic evidence to support their inclusion; the studies used an experimental design that involved nonhuman subjects; or their findings were not related to health outcomes associated with metabolic syndrome. Thus, only nine articles met the criteria for inclusion and underwent qualitative synthesis. These nine studies provided evidence of the mechanism by which dietary factors can influence gene expression, and therefore influence metabolic health, among human populations.

3.2 Characteristics of Included Studies

The nine incorporated studies were published from among a range of sources over the period of 2004 and 2018. The types of publication that comprised the nine incorporated studies were almost exclusively systematic reviews or narrative reviews that synthesise human research on nutrigenomics and metabolic health of a high standard.

These various studies have addressed the biochemical and molecular mechanisms whereby components of the diet affect gene expression, epigenetic modifications or metabolic pathways. The various metabolic outcomes that have been investigated across these nine publications are obesity; insulin resistance; type 2 diabetes; metabolic syndrome; and cardiometabolic risk. The key mechanistic patterns that were examined in these authors' investigations included nutrient-regulated transcription factors; epigenetic modifications; diet-gene interactions; and the role of inflammation-related metabolic pathways.

3.3 Summary of Evidence

The dietary components in the studies evaluated act as regulators of gene expression. Across the studies included, dietary components have been shown to regulate genes involved in lipid metabolism, glucose balance, and inflammatory signals. Various dietary components such as fatty acids, carbohydrates, micronutrients, and bioactive compounds modulate the activity of transcriptional regulators (e.g., fatty acid and carbohydrate sensitive transcriptional regulators, such as PPARs, SREBP, and NFkB), which control metabolic processes.

Studies have also identified the role of epigenetic mechanisms (including DNA methylation and histone modifications) as mediators of the long-term impact of diet on metabolism. Finally, genetic variation represents a major contributor to the different responses individuals experience from the same type of diet, therefore supporting the concept that personalized nutrition will be necessary to reduce the incidence of metabolic diseases.

Table 1. Characteristics of Included Studies

Author (Year)	Study Type	Population Focus	Dietary Factors Examined	Key Molecular / Biochemical Mechanisms	Metabolic Outcomes
Afman & Müller (2006) (16)	Narrative review	Humans	Fatty acids, carbohydrates, micronutrients	Regulation of PPARs, SREBPs, NF-κB; gene expression modulation	Lipid metabolism, insulin sensitivity
Corella & Ordovás (2014) (17)	Narrative review	Humans	Dietary fats, Mediterranean diet	Gene–diet interactions affecting lipid and glucose pathways	Obesity, metabolic syndrome, T2DM
Kaput & Rodriguez (2004) (18)	Narrative review	Humans	Macronutrients, bioactive compounds	Nutrient-responsive gene regulation and signaling pathways	Metabolic disease susceptibility
Ferguson et al.	Narrative	Humans	Dietary patterns,	Integration of nutrigen	Cardiometabolic

(2016) (19)	review		bioactive nutrients	omics, microbiome, inflammation pathways	disease risk
Mathers (2017) (20)	Narrative review	Humans	Folate, fatty acids, bioactives	DNA methylation and epigenetic regulation of metabolic genes	Metabolic disorders
Milagro et al. (2013) (21)	Narrative review	Humans	Dietary components influencing obesity	Epigenetic modifications affecting adipogenesis and energy balance	Obesity
Barres & Zierath (2011) (22)	Narrative review	Humans	Diet-related metabolic exposures	DNA methylation changes in insulin and mitochondrial genes	Insulin resistance, T2DM
Phillips (2013) (14)	Narrative review	Humans	Macronutrient composition	Genetic polymorphisms influencing metabolic response to diet	Obesity, metabolic syndrome
Ordovás et al. (2018) (23)	Narrative review	Humans	Personalized dietary patterns	Nutrigenetic modulation of lipid and glucose metabolism	Metabolic syndrome

4. Discussion

Through systematic review, we analysed the literature to provide evidence for the biochemical and molecular mechanisms by which nutrigenomics may affect human metabolic health. The studies reviewed demonstrate how nutritional elements influence gene expression, epigenetic events, and metabolic signalling pathways, and as such contribute to the development of overweight and obesity, insulin resistance, type 2 diabetes, and metabolic syndrome in mankind (Afman & Müller, 2006; Corella & Ordovás, 2014; Mathers, 2017) (16,20,23).

Several studies have identified nutrients as bioactive signalling molecules capable of modulating transcription factors that regulate metabolism. In particular, Afman and Müller (2006) provided evidence that dietary fatty acids and carbohydrates can regulate the transcriptional activity of PPARs, SREBPs, and NF-κB, and that as such, they can have a direct effect on lipid metabolism, glucose homeostasis, and inflammatory responses (16). In the same way, Kaput and Rodriguez (2004) have highlighted that nutrient-induced gene expression occurs through coordinated mechanisms of transcription and post-transcription regulation (18). Therefore, the metabolic responses of an individual to dietary intake can vary greatly. Epigenetic regulation appears to be a critical pathway by which the consumption of certain nutrients can lead to long-term metabolic outcomes (24). According to Mathers (2017) and Milagro et al. (2013), the consumption of various nutrients such as folate, fatty acids and bioactive food components has an effect on DNA methylation and histone modifications in genes associated with insulin signalling, energy metabolism, and adipose tissue development (20,21). Because of these effects, it appears that biomolecular changes in diet-driven epigenetics result in changes to the metabolic phenotype of individuals. Therefore, dietary exposures appear to exert long-term effects on a person's susceptibility to disease (25). Barres and Zierath (2016) showed that the presence of differences (alterations) in methylation patterns for mitochondrial function and insulin responsiveness genes can link epigenetics, nutrition and metabolic dysfunction (insulin resistance and type II diabetes) (22).

Gene–diet interactions consistently identified as statistically significant and/or major determinants of metabolic health; for example, Corella and Ordovás (2014) demonstrated that gene variants affecting lipid transport, glucose metabolism, and inflammation respond differently to dietary fats and to specific dietary patterns, including but not limited to the Mediterranean Diet, and that these interactions have a significant effect on obesity risk, lipid profiles and glycemic control (23). Evidence to support this notion was provided by Phillips (2013) who demonstrated that common genetic polymorphisms in metabolic genes modulate one's susceptibility to both obesity and metabolic syndrome in response to the ratio of macronutrient composition within our diets; thereby reinforcing the importance of nutrigenetic factors when assessing the stratification of risk for metabolic diseases (14).

Ferguson et al. (2016) further emphasize the importance of integrating nutrigenomics with other biological systems (i.e. host), and highlight the interaction between dietary factors, the host, gut microbiome, and inflammatory pathways to the incidence of cardiometabolic disease. Their work suggests that the impact of nutrigenomics on metabolic health occurs through multiple levels of omics

interactions, and hence complicates the development of uniform public health recommendations (19).

Caputo and Rodriguez (2004) and Mathers (2017) direct their readers to randomized controlled trials and observational studies on dietary patterns with respect to metabolic health outcomes; however, the number of human studies investigating into the biochemical and molecular mechanisms controlling nutrigenomic interactions is limited (18,20). Most primary research articles concentrate on clinical outcomes (e.g. body weight, lipids, glycemics) without focusing attention on molecular endpoints (e.g. gene expression, epigenetic modification, and molecular signalling pathways); thus, the evidence base for mechanisms involved is predominantly derived from integrative review articles that aggregate results of experimental, clinical, and population studies (Afman & Müller, 2006; Corella & Ordovás, 2014) (16,23). Consequently, there is a critical need to conduct more human-based studies incorporating molecular endpoints as part of the research design, to establish causal relationships in nutrigenomic research.

5. Limitations

The limitations of this systematic review can be detailed as follows: 1) The majority of the studies included in this review are narrative and integrative reviews with little representation of primary RCTs or large scale observational studies with molecular endpoints; 2) Due to differences in design and exposure to dietary factors, genetic markers targeted, and metabolic output due to heterogeneity between the studies, it was not possible to perform a quantitative synthesis or meta-analysis; 3) By limiting search results to studies published in English, the search may have missed many potentially relevant research studies reported in other languages. Nevertheless, despite the above limitations, the current systematic review offers a focused, mechanistically-oriented synthesis of the existing literature related to diet, the regulation of genes, and metabolic health.

6. Conclusion

This systematic review has shown how important the different aspects of nutrigenomics (genes and food) to metabolic (health) have to do with the way that the food we eat affects our health. In addition, the authors conclude that through nutrient-induced modulation of gene expression, epigenetic regulation, and metabolic signalling pathways, there is a wide range of differences between individuals in their susceptibility (for example, obesity and heart disease) for developing metabolic disorders. The potential of nutrigenomics to support precision nutrition strategies is well supported by the current evidence. However, to take full advantage of the knowledge generated from nutrigenomic studies (nutritional genomics), future research needs to be specifically designed to combine the use of food (dietary interventions) with both molecular and metabolic (biochemical) assessments within the same human study. Ultimately, the authors propose that future research should lead to prudently developed and applied approaches to the prevention and management of metabolic diseases using nutrigenomic approaches.

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