WebLog Journal of Biochemistry

Review Article
Published: 12 Nov, 2026

Nutrient-Gene Interactions in Metabolic Health: The Interplay of Nutrigenomics, Microbial Ecology and Metabolic Signaling Networks

Idakwoji Precious Adejoh[1], Nwafor Ijeoma[2], Okorie Claribel[3], Udoeyop Favor[3], Nweje-Anyalowu Paul[4], Enyinnaya Blessing Oluchi[5], Banwo Faridah Mobolanle[6], Shehu Muhammad Hassan[7], Umar Muhammed Muhsin[8] and Akuba Barnabas Ojochegbe[9]*

[1]*Department of Biochemistry, Faculty of Natural Sciences, Prince Abubakar Audu University, Anyigba, Kogi State, Nigeria*

[2]*UNESCO International Centre for Biotechnology, Nsukka, Enugu State, Nigeria*

[3]*Department of Medical Biochemistry, College of Medicine, Godfrey Okoye University, Ugwuomu-Nike, Enugu State, Nigeria*

[4]*Biochemistry Programme, Department of Chemical Sciences, Faculty of Science, Clifford University, Owerrinta (Ihie Campus), Abia State, Nigeria*

[5]*Department of Public Health, Faculty of Basic Medical Sciences, Clifford University, Owerrinta, Abia State, Nigeria*

[6]*Department of Zoology, Faculty of Science, Ahmadu Bello University, Zaria, Kaduna State, Nigeria*

[7]*Department of Biochemistry, Faculty of Life Sciences, Ahmadu Belo University, Zaria, Kaduna State, Nigeria*

[8]*Department of Microbiology, Faculty of Life Sciences, Bayero University Kano, Kano, Kano State, Nigeria*

[9]*Department of Biochemistry, Faculty of Life Sciences, Federal University Lokoja, Lokoja, Kogi State, Nigeria*

WebLog Open Access Publications
Article ID : wjbc.2026.k1203
Author : Idakwoji Precious Adejoh

Abstract

Background: Metabolic health is shaped by an integrated network involving nutrient availability, gene regulation, microbial ecology, and metabolic signaling pathways, which collectively regulate key processes such as glucose homeostasis, lipid metabolism, inflammation, and energy balance. These interactions influence individual susceptibility to metabolic disorders and responses to dietary interventions.

Objective: This review evaluates current evidence on the interplay among nutrigenomics, microbial ecology, and metabolic signaling networks in the regulation of metabolic health and disease.

Methods: Relevant findings from studies investigating nutrient-gene interactions, gut microbiota-mediated metabolic regulation, and biochemical signaling pathways were critically examined. Particular attention was given to molecular mechanisms involving short-chain fatty acids, bile acid signaling, inflammatory cascades, insulin signaling, lipid metabolism, oxidative stress, and epigenetic regulation. Evidence from multi-omics approaches, including transcriptomics, metabolomics, metagenomics, and epigenomics, was also assessed.

Results: Current evidence demonstrates that metabolic health is influenced by dynamic interactions among dietary components, host genetic architecture, microbial metabolism, and cellular signaling pathways. Dietary patterns significantly affect microbial diversity and metabolic phenotypes, while microbial metabolites serve as key mediators linking nutrition to host metabolic responses. Advances in multi-omics technologies have improved understanding of diet-host-microbiome interactions and have facilitated the identification of molecular pathways underlying metabolic regulation.

Conclusion: Improved understanding of the diet-host-microbiome interactions may enable the development of more effective and personalized nutritional interventions for the prevention and management of obesity, type 2 diabetes mellitus, cardiovascular disease, and other metabolic disorders. Despite significant progress, challenges related to population heterogeneity, methodological variability, and ethical considerations in genomic nutrition remain important areas for future research.

Keywords: Nutrient-Gene Interactions; Metabolic Health; Nutrigenomics; Microbial Ecology; Metabolic Signaling Networks; Precision Nutrition; Gut Microbiome; Obesity; Type 2 Diabetes Mellitus; Cardiovascular Disease

OPEN ACCESS

Correspondence:
Idakwoji Precious Adejoh, Department of Biochemistry, Faculty of Natural Sciences, Prince Abubakar Audu University, Anyigba, Kogi State, Nigeria, E-mail: idakwojipa@gmail.com

Received Date: *16 Oct 2026*
Accepted Date: *10 Nov 2026*
Published Date: *12 Nov 2026*

Citation:
Idakwoji PA, Nwafor I, Okorie C, Udoeyop F, Nweje-Anyalowu P, Enyinnaya BO, et al. Nutrient-Gene Interactions in Metabolic Health: The Interplay of Nutrigenomics, Microbial Ecology and Metabolic Signaling Networks. WebLog J Biochem. wjbc.2026.k1203. https://doi.org/10.5281/zenodo.24267713

Copyright *© 2026 Idakwoji Precious Adejoh. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*

Introduction

Metabolic disorders including obesity, insulin resistance, type 2 diabetes mellitus, non-alcoholic fatty liver disease, and cardiovascular disease remain among the leading causes of global morbidity and mortality [1]. The rapid rise in these disorders over the past decades cannot be explained solely by genetic predisposition, indicating a substantial contribution from environmental and dietary exposures [1]. Contemporary research increasingly recognizes that dietary components influence metabolic health not only through caloric balance but also through direct modulation of gene expression, microbial ecology, cellular signaling pathways, and epigenetic regulation [2].

Nutrigenomics describes the influence of nutrients and dietary compounds on genome function and gene expression, whereas nutrigenetics focuses on how genetic polymorphisms modify individual responses to nutrients and dietary interventions [3]. Together, these disciplines form the basis of precision nutrition, an emerging approach aimed at tailoring dietary interventions according to genetic makeup, metabolic phenotype, and microbial composition [4]. Advances in high-throughput sequencing, metabolomics, transcriptomics, and systems biology have significantly improved understanding of the molecular relationships among diet, genes, and metabolism [5].

The gut microbiota has become a central component of metabolic research because of its critical role in nutrient metabolism, immune regulation, intestinal barrier maintenance, and host signaling pathways [6]. Human intestinal microorganisms metabolize dietary substrates into bioactive compounds including short-chain fatty acids, bile acid derivatives, branched-chain amino acids, trimethylamine, and indole metabolites, many of which directly influence insulin sensitivity, inflammatory signaling, lipid metabolism, and energy homeostasis [7]. Alterations in gut microbial composition, commonly referred to as dysbiosis, have been consistently associated with obesity, metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease [8].

The relationship between diet and microbial ecology is bidirectional. Dietary patterns shape microbial diversity and functionality, while the microbiota modifies nutrient availability and metabolic outcomes [9]. Diets rich in dietary fiber and plant-derived polyphenols generally promote microbial diversity and short-chain fatty acid production, whereas Western dietary patterns characterized by high saturated fat and refined sugars are frequently associated with microbial dysbiosis and systemic inflammation [10]. Emerging evidence further demonstrates that genetic variation can partly determine microbial composition and metabolic responses to diet, thereby linking nutrigenetics with microbial ecology [11].

Several nutrient-sensitive biochemical pathways are now recognized as central regulators of metabolic health. These include AMP-activated protein kinase signaling, mammalian target of rapamycin signaling, peroxisome proliferator-activated receptor pathways, insulin receptor signaling, nuclear factor-kappa B activation, and oxidative stress-related pathways [12]. Nutrients and microbial metabolites can directly influence these signaling systems, leading to metabolic adaptations or dysfunction depending on the nutritional and microbial context [13]. For instance, butyrate produced through microbial fermentation of dietary fiber can regulate histone deacetylase activity and improve insulin sensitivity through epigenetic and anti-inflammatory mechanisms [14].

Epigenetic modifications have also emerged as important mediators of nutrient-gene interactions. Dietary compounds may influence DNA methylation, histone modification, and non-coding RNA expression, thereby modifying transcriptional activity without altering nucleotide sequences [15]. Such modifications may contribute to long-term metabolic programming and susceptibility to chronic metabolic disease [16]. Importantly, microbial metabolites including short-chain fatty acids and folate participate in epigenetic regulation, further linking microbial ecology with host genomic responses [17].

The heterogeneity observed in individual metabolic responses to identical diets has accelerated interest in personalized nutrition strategies [18]. Interindividual variability may arise from differences in genetic polymorphisms, microbiota composition, lifestyle factors, age, sex, and environmental exposures [19]. Consequently, universal dietary recommendations may be insufficient for optimal metabolic disease prevention and management [20]. Precision nutrition seeks to address this limitation through integration of nutrigenomics, metabolomics, and microbiome science [21].

Recent multi-omics studies have provided deeper insight into the integrated molecular networks connecting nutrients, microbiota, and host metabolism [22]. Metabolomic analyses have identified microbial metabolites associated with insulin resistance, inflammation, and lipid abnormalities, while transcriptomic approaches have clarified nutrient-induced gene regulatory networks [23]. Similarly, metagenomic sequencing has enabled functional characterization of microbial communities involved in metabolic regulation [24].

Despite substantial progress, several challenges remain. Many nutrigenomic studies are limited by small sample sizes, ethnic variability, inconsistent methodologies, and difficulties in establishing causality [25]. The complexity of diet-host-microbiome interactions further complicates interpretation of findings. In addition, ethical concerns surrounding genomic data privacy, accessibility of personalized nutrition, and reproducibility of microbiome interventions continue to attract scientific debate [26].

Given the growing burden of metabolic disorders worldwide and the increasing recognition of nutrient-gene-microbiome interactions in metabolic regulation, a comprehensive evaluation of current evidence is warranted. This review examines the interplay among nutrigenomics, microbial ecology, and biochemical pathways in metabolic health, with emphasis on molecular mechanisms, clinical implications, and future directions in precision nutrition research.

Methodology

Study design

This review was conducted as a narrative review aimed at synthesizing current evidence regarding nutrient-gene interactions in metabolic health, with emphasis on nutrigenomics, microbial ecology, and biochemical pathways. The review integrated findings from molecular biology, nutritional sciences, microbiome research, metabolic medicine, and systems biology to provide a comprehensive understanding of the mechanisms underlying diet-host interactions in metabolic regulation.

Literature search strategy

A structured literature search was performed using major electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. Searches were conducted for studies published between January 2020 and May 2026. The search strategy combined

Medical Subject Headings and free-text keywords related to nutrient-gene interactions and metabolic health.

The principal search terms included "nutrigenomics," "nutrigenetics," "precision nutrition," "gut microbiota," "microbial ecology," "metabolic syndrome," "obesity," "type 2 diabetes," "epigenetics," "metabolomics," "gene-diet interaction," "short-chain fatty acids," "insulin resistance," "dietary polyphenols," "lipid metabolism," and "metabolic inflammation". Boolean operators including AND and OR were used to refine the search process.

Eligibility criteria

Studies were included if they satisfied the following criteria:

i. Published between 2020 and 2026.

ii. Peer-reviewed original research articles, systematic reviews, meta-analyses, or high-quality narrative reviews.

iii. Focused on nutrient-gene interactions, microbiome-metabolism relationships, or nutrient-mediated biochemical pathways associated with metabolic health.

iv. Included human studies, translational studies, or mechanistic experimental investigations relevant to metabolic regulation.

v. Published in the English language.

Studies were excluded if they:

i. Were conference abstracts without complete data.

ii. Included non-verifiable or duplicated findings.

iii. Focused primarily on unrelated disease conditions without metabolic relevance.

iv. Were published in predatory or non-indexed journals lacking scientific rigor.

Study selection and data extraction

Titles and abstracts retrieved from database searches were screened for relevance to the objectives of the review. Full-text articles were subsequently evaluated for methodological quality, scientific relevance, and suitability for inclusion. Information extracted from eligible studies included study design, population characteristics, dietary interventions or nutrient exposures, genetic variants examined, microbial outcomes, metabolic biomarkers, molecular pathways involved, and major conclusions.

Particular attention was given to studies investigating molecular signaling pathways such as AMP-activated protein kinase signaling, insulin receptor signaling, mammalian target of rapamycin pathways, inflammatory signaling cascades, oxidative stress responses, bile acid metabolism, and epigenetic modifications. Studies involving multi-omics approaches including metagenomics, transcriptomics, proteomics, and metabolomics were also prioritized because of their relevance to integrated metabolic regulation.

Quality assessment

Although narrative reviews do not universally require formal risk-of-bias scoring systems, methodological quality was critically evaluated using established indicators including study design, sample size adequacy, reproducibility of findings, clarity of analytical methods, statistical rigor, and biological plausibility. Greater emphasis was placed on large-scale cohort studies, randomized controlled trials, multi-omics analyses, and mechanistic studies with validated methodologies.

Data synthesis

Extracted evidence was synthesized thematically according to major areas relevant to metabolic health. These included nutrigenomics and metabolic regulation, gut microbial ecology, nutrient-sensitive biochemical pathways, epigenetic regulation, precision nutrition, dietary modulation of microbial metabolites, and translational applications in metabolic disorders. Findings were integrated narratively to highlight converging evidence, mechanistic relationships, and emerging concepts in the field.

Limitations of the review methodology

As a narrative review, this study may be limited by selective interpretation and potential publication bias associated with available literature. Variability in study populations, dietary assessment methods, microbiome sequencing techniques, and analytical platforms also contributed to heterogeneity among included studies. Furthermore, differences in genetic backgrounds and environmental exposures across populations may influence the generalizability of findings related to nutrient-gene interactions and microbial metabolism.

Nutrigenomics and the Molecular Regulation of Metabolic Health

Nutrigenomics has transformed understanding of the relationship between diet and metabolic disease by demonstrating that nutrients function not only as energy substrates but also as molecular regulators capable of influencing gene transcription, cellular signaling, and metabolic phenotype [27]. Nutrient-derived molecules can activate transcription factors, alter chromatin structure, regulate epigenetic enzymes, and modify intracellular signaling cascades that collectively determine metabolic homeostasis. These interactions are particularly important in obesity, insulin resistance, dyslipidemia, metabolic syndrome, and type 2 diabetes mellitus, where dysregulated nutrient sensing contributes substantially to disease progression [28].

At the cellular level, nutrient-gene interactions are mediated through specialized nutrient-sensing pathways that detect fluctuations in glucose, fatty acids, amino acids, and microbial metabolites [29]. Among the most extensively studied pathways is AMP-activated protein kinase signaling, which functions as a central energy sensor regulating glucose uptake, fatty acid oxidation, mitochondrial biogenesis, and insulin sensitivity [30]. Activation of AMP-activated protein kinase by dietary polyphenols, caloric restriction, and short-chain fatty acids has been associated with improved metabolic outcomes and reduced inflammatory signaling. Another critical nutrient-responsive pathway is the mammalian target of rapamycin complex pathway, which integrates amino acid availability, insulin signaling, and cellular growth responses [31]. Chronic activation of mammalian target of rapamycin signaling by excessive caloric intake and high saturated fat consumption has been linked to obesity, impaired insulin signaling, and metabolic inflammation. Nutritional modulation of this pathway through dietary protein balance and bioactive phytochemicals may therefore influence metabolic disease risk [32].

Peroxisome proliferator-activated receptors also occupy a major position in nutrigenomic regulation because of their role in lipid metabolism, adipogenesis, glucose utilization, and inflammatory control. Dietary fatty acids serve as ligands for these nuclear receptors

and influence expression of genes involved in lipid transport, β-oxidation, and adipocyte differentiation [30, 31]. Polyunsaturated fatty acids, especially omega-3 fatty acids, have demonstrated favorable effects on peroxisome proliferator-activated receptor activation and downstream metabolic regulation [33].

Insulin signaling pathways are highly sensitive to nutrient composition and metabolic stress [27]. Diets characterized by excessive refined carbohydrates and saturated fats promote chronic hyperinsulinemia, oxidative stress, and activation of pro-inflammatory mediators that impair insulin receptor substrate signaling [29]. Conversely, diets rich in fiber, polyphenols, and unsaturated fats may enhance insulin sensitivity through improved mitochondrial function and reduced inflammatory activity [30]. Evidence from transcriptomic studies further suggests that dietary interventions can alter expression of genes associated with glucose transport, adipokine secretion, and hepatic gluconeogenesis [30]. Nuclear factor-kappa B signaling represents another important intersection between nutrition and metabolic dysfunction [32]. Persistent activation of this inflammatory transcription factor contributes to chronic low-grade inflammation characteristic of obesity and metabolic syndrome [32]. Saturated fatty acids and endotoxins derived from gut dysbiosis stimulate inflammatory cytokine production through toll-like receptor-mediated activation of nuclear factor-kappa B pathways. In contrast, anti-inflammatory dietary compounds including flavonoids, carotenoids, and omega-3 fatty acids can suppress inflammatory transcriptional responses and improve metabolic regulation.

Oxidative stress also plays a significant role in nutrient-mediated metabolic dysfunction [23]. Excess caloric intake, mitochondrial overload, and impaired antioxidant defenses promote generation of reactive oxygen species capable of damaging proteins, lipids, and DNA [8]. Nutritional antioxidants including vitamins C and E, carotenoids, selenium, and polyphenols may mitigate oxidative injury and influence redox-sensitive gene expression [33]. Several nutrigenomic investigations have demonstrated associations between antioxidant-rich diets and reduced expression of oxidative stress-related inflammatory genes [34].

Epigenetic regulation has emerged as one of the most important mechanisms linking diet with long-term metabolic outcomes [20, 31]. Nutrients can influence DNA methylation patterns, histone acetylation, chromatin remodeling, and non-coding RNA expression, thereby modifying transcriptional activity without altering DNA sequence [35]. Folate, choline, methionine, vitamin B12, and other methyl-donor nutrients contribute directly to one-carbon metabolism and methylation reactions involved in epigenetic regulation [35]. Early-life nutritional exposures may therefore establish epigenetic patterns that influence susceptibility to metabolic disease later in life.

MicroRNAs are increasingly recognized as mediators of nutrigenomic regulation in metabolic disorders [29]. These short non-coding RNAs regulate post-transcriptional gene expression and are responsive to dietary composition, inflammatory status, and microbial metabolites [36]. Altered expression of specific microRNAs has been linked to obesity, insulin resistance, hepatic Steatosis, and impaired lipid metabolism. Dietary polyphenols and omega-3 fatty acids may partly exert metabolic benefits through modulation of microRNA signaling pathways [37].

Interindividual variation in metabolic responses to diet is partly explained by genetic polymorphisms involved in nutrient metabolism and signaling pathways. Variants in genes such as FTO, TCF7L2, APOE, PPARG, and MTHFR have been associated with differential responses to dietary fat, carbohydrate intake, folate metabolism, and energy balance. Individuals carrying specific allelic variants may therefore demonstrate variable susceptibility to obesity or type 2 diabetes depending on dietary exposures. Such findings form the basis for precision nutrition approaches that integrate genomic information into dietary planning [38].

Large-scale multi-omics studies have strengthened understanding of nutrigenomic regulation by integrating genomic, transcriptomic, metabolomic, proteomic, and microbiome datasets [39]. These approaches have enabled identification of metabolic signatures associated with dietary patterns, insulin sensitivity, inflammatory status, and microbial metabolism [40]. Emerging evidence indicates that nutrient-induced metabolic responses involve highly interconnected networks rather than isolated pathways.

Despite growing progress, translation of nutrigenomics into clinical practice remains challenging. Many gene-diet associations demonstrate modest effect sizes and are influenced by ethnicity, environmental exposures, microbiome composition, and lifestyle factors [41]. Furthermore, inconsistencies in study design, dietary assessment methods, and statistical interpretation continue to limit reproducibility across nutrigenomic investigations [42]. Nonetheless, current evidence strongly supports the concept that nutrients can regulate gene expression and metabolic pathways in ways that significantly influence metabolic health and disease susceptibility [43].

Gut Microbial Ecology and Metabolic Homeostasis

The human gastrointestinal tract contains a highly diverse microbial ecosystem composed of bacteria, archaea, viruses, and fungi that collectively influence nutrient metabolism, immune function, endocrine signaling, and metabolic homeostasis [44]. The gut microbiota has increasingly been recognized as a metabolic organ because of its extensive capacity to metabolize dietary substrates into bioactive compounds capable of regulating host physiology [45]. Alterations in microbial composition and functionality have been strongly associated with obesity, insulin resistance, dyslipidemia, metabolic syndrome, non-alcoholic fatty liver disease, and type 2 diabetes mellitus.

Microbial colonization begins early in life and is influenced by delivery mode, infant feeding practices, antibiotic exposure, environmental conditions, and dietary habits [46]. Over time, dietary intake becomes one of the strongest determinants of microbial composition and metabolic activity. Diets rich in dietary fiber, whole grains, legumes, fruits, vegetables, and fermented foods generally support microbial diversity and metabolic stability, whereas Western dietary patterns characterized by excessive saturated fats, refined sugars, and ultra-processed foods often promote microbial dysbiosis and inflammatory responses [46].

Two dominant bacterial phyla, Firmicutes and Bacteroidetes, constitute a major proportion of the intestinal microbiota and have frequently been investigated in obesity-related metabolic disturbances [47]. Several studies have reported altered Firmicutes-to-Bacteroidetes ratios in obese individuals, although findings remain inconsistent because of differences in diet, ethnicity, sequencing techniques, and metabolic status. Beyond taxonomic composition,

microbial functional capacity appears to play a more important role in metabolic regulation than simple microbial abundance. One of the most important mechanisms through which the microbiota influences metabolic health involves microbial fermentation of dietary fibers into short-chain fatty acids including acetate, propionate, and butyrate [48]. These metabolites exert multiple beneficial metabolic effects by serving as energy substrates, strengthening intestinal barrier integrity, regulating appetite, modulating immune responses, and improving insulin sensitivity [48]. Butyrate, in particular, functions as an energy source for colonocytes and also acts as a histone deacetylase inhibitor capable of influencing epigenetic regulation and inflammatory signaling [49].

Short-chain fatty acids activate G-protein-coupled receptors including GPR41 and GPR43, thereby influencing glucose homeostasis, adipose tissue metabolism, and secretion of gut hormones such as glucagon-like peptide-1 and peptide YY [50]. Enhanced secretion of these hormones contributes to improved satiety, glucose tolerance, and insulin sensitivity [51]. Reduced production of short-chain fatty acids secondary to low-fiber dietary patterns may therefore contribute to metabolic dysfunction and chronic inflammation.

The intestinal microbiota also participates extensively in bile acid metabolism. Primary bile acids synthesized in the liver undergo microbial transformation into secondary bile acids within the intestine, producing metabolites that regulate farnesoid X receptor and Takeda G-protein receptor 5 signaling pathways [52]. These pathways influence glucose metabolism, lipid oxidation, energy expenditure, and inflammatory responses. Dysregulated bile acid metabolism has been implicated in obesity, insulin resistance, and hepatic steatosis [53].

Another important microbiota-derived metabolite associated with cardiometabolic disease is trimethylamine-N-oxide. Gut microorganisms metabolize dietary choline, phosphatidylcholine, and carnitine into trimethylamine, which is subsequently converted in the liver to trimethylamine-N-oxide [54]. Elevated circulating trimethylamine-N-oxide concentrations have been associated with atherosclerosis, cardiovascular disease, insulin resistance, and systemic inflammation. Diets rich in red meat and processed animal products tend to increase trimethylamine-N-oxide production, whereas plant-based dietary patterns generally reduce its formation [55].

Microbial dysbiosis has also been associated with altered branched-chain amino acid metabolism [56]. Elevated circulating branched-chain amino acids are frequently observed in obesity and insulin resistance and may contribute to impaired insulin signaling through activation of mammalian target of rapamycin pathways. Certain microbial species appear capable of modulating branched-chain amino acid biosynthesis and degradation, thereby influencing host metabolic responses [56].

Polyphenol-rich diets further illustrate the bidirectional relationship between diet and microbial ecology [57]. Many dietary polyphenols demonstrate poor absorption in the upper gastrointestinal tract and therefore undergo microbial biotransformation within the colon [57]. Resulting metabolites may exert anti-inflammatory, antioxidant, and insulin-sensitizing effects. Simultaneously, polyphenols can selectively promote growth of beneficial microbial taxa including Bifidobacterium and Lactobacillus species while suppressing potentially pathogenic organisms [58].

Artificial sweeteners and food additives have also attracted attention for their potential effects on microbial ecology and metabolic health [59]. Experimental studies suggest that certain non-nutritive sweeteners may alter microbial composition, impair glucose tolerance, and promote inflammatory responses in susceptible individuals [59]. Emulsifiers and preservatives commonly present in ultra-processed foods may similarly affect microbial diversity and intestinal barrier function [60].

Host genetics also contribute partly to microbial composition and metabolic interactions [61]. Polymorphisms associated with immunity, mucosal integrity, and metabolic signaling may influence microbial colonization patterns and microbial metabolite production. However, environmental exposures and diet appear to exert a substantially greater effect on microbial ecology than host genetics alone [61].

Advances in metagenomics, metabolomics, and systems biology have improved understanding of functional microbial pathways associated with metabolic health [62]. Functional profiling studies have identified microbial genes involved in carbohydrate fermentation, bile acid transformation, amino acid metabolism, and inflammatory signaling that correlate with obesity and insulin resistance. Integration of multi-omics technologies continues to reveal increasingly complex interactions among nutrients, microbial metabolites, and host cellular pathways. Therapeutic manipulation of the gut microbiota has emerged as a promising strategy for metabolic disease prevention and management [60]. Dietary fiber supplementation, prebiotics, probiotics, synbiotics, polyphenol-rich diets, and fecal microbiota transplantation have all demonstrated varying degrees of metabolic benefit in experimental and clinical studies [61, 63]. Nonetheless, responses remain highly individualized, highlighting the importance of precision microbiome-based interventions [64].

Despite substantial progress, major challenges remain in microbiome research [65]. Considerable variability exists among sequencing platforms, analytical pipelines, dietary assessment methods, and population characteristics [65]. Furthermore, many observed microbial associations remain correlative rather than causal, and long-term clinical evidence supporting microbiome-targeted therapies is still evolving [66]. Nevertheless, current evidence strongly supports the role of gut microbial ecology as a central mediator of nutrient-gene interactions and metabolic homeostasis.

Biochemical Pathways Linking Nutrients, Microbiota, and Metabolic Disease

Metabolic homeostasis is maintained through highly coordinated biochemical pathways that integrate nutrient availability, microbial metabolites, hormonal signaling, cellular energy status, and inflammatory responses [67]. Disruption of these pathways contributes substantially to obesity, insulin resistance, type 2 diabetes mellitus, cardiovascular disease, and non-alcoholic fatty liver disease. Nutrient-gene interactions and microbial ecology converge within these interconnected biochemical networks, influencing metabolic phenotype through modulation of signaling molecules, transcription factors, mitochondrial activity, and endocrine pathways [68].

Insulin signaling and glucose homeostasis

Insulin signaling represents one of the central biochemical systems governing metabolic regulation [68]. Under physiological conditions, insulin binds to insulin receptors on target tissues including skeletal muscle, adipose tissue, and liver, triggering phosphorylation

cascades involving insulin receptor substrates, phosphatidylinositol-3-kinase, and protein kinase B. This signaling network promotes glucose uptake, glycogen synthesis, lipogenesis, and suppression of hepatic gluconeogenesis [69]. Chronic overnutrition, especially diets rich in refined carbohydrates and saturated fats, contributes to impaired insulin receptor signaling and reduced glucose transporter translocation [70]. Accumulation of intracellular lipid intermediates including ceramides and diacylglycerols activates stress kinases such as c-Jun N-terminal kinase and inhibitor of nuclear factor-kappa B kinase, which interfere with insulin receptor substrate phosphorylation and promote insulin resistance [71].

Microbial metabolites further influence insulin sensitivity through several mechanisms. Short-chain fatty acids generated during microbial fermentation enhance insulin responsiveness partly through activation of AMP-activated protein kinase and increased secretion of glucagon-like peptide-1 [72]. Conversely, lipopolysaccharide-induced inflammation associated with dysbiosis contributes to insulin resistance through activation of toll-like receptor signaling and inflammatory cytokine release.

AMP-activated protein kinase and cellular energy regulation

AMP-activated protein kinase functions as a major cellular energy sensor activated during conditions of low intracellular ATP availability. Once activated, AMP-activated protein kinase stimulates catabolic pathways that generate ATP while suppressing energy-consuming anabolic processes [73]. This includes increased fatty acid oxidation, enhanced glucose uptake, inhibition of cholesterol synthesis, and suppression of hepatic lipogenesis. Several dietary bioactive compounds including resveratrol, curcumin, catechins, quercetin, and omega-3 fatty acids have demonstrated capacity to activate AMP-activated protein kinase signaling [74]. Caloric restriction and exercise also strongly stimulate this pathway, contributing to improved mitochondrial efficiency and metabolic flexibility [75]. Microbiota-derived butyrate similarly activates AMP-activated protein kinase and promotes mitochondrial function in peripheral tissues.

Defective AMP-activated protein kinase activity has been linked to obesity, hepatic steatosis, and insulin resistance. Pharmacological agents such as metformin partly exert their antidiabetic effects through activation of AMP-activated protein kinase pathways, illustrating the clinical relevance of nutrient-sensitive metabolic signaling.

Microbial regulation of branched-chain amino acid metabolism further links gut ecology with mammalian target of rapamycin activation [76]. Altered microbial pathways associated with obesity may increase circulating branched-chain amino acid concentrations and thereby influence nutrient-sensitive signaling systems.

Lipid metabolism and adipose tissue signaling

Adipose tissue functions not only as an energy storage organ but also as an active endocrine tissue involved in regulation of appetite, inflammation, insulin sensitivity, and lipid metabolism [77]. Nutrients and microbial metabolites strongly influence adipocyte differentiation, adipokine secretion, and fatty acid handling. Peroxisome proliferator-activated receptors are central regulators of lipid metabolism and adipogenesis [78]. Activation of peroxisome proliferator-activated receptor-alpha promotes fatty acid oxidation in hepatic and skeletal muscle tissues, whereas peroxisome proliferator-activated receptor-gamma regulates adipocyte differentiation and insulin sensitivity. Dietary fatty acids act as natural ligands for these receptors and can alter expression of genes involved in lipid transport and storage.

Adipose tissue inflammation represents a major feature of obesity-associated metabolic dysfunction [79]. Hypertrophic adipocytes release chemokines that recruit macrophages and other immune cells into adipose tissue, resulting in production of inflammatory cytokines including tumor necrosis factor-alpha and interleukin-6 [80]. These mediators impair insulin signaling and contribute to systemic metabolic inflammation. Short-chain fatty acids may partially counteract adipose tissue inflammation through inhibition of histone deacetylases and modulation of regulatory immune cells [81]. In addition, omega-3 fatty acids can reduce inflammatory eicosanoid production and improve adipocyte function [82].

Oxidative stress and mitochondrial dysfunction

Mitochondria play a critical role in energy metabolism through oxidative phosphorylation and ATP production. Excess nutrient availability may overload mitochondrial respiratory systems, increase generation of reactive oxygen species and promoting oxidative stress [83]. Persistent oxidative stress contributes to lipid peroxidation, DNA damage, protein oxidation, and impairment of insulin signaling pathways. Antioxidant defense systems including superoxide dismutase, catalase, glutathione peroxidase, and dietary antioxidants are essential for maintaining redox balance. Polyphenols, carotenoids, flavonoids, and vitamins may reduce oxidative injury by scavenging reactive oxygen species and modulating antioxidant gene expression [84].

Gut microbiota also influences oxidative stress responses [85]. Dysbiosis-associated inflammation can increase oxidative burden, whereas beneficial microbial metabolites may support mitochondrial function and anti-inflammatory signaling. Emerging evidence further suggests that mitochondrial dysfunction itself may alter gut barrier integrity and microbial composition, creating bidirectional metabolic disturbances [86].

Inflammatory signaling pathways

Chronic low-grade inflammation is widely recognized as a defining feature of metabolic disease. Nutrient excess, lipotoxicity, oxidative stress, and microbial endotoxins activate inflammatory pathways involving nuclear factor-kappa B, c-Jun N-terminal kinase, and nucleotide-binding oligomerization domain-like receptor protein 3 inflammasomes [82]. Activation of these pathways stimulates production of inflammatory cytokines that interfere with insulin receptor signaling and contribute to endothelial dysfunction [83]. Saturated fatty acids and trans fats can directly activate toll-like receptor-mediated inflammatory responses, whereas unsaturated fatty acids often exert anti-inflammatory effects [84, 87].

Microbial metabolites also regulate immune signaling. Butyrate promotes differentiation of regulatory T cells and suppresses inflammatory cytokine production, while dysbiosis-associated endotoxemia amplifies pro-inflammatory pathways. Persistent inflammatory signaling contributes to progression of obesity, hepatic steatosis, atherosclerosis, and insulin resistance [87].

Integrated metabolic networks

Modern metabolomic and systems biology studies demonstrate that metabolic regulation cannot be understood through isolated pathways alone [88]. Nutrients, microbial metabolites, endocrine

factors, immune mediators, and genetic regulators interact within integrated metabolic networks that collectively determine metabolic phenotype [89]. Multi-omics approaches combining transcriptomics, metabolomics, metagenomics, and proteomics have revealed highly interconnected relationships between diet, microbial ecology, and cellular metabolism. Such findings support the concept that metabolic disorders arise from disruption of complex biological systems rather than single molecular abnormalities [90]. Understanding these biochemical interactions provides a mechanistic foundation for precision nutrition and microbiome-targeted interventions in metabolic disease prevention and treatment.

Precision Nutrition and Personalized Metabolic Health

Precision nutrition has emerged as an important translational application of nutrigenomics and microbiome science in metabolic disease prevention and management [91]. Traditional dietary recommendations are generally population-based and assume relatively uniform metabolic responses to dietary interventions. However, substantial interindividual variability exists in postprandial glucose responses, lipid metabolism, appetite regulation, inflammatory activity, and body weight regulation following similar dietary exposures [91]. This variability is increasingly attributed to differences in genetic architecture, microbial ecology, metabolic phenotype, lifestyle factors, age, sex, and environmental influences. Precision nutrition seeks to tailor dietary recommendations according to individual biological characteristics, integrating information from genomics, metabolomics, transcriptomics, proteomics, and microbiome profiling [92]. The objective is to improve metabolic outcomes by identifying dietary patterns most compatible with an individual's genetic and metabolic profile. Advances in computational biology, machine learning, and multi-omics technologies have accelerated development of predictive models capable of estimating personalized metabolic responses to food intake [93].

Genetic polymorphisms contribute substantially to differential nutrient responses. Variants in genes regulating lipid metabolism, glucose transport, appetite control, inflammatory signaling, and energy expenditure may modify susceptibility to obesity and type 2 diabetes mellitus. The fat mass and obesity-associated gene is among the most extensively investigated nutrigenetic loci because of its association with obesity risk and dietary responsiveness. Individuals carrying specific fat mass and obesity-associated gene variants may demonstrate altered appetite regulation, energy intake, and sensitivity to dietary fat composition [94, 95].

Microbiome profiling has become another major component of precision nutrition [96]. Individual differences in microbial composition influence energy harvest, short-chain fatty acid production, bile acid metabolism, inflammatory signaling, and glycemic regulation. Certain microbial taxa have been associated with improved insulin sensitivity and metabolic flexibility, whereas dysbiosis-associated microbial patterns correlate with obesity and chronic inflammation. Metabolomics has further improved precision nutrition by enabling identification of circulating metabolites associated with dietary intake and metabolic risk [97]. Metabolic signatures involving branched-chain amino acids, acylcarnitines, bile acids, and microbial metabolites have been linked to insulin resistance and cardiometabolic disease. Such biomarkers may provide objective tools for evaluating dietary responses and metabolic status [98].

Nutriepigenomics represents another rapidly developing area within personalized nutrition [99]. Dietary components can influence epigenetic modifications including DNA methylation, histone modification, and microRNA expression, potentially altering long-term metabolic programming. Interindividual differences in epigenetic responsiveness may partly explain variability in dietary outcomes and disease susceptibility [99].

Precision nutrition approaches have shown promising applications in obesity management. Personalized dietary interventions based on insulin secretion patterns, glycemic responses, and genetic markers may improve adherence and weight loss outcomes compared with generalized dietary recommendations [100]. Individuals with insulin-resistant phenotypes may respond more favorably to low-glycemic or carbohydrate-restricted diets, whereas others may benefit more from Mediterranean or plant-based dietary patterns. Cardiovascular disease prevention also represents a major area of application for personalized nutrition. Nutrigenetic variation influences lipid metabolism, inflammatory responses, endothelial function, and blood pressure regulation [101]. Personalized dietary strategies involving omega-3 fatty acids, sodium intake modification, polyphenol-rich foods, and fiber optimization may therefore reduce cardiovascular risk more effectively in genetically susceptible individuals.

Artificial intelligence and machine learning models are increasingly being incorporated into precision nutrition system. These technologies can integrate large-scale datasets involving dietary patterns, genomic profiles, microbiome composition, physical activity, and metabolic biomarkers to generate individualized dietary recommendations. Such approaches may improve predictive accuracy and scalability of personalized nutrition interventions [102].

Despite promising advances, several limitations continue to hinder widespread clinical implementation of precision nutrition [98]. Many gene-diet interactions demonstrate relatively modest effect sizes and may vary considerably across ethnic populations and environmental contexts. Standardization of microbiome sequencing techniques, metabolomic analyses, and dietary assessment tools also remains a major challenge [93]. Ethical and socioeconomic concerns are equally important [103]. Accessibility of genomic testing and personalized dietary services remains limited in many low- and middle-income regions 80]. Concerns regarding privacy of genetic data, commercial exploitation of nutrigenomic information, and clinical validity of direct-to-consumer testing services continue to generate debate [67].

Furthermore, long-term randomized controlled trials evaluating clinical outcomes of precision nutrition interventions remain relatively limited [55]. Many current findings are based on observational studies, short-term interventions, or highly controlled research settings that may not fully reflect real-world dietary behavior. Greater diversity in study populations is also required because most nutrigenomic datasets are derived predominantly from European ancestry cohorts. Nevertheless, precision nutrition represents a major shift in nutritional science from generalized dietary advice toward individualized metabolic management [104]. Integration of nutrigenomics, microbiome science, metabolomics, and systems biology has the potential to improve prevention and treatment strategies for obesity, diabetes mellitus, cardiovascular disease, and other metabolic disorders. Continued advances in multi-omics technologies and computational modeling will likely further refine understanding of nutrient-gene interactions and their applications in clinical nutrition [105].

Clinical Applications and Therapeutic Implications

The expanding understanding of nutrient-gene interactions, microbial ecology, and metabolic signaling pathways has generated substantial interest in the development of clinically applicable nutritional interventions for metabolic disorders [106]. Nutritional therapy is increasingly recognized not merely as supportive care but as a central component of metabolic disease prevention and treatment [94]. Integration of nutrigenomics, microbiome science, and systems biology has broadened opportunities for targeted dietary interventions capable of modulating metabolic risk at molecular and physiological levels [108].

Nutritional management of obesity

Obesity remains one of the most important global drivers of metabolic disease and is strongly associated with insulin resistance, cardiovascular disease, non-alcoholic fatty liver disease, and chronic inflammation. Conventional calorie-restriction approaches often produce variable outcomes because individuals differ considerably in energy expenditure, appetite regulation, hormonal responses, and nutrient metabolism [109].

Dietary patterns rich in dietary fiber, unsaturated fats, plant polyphenols, and minimally processed foods consistently demonstrate beneficial effects on body weight regulation and metabolic function. Mediterranean dietary patterns have shown favorable outcomes in reducing adiposity, improving insulin sensitivity, and lowering inflammatory markers. Such diets also support microbial diversity and short-chain fatty acid production, which contribute to appetite regulation and improved metabolic signaling [110].

Time-restricted feeding and intermittent fasting strategies have also attracted attention for their influence on circadian metabolic regulation and insulin sensitivity [111]. These approaches may improve mitochondrial efficiency, autophagy, and glucose metabolism independently of total caloric reduction. Emerging evidence further suggests that fasting-associated microbial shifts may partly mediate metabolic benefits [81].

Type 2 diabetes mellitus

Type 2 diabetes mellitus is characterized by insulin resistance, impaired pancreatic beta-cell function, chronic inflammation, and altered glucose homeostasis. Nutritional therapy remains fundamental in diabetes prevention and management because dietary composition strongly influences glycemic control and metabolic signaling [112].

Low-glycemic-index diets have demonstrated efficacy in improving postprandial glucose regulation and insulin sensitivity. Increased dietary fiber intake slows glucose absorption, improves satiety, and supports microbial production of short-chain fatty acids that enhance glucose metabolism. Whole grains, legumes, vegetables, and fermented foods therefore represent important components of diabetes-focused nutritional interventions [113].

Personalized nutritional strategies based on glycemic responsiveness and genetic susceptibility may improve diabetes management. Variability in postprandial glycemic responses indicates that individuals metabolize identical meals differently due to interactions involving microbiota composition, insulin secretion capacity, and nutrient-sensitive signaling pathways [114].

Omega-3 fatty acids, polyphenols, and antioxidant-rich foods may also attenuate oxidative stress and inflammation associated with diabetes progression. Bioactive compounds including curcumin, catechins, quercetin, and resveratrol have demonstrated modulatory effects on AMP-activated protein kinase signaling, inflammatory pathways, and mitochondrial function.

Microbiome-targeted interventions are increasingly being investigated in diabetes therapy [115]. Probiotics, prebiotics, synbiotics, and dietary fiber supplementation may improve insulin sensitivity and reduce inflammatory markers through restoration of microbial balance and enhancement of intestinal barrier integrity.

Cardiovascular disease

Cardiovascular disease remains a leading cause of mortality globally and is closely linked to dyslipidemia, hypertension, chronic inflammation, oxidative stress, and endothelial dysfunction. Dietary factors significantly influence cardiovascular risk through modulation of lipid metabolism, inflammatory signaling, vascular function, and gut microbial metabolism [116].

The Mediterranean diet remains among the most extensively studied cardioprotective dietary patterns. High intake of fruits, vegetables, legumes, nuts, olive oil, and marine-derived omega-3 fatty acids has consistently been associated with reduced cardiovascular events and improved endothelial function [117]. Polyphenol-rich foods including berries, cocoa, green tea, and extra virgin olive oil exert antioxidant and anti-inflammatory effects that may reduce atherosclerotic progression.

Microbial metabolism of dietary nutrients also contributes to cardiovascular risk. Conversion of dietary choline and carnitine into trimethylamine N-oxide by gut microbiota has been associated with atherosclerosis and adverse cardiovascular outcomes [118]. Dietary modulation of microbial composition may therefore represent a therapeutic strategy for reducing cardiometabolic risk.

Sodium sensitivity demonstrates substantial interindividual variation influenced partly by genetic and environmental factors [119]. Personalized sodium restriction strategies may therefore be more effective than generalized recommendations in reducing hypertension risk among susceptible populations.

Probiotics, prebiotics, and synbiotics in clinical practice

Manipulation of the gut microbiota through probiotics, prebiotics, and synbiotics has become an important area of metabolic research [120]. Probiotics are live microorganisms that confer health benefits when administered in adequate amounts, whereas prebiotics are substrates selectively utilized by beneficial microbes. Synbiotics combine both approaches to enhance microbial modulation [120].

Several probiotic strains including Lactobacillus and Bifidobacterium species have demonstrated modest beneficial effects on insulin sensitivity, inflammatory status, lipid metabolism, and body weight regulation. Prebiotic fibers such as inulin, fructooligosaccharides, and resistant starches promote growth of short-chain fatty acid-producing bacteria and improve gut barrier function [121].

Despite encouraging findings, clinical responses to microbiome-targeted interventions remain highly variable. Baseline microbial composition, host genetics, dietary patterns, medication use, and environmental exposures likely influence therapeutic responsiveness. Standardization of probiotic formulations and dosing strategies also remains a challenge.

Nutraceuticals and functional foods

Nutraceuticals and functional foods are increasingly incorporated into metabolic health interventions because of their potential to modulate oxidative stress, inflammation, insulin signaling, and microbial ecology [121]. Polyphenols, omega-3 fatty acids, carotenoids, phytosterols, flavonoids, and bioactive peptides have received considerable attention for their metabolic benefits.

Curcumin has demonstrated anti-inflammatory and antioxidant properties through modulation of nuclear factor-kappa B signaling and AMP-activated protein kinase activation [122]. Resveratrol may improve mitochondrial function and insulin sensitivity, while green tea catechins have been associated with improved lipid metabolism and reduced oxidative stress.

Fermented foods including yogurt, kefir, kimchi, and fermented vegetables may provide metabolic benefits through delivery of bioactive metabolites and modulation of gut microbiota composition. Such foods may contribute to improved intestinal barrier function, reduced inflammation, and enhanced microbial diversity.

Challenges in clinical translation

Despite substantial progress, several barriers continue to limit widespread clinical implementation of nutrigenomics and microbiome-guided therapies. Many identified gene-diet interactions exhibit relatively small effect sizes and may not consistently predict clinical outcomes across populations [123]. Heterogeneity in dietary assessment methods, microbiome sequencing techniques, and metabolomic analyses further complicates interpretation of findings.

Cost and accessibility also remain important limitations, especially in low-resource settings. Personalized genomic and microbiome testing may not yet be feasible for routine clinical practice in many regions. In addition, healthcare professionals often receive limited formal training in nutrigenomics and precision nutrition [124].

Ethical considerations involving genetic privacy, informed consent, and commercialization of nutrigenomic testing require careful regulatory oversight. Direct-to-consumer nutrigenetic services may sometimes provide recommendations lacking strong scientific validation, raising concerns regarding misinformation and inappropriate dietary guidance.

Future therapeutic directions

Future therapeutic strategies will likely involve integration of multi-omics technologies with artificial intelligence and systems biology approaches. Machine learning models capable of integrating genomic, metabolomic, microbiome, dietary, and clinical data may improve prediction of individualized metabolic responses [125].

Microbiome engineering, precision probiotics, postbiotics, and metabolite-based therapies are also emerging as promising areas of metabolic intervention. Advances in nutriepigenomics may further support development of targeted nutritional approaches capable of modifying epigenetic pathways involved in metabolic disease susceptibility. Ultimately, integration of nutritional science with molecular medicine may facilitate more effective prevention and management of obesity, diabetes mellitus, cardiovascular disease, and related metabolic disorders [126].

Challenges, Research Gaps, and Future Perspectives

Despite remarkable advances in nutrigenomics, microbiome science, and metabolic systems biology, major scientific and translational challenges continue to limit full understanding of nutrient-gene interactions in metabolic health. Human metabolism is regulated through highly interconnected biological networks influenced simultaneously by genetic variation, environmental exposures, dietary habits, microbial ecology, developmental programming, lifestyle behaviors, medication use, and socioeconomic conditions. The complexity of these interactions complicates interpretation of mechanistic findings and limits the reproducibility of many nutrigenomic associations [127].

Complexity of human nutrigenomic responses

One of the major limitations in nutrigenomic research is the substantial heterogeneity observed in metabolic responses to dietary intake. Individuals consuming identical diets may exhibit markedly different responses in glucose metabolism, lipid handling, inflammatory activity, and weight regulation because of differences in genetic architecture and environmental exposures. Many gene-diet associations identified in observational studies demonstrate relatively small effect sizes and may not consistently replicate across populations. In several cases, initial associations between genetic polymorphisms and dietary responsiveness have weakened after adjustment for confounding variables including physical activity, socioeconomic status, medication use, and body composition [128].

Polygenic regulation further complicates interpretation because metabolic traits are rarely controlled by single genes. Obesity, insulin resistance, and cardiovascular disease involve interactions among numerous loci affecting appetite regulation, adipogenesis, mitochondrial function, inflammatory signaling, and endocrine regulation [129]. Consequently, isolated single-nucleotide polymorphisms often explain only a limited proportion of disease susceptibility.

Gene-environment interactions also vary across ethnic and geographical populations differ substantially among populations, limiting the generalizability of findings derived predominantly from European cohorts [129]. Greater representation of African, Asian, Latin American, and indigenous populations is therefore essential for development of globally applicable precision nutrition strategies.

Challenges in microbiome research

Microbiome science has rapidly transformed understanding of metabolic regulation, yet several methodological limitations remain unresolved. Microbial composition is highly dynamic and influenced by diet, antibiotics, medications, circadian rhythms, infection, geography, age, and host immunity. As a result, microbial signatures associated with metabolic disease may vary considerably across studies.

Standardization of microbiome sampling, sequencing, bioinformatic processing, and analytical interpretation remains incomplete [130]. Variability in DNA extraction methods, sequencing platforms, and taxonomic classification pipelines can substantially affect microbial profiling outcomes [130]. Such inconsistencies hinder cross-study comparisons and complicate translation into clinical practice. The majority of microbiome studies also rely heavily on fecal sampling, which may not fully represent microbial communities present within different regions of the gastrointestinal tract. Functional characterization of microbial metabolites and host-microbe signaling pathways therefore remains incomplete.

Limitations of current dietary assessment methods

Accurate dietary assessment remains one of the most persistent challenges in nutritional science. Self-reported dietary intake methods including food frequency questionnaires, dietary recalls, and food diaries are susceptible to recall bias, underreporting, and measurement error. Such limitations reduce the precision of gene-diet interaction studies and may obscure biologically significant relationships [131].

Variability in food composition further complicates nutritional analysis. Nutrient concentrations in foods can differ according to agricultural practices, processing methods, storage conditions, preparation techniques, and geographical origin. Bioavailability of nutrients also varies substantially depending on food matrix interactions, microbial metabolism, and individual digestive physiology.

Emerging technologies including digital dietary monitoring, wearable biosensors, metabolomic biomarkers, and artificial intelligence-assisted dietary analysis may improve precision of nutritional assessment in future studies [132]. However, widespread implementation of these technologies remains limited by cost, accessibility, and validation requirements.

Multi-omics integration and systems biology

Modern metabolic research increasingly relies on integration of genomics, transcriptomics, proteomics, metabolomics, epigenomics, and metagenomics to understand biological complexity [133]. Multi-omics approaches provide opportunities to identify interconnected pathways linking nutrition, microbial ecology, and metabolic disease.

Nevertheless, integration of high-dimensional biological datasets presents major computational and analytical challenges. Differences in data structure, sequencing depth, normalization methods, and analytical pipelines complicate interpretation of multi-omics finding. Advanced bioinformatics and machine learning tools are therefore required to manage large-scale datasets and identify biologically meaningful interactions [133].

Interpretability of computational models also remains an important concern. Highly complex predictive algorithms may generate statistically accurate outputs without fully explaining underlying biological mechanisms. Greater emphasis on mechanistic validation will therefore be essential for translating systems biology findings into clinically useful nutritional strategies [134].

Ethical, legal, and social considerations

Expansion of nutrigenomics and precision nutrition raises important ethical and societal concerns [. Genetic testing generates sensitive personal information that requires careful protection regarding privacy, ownership, and data security. Misuse of genomic information by commercial entities or insurance systems represents a continuing concern in precision medicine.

Direct-to-consumer nutrigenomic testing has expanded rapidly, although scientific validity and clinical utility of some commercial services remain uncertain [135]. Consumers may receive dietary recommendations lacking strong evidence or based on incomplete interpretation of genetic findings. Inappropriate dietary modification resulting from inaccurate testing could potentially contribute to nutritional imbalance or unnecessary dietary restriction.

Socioeconomic disparities also influence access to precision nutrition technologies. Genomic sequencing, metabolomic testing, and microbiome profiling remain expensive in many regions, potentially widening healthcare inequalities between high-income and low-income populations [136]. Ensuring equitable access to evidence-based nutritional care therefore represents an important public health priority.

Artificial intelligence and digital health technologies

Artificial intelligence is increasingly being integrated into precision nutrition and metabolic health research [137]. Machine learning algorithms can analyze large datasets involving dietary intake, microbiome composition, genomic variation, clinical biomarkers, and behavioral patterns to generate individualized dietary recommendations [138].

Digital health technologies including continuous glucose monitors, wearable activity trackers, smart dietary applications, and remote monitoring systems may facilitate real-time metabolic assessment and personalized intervention strategies [139]. Such technologies may improve dietary adherence, behavioral modification, and long-term disease management [140].

However, reliability and interpretability of artificial intelligence systems remain important considerations. Predictive models require rigorous validation across diverse populations before clinical implementation. Ethical oversight is equally necessary to prevent algorithmic bias, data misuse, and inequitable healthcare delivery.

Future perspectives

Future progress in nutrigenomics and metabolic medicine will likely depend on integration of systems biology, microbiome science, computational biology, and clinical nutrition. Advances in sequencing technologies, metabolomic profiling, and bioinformatics are expected to improve understanding of complex nutrient-gene interactions and microbial metabolic networks [141].

Precision nutrition may eventually transition from a largely experimental field into routine clinical practice [141]. Personalized dietary interventions guided by genomic, microbial, and metabolic profiling could support more effective prevention and management of obesity, diabetes mellitus, cardiovascular disease, and metabolic-associated liver disease [142].

Microbiome engineering, postbiotic therapies, targeted metabolite supplementation, and epigenetic nutritional interventions represent promising therapeutic frontiers [143]. Improved mechanistic understanding of host-microbe interactions may further facilitate development of novel metabolic therapies capable of restoring metabolic homeostasis.

Ultimately, successful translation of nutrigenomics into clinical medicine will require rigorous scientific validation, standardized methodologies, interdisciplinary collaboration, ethical oversight, and equitable healthcare implementation [143]. Continued research in this field holds substantial potential for transforming approaches to metabolic disease prevention and nutritional therapy in the coming decades.

Conclusion

Nutrient-gene interactions represent one of the most rapidly evolving areas in metabolic health research, offering important insights into the molecular basis of interindividual variability in disease susceptibility, metabolic regulation, and dietary

responsiveness. The integration of nutrigenomics, microbial ecology, epigenetics, metabolomics, and systems biology has substantially improved understanding of how dietary factors influence human physiology through complex regulatory networks involving genes, signaling pathways, microbial metabolites, and cellular biochemical processes.

Current evidence demonstrates that nutrients function not only as substrates for energy production but also as regulatory molecules capable of modulating gene expression, inflammatory signaling, oxidative stress responses, mitochondrial activity, endocrine regulation, and immune function. Dietary components interact with transcription factors, epigenetic regulators, and metabolic enzymes to influence pathways associated with obesity, insulin resistance, cardiovascular disease, type 2 diabetes mellitus, and metabolic-associated fatty liver disease.

The gut microbiota has emerged as a major mediator linking nutrition to metabolic health. Microbial metabolites including short-chain fatty acids, bile acid derivatives, trimethylamine N-oxide, and indole compounds participate in host metabolic regulation through effects on intestinal integrity, immune signaling, glucose homeostasis, lipid metabolism, and inflammatory pathways. Alterations in microbial composition and metabolic activity are increasingly recognized as important contributors to metabolic dysfunction and chronic disease progression.

Advances in high-throughput sequencing, metabolomic profiling, computational biology, and artificial intelligence are progressively transforming precision nutrition from a theoretical framework into a clinically relevant discipline. Personalized dietary interventions based on genomic variation, microbial ecology, metabolic biomarkers, and lifestyle characteristics may eventually improve prevention and management strategies for metabolic disorders. However, important scientific and practical limitations remain unresolved, including inconsistent reproducibility of gene-diet associations, methodological heterogeneity, limited population diversity in research cohorts, and challenges related to clinical translation.

The future of metabolic medicine will likely depend on interdisciplinary integration of nutrition science, molecular biology, microbiome research, bioinformatics, and clinical medicine. Longitudinal human studies, standardized analytical approaches, and rigorous mechanistic investigations will be essential for validating clinically applicable nutrigenomic and microbiome-guided interventions.

In conclusion, nutrient-gene interactions constitute a central component of metabolic regulation and disease pathogenesis. Improved understanding of the interplay among dietary factors, host genetics, microbial ecology, and biochemical pathways may facilitate development of more precise, preventive, and individualized approaches to metabolic health management in the coming decades.

References

1. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol. 2021; 19(1): 55-71.
2. Sanz Y, Cryan JF, Deschasaux-Tanguy M, Elinav E, Lambrecht R, Corthésy B, et al. The gut microbiome connects nutrition and human health. Nat Rev Gastroenterol Hepatol. 2025; 22: 534-555.
3. Lagoumintzis G, Patrinos GP. Triangulating nutrigenomics, metabolomics and microbiomics toward personalized nutrition and healthy living. Hum Genomics. 2023; 17: 109.
4. Çelik E, Kocyigit E, Bingöl FG, Karaçolak C, Cemali Ö, Simonelli M, et al. Multiomics: the intersection of personalized nutrition in cardiometabolic diseases. J Transl Med. 2026; 24: 363.
5. Li Z, Samui S, Liu J, Yang Y, Liu X, Chen Q, et al. Gut microbiome and metabolic health: mechanisms and precision interventions. Gut Microbes. 2026; 18(1): 2644677.
6. Pillai SS, Ashraf AP. Gut microbiota and metabolic health: from dysbiosis to therapeutics. Diabetes Ther. 2026; 17(4): 483-497.
7. Liu S, Domingo-Vidal M, Madhu B, Binyamin D, Thaiss CA, Levy M, et al. Metabotherapy for intestinal disease: using metabolites to prevent and treat disorders of the gut. Nat Rev Gastroenterol Hepatol. 2026; 23(6): 475-492.
8. Balamurugan J, Adeyeye SAO. Artificial intelligence in nutrigenomics: a critical review on functional food insights and personalized nutrition pathways. J Hum Nutr Diet. 2026; 39(1): e70200.
9. Rahimah S, Tallei TE, Savitri M, Yamada C, Kim HJ, Choi M, et al. Molecular basis of precision nutrition: food components, microbiome-derived metabolites, and multi-omics modeling. Food Chem Mol Sci. 2026; 12: 100411.
10. Rahimah S, Tallei TE, Savitri M, Yamada C, Kim HJ, Choi M, et al. Functional foods and dietary matrices for metabolic improvement: an integrative review of mechanisms, evidence, and future directions. J Funct Foods. 2026; 139: 107240.
11. Phillips CM. Nutrigenetics and metabolic disease: current status and implications for personalised nutrition. Nutrients. 2020; 12(11): 3315.
12. Ferguson LR, De Caterina R, Görman U, Allayee H, Kohlmeier M, Prasad C, et al. Guide and position of the International Society of Nutrigenetics/Nutrigenomics on personalised nutrition: part 1 - Fields of Precision Nutrition. J Nutrigenet Nutrigenomics. 2020; 13(1): 1-49.
13. Dabke K, Hendrick G, Devkota S. The gut microbiome and metabolic syndrome. J Clin Invest. 2019; 129(10): 4050-4057.
14. Deschasaux-Tanguy M, Neufcourt L, Julia C, Allès B, Hercberg S, Latino-Martel P, et al. Nutritional metabolomics and metabolic health: current perspectives. Nutrients. 2021; 13(4): 1148.
15. Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. Nat Rev Gastroenterol Hepatol. 2019; 16(1): 35-56.
16. Heianza Y, Qi L. Gene-diet interaction and precision nutrition in obesity. Int J Mol Sci. 2017; 18(4): 787.
17. Ordovás JM, Ferguson LR, Tai ES, Mathers JC. Personalised nutrition and health. BMJ. 2018; 361: bmj.k2173.
18. Kolb H, Martin S. Environmental and lifestyle factors in the pathogenesis and prevention of type 2 diabetes. BMC Med. 2017; 15: 131.
19. Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, et al. Personalized nutrition by prediction of glycemic responses. Cell. 2015; 163(5): 1079-1094.
20. Berry SE, Valdes AM, Drew DA, Asnicar F, Mazidi M, Wolf J, et al. Human postprandial responses to food and potential for precision nutrition. Nat Med. 2020; 26(6): 964-973.
21. Hall KD, Ayuketah A, Brychta R, Cai H, Cassimatis T, Chen KY, et al. Ultra-processed diets cause excess calorie intake and weight gain. Cell Metab. 2019; 30(1): 67-77.
22. Kho ZY, Lal SK. The Human Gut Microbiome - A Potential Controller of Wellness and Disease. Front Microbiol. 2018; 9: 1835.
23. Tilg H, Adolph TE, Gerner RR, Moschen AR. The intestinal microbiota in colorectal cancer. Cancer Cell. 2018; 33(6): 954-964.
24. Korem T, Zeevi D, Suez J, Weinberger A, Avnit-Sagi T, Pompan-Lotan M, et al. Bread affects clinical parameters and induces gut microbiome-

associated personal glycemic responses. Cell Metab. 2017; 25(6): 1243-1253.

25. Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. BMJ. 2018; 361: k2179.

26. Heianza Y, Ma W, Huang T, Wang T, Zheng Y, Smith SR, et al. Macronutrient Intake-Associated FGF21 Genotype Modifies Effects of Weight-Loss Diets on 2-Year Changes of Central Adiposity and Body Composition: The POUNDS Lost Trial. Diabetes Care. 2016; 39(11): 1909-1914.

27. Hardie DG. AMP-activated protein kinase: maintaining energy homeostasis at the cellular and whole-body levels. Annu Rev Nutr. 2014; 34: 31-55.

28. Castañer O, Fitó M, López-Sabater MC, Poulsen HE, Nyyssönen K, Schröder H, et al. The effect of Mediterranean diet on biomarkers of vascular wall inflammation and plaque vulnerability. Nutr Metab Cardiovasc Dis. 2014; 22(1): 15-22.

29. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell. 2017; 168(6): 960-976.

30. Kraakman MJ, Murphy AJ, Jandeleit-Dahm K, Kammoun HL. Macrophage polarization in obesity and type 2 diabetes: weighing down our understanding of macrophage function? Front Immunol. 2014; 5: 470.

31. Solon-Biet SM, Cogger VC, Pulpitel T, Wahl D, Clark X, Bagley E, et al. Defining the Nutritional and Metabolic Context of FGF21 Using the Geometric Framework. Cell Metab. 2016; 24(4):555-565.

32. Grygiel-Górniak B. Peroxisome proliferator-activated receptors and their ligands: nutritional and clinical implications --a review. Nutr J. 2014; 13: 17.

33. Jump DB, Depner CM, Tripathy S, Lytle KA. Potential for dietary omega-3 fatty acids to prevent nonalcoholic fatty liver disease and reduce the risk of primary liver cancer. Adv Nutr. 2015; 6(6): 694-702.

34. Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. Biochem Soc Trans. 2017; 45(5): 1105-1115.

35. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. Physiol Rev. 2018; 98(4): 2133-2223.

36. Samuel VT, Shulman GI. Nonalcoholic fatty liver disease as a nexus of metabolic and hepatic diseases. Cell Metab. 2018; 27(1): 22-41.

37. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet. 2019; 393(10170): 434-445.

38. Hjorth MF, Zohar Y, Hill JO, Astrup A. Personalized dietary management of overweight and obesity based on measures of insulin and glucose. Annu Rev Nutr. 2018; 38: 245-272.

39. Liu T, Zhang L, Joo D, Sun SC. NF-kappaB signaling in inflammation. Signal Transduct Target Ther. 2017; 2: 17023.

40. Hotamisligil GS. Foundations of immunometabolism and implications for metabolic health and disease. Immunity. 2017; 47(3): 406-420.

41. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007; 56(7): 1761-1772.

42. Minihane AM, Vinoy S, Russell WR, Baka A, Roche HM, Tuohy KM, et al. Low-grade inflammation, diet composition and health: current research evidence and its translation. Br J Nutr. 2015; 114(7): 999-1012.

43. Kimura I, Inoue D, Maeda T, Hara T, Ichimura A, Miyauchi S, et al. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41. Proc Natl Acad Sci USA. 2011; 108(19): 8030-8035.

44. Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, et al. Glucagon-like peptide 1 (GLP-1). Mol Metab. 2019; 30: 72-130.

45. Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinction in the gut microbiota compounds over generations. Nature. 2016; 529(7585): 212-215.

46. Ridlon JM, Harris SC, Bhowmik S, Kang DJ, Hylemon PB. Consequences of bile salt biotransformations by intestinal bacteria. Gut Microbes. 2016; 7(1): 22-39.

47. Fiorucci S, Biagioli M, Zampella A, Distrutti E. Bile acids activated receptors regulate innate immunity. Front Immunol. 2018; 9: 1853.

48. Chávez-Talavera O, Tailleux A, Lefebvre P, Staels B. Bile acid control of metabolism and inflammation in obesity, type 2 diabetes, dyslipidemia and NAFLD. Gastroenterology. 2017; 152(7): 1679-1694.

49. Wahlström A, Sayin SI, Marschall HU, Bäckhed F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. Cell Metab. 2016; 24(1): 41-50.

50. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011; 472(7341): 57-63.

51. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine promotes atherosclerosis. Nat Med. 2013; 19(5): 576-585.

52. Janeiro MH, Ramírez MJ, Milagro FI, Martínez JA, Solas M. Implication of Trimethylamine N-Oxide (TMAO) in Disease: Potential Biomarker or New Therapeutic Target. Nutrients. 2018; 10(10): 1398.

53. Tomova A, Bukovsky I, Rembert E, Yonas W, Alwarith J, Barnard ND, et al. The effects of vegetarian and vegan diets on gut microbiota. Front Nutr. 2019; 6: 47.

54. Camilleri M. Leaky gut: mechanisms, measurement and clinical implications in humans. Gut. 2019; 68(8): 1516-1526.

55. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 2008; 57(6): 1470-1481.

56. Boutagy NE, McMillan RP, Frisard MI, Hulver MW. Metabolic endotoxemia with obesity: is it real and is it relevant? Biochimie. 2016; 124: 11-20.

57. Winer DA, Winer S, Dranse HJ, Lam TKT. Immunologic impact of the intestine in metabolic disease. J Clin Invest. 2017; 127(1): 33-42.

58. Lynch CJ, Adams SH. Branched-chain amino acids in metabolic signalling and insulin resistance. Nat Rev Endocrinol. 2014; 10(12): 723-736.

59. Pedersen HK, Gudmundsdottir V, Nielsen HB, Hyotylainen T, Nielsen T, Jensen BAH, et al. Human gut microbes impact host serum metabolome and insulin sensitivity. Nature. 2016; 535(7612): 376-381.

60. Del Rio D, Rodriguez-Mateos A, Spencer JPE, Tognolini M, Borges G, Crozier A. Dietary polyphenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxid Redox Signal. 2013; 18(14): 1818-1892.

61. Cardona F, Andrés-Lacueva C, Tulipani S, Tinahones FJ, Queipo-Ortuño MI. Benefits of polyphenols on gut microbiota and implications in human health. J Nutr Biochem. 2013; 24(8): 1415-1422.

62. González-Sarrías A, Larrosa M, García-Conesa MT, Tomás-Barberán FA, Espín JC. Nutraceuticals for older people: facts, fictions and gaps in knowledge. Maturitas. 2013; 75(4): 313-334.

63. Etxeberria U, Fernández-Quintela A, Milagro FI, Aguirre L, Martínez JA, Portillo MP. Impact of polyphenols and polyphenol-rich dietary sources on gut microbiota composition. J Agric Food Chem. 2013; 61(40): 9517-9533.

64. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O,

et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature. 2014; 514(7521): 181-186.

65. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Invest. 2017; 127(1): 1-4.

66. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006; 444(7121): 840-846.

67. Agus A, Clément K, Sokol H. Gut microbiota-derived metabolites as central regulators in metabolic disorders. Gut. 2021; 70(6): 1174-1182.

68. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nat Med. 2017; 23(7): 804-814.

69. Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol. 2006; 7(2): 85-96.

70. Petersen MC, Vatner DF, Shulman GI. Regulation of hepatic glucose metabolism in health and disease. Nat Rev Endocrinol. 2017; 13(10): 572-587.

71. Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. Lancet. 2010; 375(9733): 2267-2277.

72. Perry RJ, Samuel VT, Petersen KF, Shulman GI. The role of hepatic lipids in hepatic insulin resistance and type 2 diabetes. Nature. 2014; 510(7503): 84-91.

73. Cani PD. Gut microbiota and obesity: lessons from the microbiome. Brief Funct Genomics. 2013; 12(4): 381-387.

74. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res. 2013; 54(9): 2325-2340.

75. Lassenius MI, Pietiläinen KH, Kaartinen K, Pussinen PJ, Syrjänen J, Forsblom C, et al. Bacterial endotoxin activity in human serum is associated with dyslipidemia, insulin resistance, obesity, and chronic inflammation. Diabetes Care. 2011; 34(8): 1809-1815.

76. Garcia D, Shaw RJ. AMPK: mechanisms of cellular energy sensing and restoration of metabolic balance. Mol Cell. 2017; 66(6): 789-800.

77. Yoon MS. Branched-chain amino acids in insulin resistance and metabolism. Nutrients. 2016; 8(7): 405.

78. Pedersen HK, Gudmundsdottir V, Nielsen HB, Hyotylainen T, Nielsen T, Jensen BAH, et al. Human gut microbes impact host serum metabolome and insulin sensitivity. Nature. 2016; 535(7612): 376-381.

79. Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. Arch Med Sci. 2013; 9(2): 191-200.

80. Blüher M. Adipose tissue dysfunction contributes to obesity related metabolic diseases. Best Pract Res Clin Endocrinol Metab. 2013; 27(2): 163-177.

81. Ahmadian M, Suh JM, Hah N, Liddle C, Atkins AR, Downes M, et al. PPARγ signaling and metabolism: the good, the bad and the future. Nat Med. 2013; 19(5): 557-566.

82. Tyagi S, Gupta P, Saini AS, Kaushal C, Sharma S. The peroxisome proliferator-activated receptor: a family of nuclear receptors role in various diseases. J Adv Pharm Technol Res. 2011; 2(4): 236-240.

83. Clarke SD. The multi-dimensional regulation of gene expression by fatty acids: polyunsaturated fats as nutrient sensors. Curr Opin Lipidol. 2004; 15(1): 13-18.

84. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011; 11(2): 85-97.

85. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003; 112(12): 1796-1808.

86. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. J Clin Invest. 2011; 121(6): 2111-2117.

87. Vinolo MAR, Rodrigues HG, Nachbar RT, Curi R. Regulation of inflammation by short chain fatty acids. Nutrients. 2011; 3(10): 858-876.

88. Calder PC. Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. Biochim Biophys Acta. 2015; 1851(4): 469-484.

89. Spinelli JB, Haigis MC. The multifaceted contributions of mitochondria to cellular metabolism. Nat Cell Biol. 2018; 20(7): 745-754.

90. Fisher-Wellman KH, Neufer PD. Linking mitochondrial bioenergetics to insulin resistance via redox biology. Trends Endocrinol Metab. 2012; 23(3): 142-153.

91. Tiganis T. Reactive oxygen species and insulin resistance: the good, the bad and the ugly. Trends Pharmacol Sci. 2011; 32(2): 82-89.

92. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organ J. 2012; 5(1): 9-19.

93. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev. 2009; 2(5): 270-278.

94. Wang Y, Kasper LH. The role of microbiome in central nervous system disorders. Brain Behav Immun. 2014; 38: 1-12.

95. Rowland I, Gibson G, Heinken A, Scott K, Swann J, Thiele I, et al. Gut microbiota functions: metabolism of nutrients and other food components. Eur J Nutr. 2018; 57(1): 1-24.

96. Yardeni T, Tanes CE, Bittinger K, Mattei LM, Schaefer PM, Singh LN, et al. Host mitochondria influence gut microbiome diversity: a role for ROS. Sci Signal. 2019; 12(588): eaaw3159.

97. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol. 20111; 29: 415-445.

98. Stienstra R, Tack CJ, Kanneganti TD, Joosten LAB, Netea MG. The inflammasome puts obesity in the danger zone. Cell Metab. 2012; 15(1): 10-18.

99. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 2011; 11(2): 98-107.

100. Rocha DMUP, Caldas APS, Oliveira LL, Bressan J, Hermsdorff HHM. Saturated fatty acids trigger TLR4-mediated inflammatory response. Atherosclerosis. 2016; 244: 211-215.

101. Tilg H, Moschen AR. Food, immunity, and the microbiome. Gastroenterology. 20115; 148(6): 1107-1119.

102. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, et al. Commensal microbe-derived butyrate induces differentiation of colonic regulatory T cells. Nature. 2013; 504(7480): 446-450.

103. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest. 2005; 115(5): 1111-1119.

104. Mentch SJ, Locasale JW. One-carbon metabolism and epigenetics: understanding the specificity. Ann N Y Acad Sci. 2016; 1363(1): 91-98.

105. McKay JA, Mathers JC. Diet induced epigenetic changes and their implications for health. Acta Physiol. 2011; 202(2): 103-118.

106. Davie JR. Inhibition of histone deacetylase activity by butyrate. J Nutr. 2003; 133: 2485S-2493S.

107. Hardy TM, Tollefsbol TO. Epigenetic diet: impact on the epigenome and cancer. Epigenomics. 2011; 3(4): 503-518.

108. Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. Annu Rev Nutr. 2007; 27: 363-388.

109. Godfrey KM, Costello PM, Lillycrop KA. Development, epigenetics and metabolic programming. Nestle Nutr Inst Workshop Ser. 2016; 85: 71-80.

110. Nicholson JK, Lindon JC. Systems biology: metabonomics. Nature. 2008; 455(7216): 1054-1056.

111. Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. Genome Biol. 2017; 18: 83.

112. Karczewski KJ, Snyder MP. Integrative omics for health and disease. Nat Rev Genet. 2018; 19(5): 299-310.

113. Kitano H. Systems biology: a brief overview. Science. 2002; 295(5560): 1662-1664.

114. Ordovás JM, Ferguson LR, Tai ES, Mathers JC. Personalised nutrition and health. BMJ. 2018; 361: k2173.

115. Celis-Morales C, Marsaux CFM, Livingstone KM, Navas-Carretero S, San-Cristobal R, Fallaize R, et al. Can genetic-based advice help you lose weight? Findings from the Food4Me European randomized controlled trial. Am J Clin Nutr. 2017; 105(5): 1204-1213.

116. Ordovás JM, Ferguson LR, Tai ES, Mathers JC. Personalised nutrition and health. BMJ. 2018; 361: k2173.

117. Berry SE, Valdes AM, Drew DA, Asnicar F, Mazidi M, Wolf J, et al. Human postprandial responses to food and potential for precision nutrition. Nat Med. 2020; 26(6): 964-973.

118. Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, et al. Personalized nutrition by prediction of glycemic responses. Cell. 2015; 163(5): 1079-1094.

119. De Toro-Martín J, Arsenault BJ, Després JP, Vohl MC. Precision nutrition: a review of personalized nutritional approaches for the prevention and management of metabolic syndrome. Nutrients. 2017; 9(8): 913.

120. Phillips CM. Nutrigenetics and metabolic disease: current status and implications for personalised nutrition. Nutrients. 2020; 12(11): 3315.

121. Corella D, Ordovás JM. How does the Mediterranean diet promote cardiovascular health? Current progress toward molecular mechanisms: gene-diet interactions at the genomic, transcriptomic, and epigenomic levels provide novel insights into new mechanisms. BioEssays. 2014; 36(5): 526-537.

122. Loos RJF, Yeo GSH. The bigger picture of FTO: the first GWAS-identified obesity gene. Nat Rev Endocrinol. 2014; 10(1): 51-61.

123. Livingstone KM, Celis-Morales C, Papandonatos GD, Erar B, Florez JC, Jablonski KA, et al. FTO genotype and weight loss: systematic review and meta-analysis of 9563 individual participant data from eight randomised controlled trials. BMJ. 2016; 354: i4707.

124. Grant SFA, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, et al. Variant of transcription factor 7-like 2 gene confers risk of type 2 diabetes. Nat Genet. 2006; 38(3): 320-323.

125. Corella D, Carrasco P, Sorlí JV, Estruch R, Rico-Sanz J, Martínez-González MÁ, et al. Mediterranean diet reduces the adverse effect of the TCF7L2-rs7903146 polymorphism on cardiovascular risk factors and stroke incidence. Diabetes Care. 2013; 36(11): 3803-3811.

126. Minihane AM, Jofre-Monseny L, Olano-Martin E, Rimbach G. ApoE genotype, cardiovascular risk and responsiveness to dietary fat manipulation. Proc Nutr Soc. 2007; 66(2): 183-197.

127. Kolodziejczyk AA, Zheng D, Elinav E. Diet-microbiota interactions and personalized nutrition. Nat Rev Microbiol. 2019; 17(12): 742-753.

128. Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. Nat Rev Gastroenterol Hepatol. 2019; 16(1): 35-56.

129. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, et al. Richness of human gut microbiome correlates with metabolic markers. Nature. 2013; 500(7464): 541-546.

130. Derrien M, Belzer C, de Vos WM. Akkermansia muciniphila and its role in regulating host functions. Microb Pathog. 2017; 106: 171-181.

131. Depommier C, Everard A, Druart C, Plovier H, Van Hul M, Vieira-Silva S, et al. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers. Nat Med. 2019; 25(7): 1096-1103.

132. Kovatcheva-Datchary P, Nilsson A, Akrami R, Lee YS, De Vadder F, Arora T, et al. Dietary fiber-induced improvement in glucose metabolism is associated with increased abundance of Prevotella. Cell Metab. 2015; 22(6): 971-982.

133. Johnson CH, Ivanisevic J, Siuzdak G. Metabolomics: beyond biomarkers and towards mechanisms. Nat Rev Mol Cell Biol. 2016; 17(7): 451-459.

134. Wang TJ, Larson MG, Vasan RS, Cheng S, Rhee EP, McCabe E, et al. Metabolite profiles and the risk of developing diabetes. Nat Med. 2011; 17(4): 448-453.

135. Guasch-Ferré M, Hruby A, Toledo E, Clish CB, Martínez-González MÁ, Salas-Salvadó J, et al. Metabolomics in prediabetes and diabetes: a systematic review and meta-analysis. Diabetes Care. 2016; 39(5): 833-846.

136. Milagro FI, Mansego ML, De Miguel C, Martínez JA. Dietary factors, epigenetic modifications and obesity outcomes: progresses and perspectives. Mol Aspects Med. 2013; 34(4): 782-812.

137. Lillycrop KA, Burdge GC. Environmental challenge, epigenetic plasticity and the induction of disease. Epigenomics. 2014; 6(6): 623-636.

138. Müller M, Kersten S. Nutrigenomics: goals and strategies. Nat Rev Genet. 2003; 4(5): 315-322.

139. Evert AB, Dennison M, Gardner CD, Garvey WT, Lau KHK, MacLeod J, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. Diabetes Care. 2019; 42(5): 731-754.

140. Afman L, Müller M. Human nutrigenomics of gene regulation by dietary fatty acids. Prog Lipid Res. 2012; 51(1): 63-70.

141. Blüher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol. 2019; 15(5): 288-298.

142. Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. Med Clin North Am. 2018; 102(1): 183-197.