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# Nutrigenomics, the Microbiome, and Gene-Environment Interactions: New Directions in Cardiovascular Disease Research, Prevention, and Treatment:

## A Scientific Statement From the American Heart Association

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## Abstract

Cardiometabolic diseases are the leading cause of death worldwide and are strongly linked to both genetic and nutritional factors. The field of nutrigenomics encompasses multiple approaches aimed at understanding the effects of diet on health or disease development, including nutrigenetic studies investigating the relationship between genetic variants and diet in modulating cardiometabolic risk, as well as the effects of dietary components on multiple “omic” measures, including transcriptomics, metabolomics, proteomics, lipidomics, epigenetic modifications, and the microbiome. Here, we describe the current state of the field of nutrigenomics with respect to cardiometabolic disease research and outline a direction for the integration of multiple omics techniques in future nutrigenomic studies aimed at understanding mechanisms and developing new therapeutic options for cardiometabolic disease treatment and prevention.

### Keywords

AHA Scientific Statements; diet; metagenomics; microbiota; nutrigenetics; nutrigenomics; nutritional status

Nutrigenomics is a growing field that has received increased attention over the past decade.[1–5] The interpretation and scope of nutrigenomics may vary, but it can be thought to encompass the spectrum of nutritional genomics research, including classic nutrigenetics studies of gene-diet interactions and molecular nutrition, in vitro and in vivo models, human nutrition studies, and the application of large-scale, unbiased studies using high-throughput “omics” techniques to study the effects of nutrients on the body.[6] As the Figure shows, diet and the genome may influence cardiometabolic health through a variety of interconnected intermediates, perturbations in which can be measured through omics technologies, including RNA expression (transcriptome), epigenetic modifications (epigenome), metabolites (metabolome), lipids (lipidome), proteins (proteome), and resident microbial communities (microbiome). Although it is clear that both nutrients and genes play a distinct role in determining health, the complex interactions among genes, diet, and downstream networks are not well understood. The application of nutrigenomics approaches to questions of human health and disease is an important component in understanding the complexities of the interplay between basic metabolic processes and external influences in disease processes and has important implications for the development of more targeted strategies in disease prevention and treatment. Analogous to pharmacogenomics, nutrigenomics has the potential to identify genetic predictors of disease-relevant responses to diet, and this potential and its applicability in the context of personalized nutrition have popular appeal. However, nutrigenomics has also been the subject of much hyperbole and has been ascribed much promise, particularly in the arenas of personalized nutrition, functional foods, and nutraceuticals. Unfortunately, the science has not yet fully delivered on this unrealized potential. More than a third of the searchable articles in PubMed on nutrigenomics are review articles, and despite enthusiasm about possible clinical applications, the evidence base remains limited. In this American Heart Association scientific statement, we consider the state of the field of nutrigenomics with respect to cardiometabolic disease, highlight what we know and what is lacking, and propose future directions required to advance the field.

## Nutritional Epidemiology

The study of nutrition and cardiometabolic diseases began in the 1950s with the classic diet-heart hypothesis based on ecological studies linking saturated fat and cardiovascular disease (CVD) mortality.[7] These conclusions were supported by small short-term human feeding studies designed to show that replacement of carbohydrate or polyunsaturated fatty acids (PUFAs) with saturated fatty acids (SFAs) increased total cholesterol.[8] A growing evidence base that includes millions of participants who have provided detailed dietary and lifestyle data and biological specimens has shaped our understanding of biological pathways for micronutrient and macronutrient metabolism and their effects on disease. Findings from these efforts serve as the foundation for the evolution of contemporary dietary guidelines,[9] which are refined as new technologies and methods permit ever more rigorous standards for defining optimal nutritional guidelines. For example, the earlier Dietary Guidelines for Americans (2000)[10] recommended a low-fat diet by replacing dietary SFAs with carbohydrate. However, on the basis of hundreds of metabolic intervention studies, cohort studies, and long-term, large, clinical trials of moderate– to high–monounsaturated fatty acid and moderate- to high-PUFA diets, updated guidelines do not emphasize total fat but instead advise replacing foods high in SFAs with food sources of unsaturated fatty acids.

The inclusion of biospecimens in observational and intervention studies enhances the potential to apply nutrigenomics within large-scale human studies, but with the knowledge that nutrition assessment is not without limitations. The limitations of observational cohort studies and of randomized, clinical trials have been discussed at length and are beyond the scope of this review,[11] but we highlight important aspects to provide context about why additional insights can be gained through incorporation of measures of the genome, epigenome, metabolome, proteome, microbiome, and other relevant factors.

Observational epidemiological studies have been instrumental in our understanding of nutrition and CVD because many have been ongoing for decades and include hundreds of thousands of participants, as reviewed elsewhere.[12,13] Importantly, they capture intake of foods and nutrients as customarily consumed rather than as a supplement or from controlled diets prepared for experimental purposes, but they generally do not have repeated measures of diet over the life course and may be confounded by changes in the food supply, limiting inferences that can be made. The inability to account for other diet, lifestyle, and health characteristics of participants is potentially confounding, but this can be addressed directly through randomization in intervention trials. However, unlike randomized trials of pharmaceutical interventions, trials of nutrients or dietary patterns can give biased or uninformative results when secular trends in the background diet or fortification dilute or mask the effect of the intervention. For example, in the 1990s, many trials were initiated to study folate supplementation on the effects of CVD, but by the mid-1990s, >50 countries worldwide initiated folate fortification, adding 200 to 400 μg/d to the average diet, which ultimately may have been enough to increase folate status in trial participants at highest risk for CVD. Trials are also limited, especially those with clinical end points, because such studies typically test only a single dose, are limited in duration by cost and adherence, and create an artificial environment to test a nutrient or food pattern. Most midlength dietary pattern trials of 1 to 4 years must either provide all foods for consumption (which is simple

for the participant but not feasible as a long-term solution) or use weekly or monthly training sessions with dietitians, health coaches, and wellness programs, all of which may be cost-prohibitive. Even trials with the most intensive support systems can experience poor adherence as participants grow weary of the prescribed dietary pattern and either revert to previous dietary habits or adhere to the experimental diets only before clinical examination assessments.

Studies of nutrition and cardiometabolic disease have taught us much over the past half-century, but most important, they have taught us that conclusions are most sound when supported by short-term dietary intervention studies to understand plausible biological mechanisms and long-term observational epidemiological studies to understand the impact of decades of exposure. In some unique situations in which results from both study types are consistent, large, long-term trials are initiated. The most conclusive trials for cardiometabolic disease have been based on dietary pattern such as the Dietary Approaches to Stop Hypertension (DASH) dietary patterns trials,[14] the Diabetes Prevention Program,[15] the Dietary Intervention Randomized Controlled Trial for weight loss,[16] and the Lyon Diet Heart study,[17] as well as the Prevention con Dieta Mediterránea (PREDIMED) trial for CVD reduction.[18] In PREDIMED, the reduction in CVD among individuals randomized to a Mediterranean diet plus extravirgin olive oil or mixed nuts corroborates decades-long cohort studies and short-term trials reporting benefits of the Mediterranean diet and its components, including olive oil, nuts, fruits and vegetables, whole grains, and wine.[19] These highly successful initiatives have greatly enhanced our knowledge of diet at a population level, and the incorporation of omics into future nutrition studies will help us understand the mechanisms of action underlying a healthy diet.

## Nutritional Assessment

The importance of using appropriate nutrition assessment tools should not be underestimated, and a combination of diet and biochemical measures may be required to provide a comprehensive assessment of short-term and long-term exposure. The best tools provide an integrated measure of exposure because, for nutrition (except for mega-dose supplements or accidental contamination or poisoning), variation in exposure is modest and complex metabolic systems buffer extreme exposures. The major dietary tools that have been incorporated into large observational studies include 24-hour recalls, diet records, and food frequency questionnaires. Each of these has strengths and weaknesses, but each also provides insights and a foundation of research methods applicable to studies.

The 24-hour recall and single-day diet record are the best methods to assess a 1-day intake. They allow direct quantification of specific foods and thus limit error resulting from estimation of intake. The 24-hour recall may be more susceptible to error because of memory recall or modifications in responses to be more socially acceptable to the interviewer, but careful scripting of a well-trained interviewer can minimize this problem, and online methods that are computer assisted with multistep quality control have reduced errors.[20,21] Diet records, in which the participant weighs and records everything consumed in a day as it is eaten, generally are considered the gold standard for assessing short-term intake[22] because they do not rely on memory or estimation of portion size, but with multiday

assessments, they can be burdensome on study subjects, thus leading to underassessment or changes in diet to reduce the burden of recording.

A single 24-hour recall or diet record is not a representative measure of average intake because of the great fluctuations in nutrient estimates caused by consumption of a single nutrient-dense food, for example, carrots and liver, fish, and berries and tea, which could lead to substantial misclassification of average intake of vitamin A, omega-3 fatty acids, or polyphenols, respectively. Recalls or records are frequently spread out over several months or even a year to better estimate fluctuations in intake. For large studies, multiple assessments can be burdensome or cost-prohibitive, which has led many studies to shift these measures to computerized protocols.[23–25] Alternatively, the semiquantitative food frequency questionnaire (SFFQ) can be used as the primary method for estimating nutrient intake over a longer period of time. Participants are provided with a list of 100 to 150 commonly consumed foods and portion sizes and are usually asked to estimate intake over a 3- to 12-month period, individually incorporating fluctuations in weekly or seasonal patterns into their grid of fixed response categories. The SFFQ can be developed to be culturally specific, readily computerized and inexpensive, anonymizable, and less burdensome to study subjects than other dietary methods. The quality of the assessment tool is determined by the comprehensiveness of the food list provided, the clarity of provided instructions, and the ability of subjects to recall and properly estimate average intake of listed foods. The SFFQ is best used to rank individuals in a population by their intake of a nutrient or food item because of systematic underestimation or overestimation. When SFFQs are validated against gold standards such as multiple days of diet records or biochemical markers in blood, adipose tissue, or hair, some foods and nutrients are better estimated than others. The SFFQ has been well validated for assessing micronutrients, fatty acids, and many other important nutritional determinants of disease. However, the SFFQ is not good at estimating sodium intake because of great fluctuations in similar foods (homemade food versus highly processed store-bought version) or trace metals such as selenium that are dependent on soil composition. This limitation in the granularity of dietary studies highlights the need for additional methods of characterizing nutrients that are not well characterized by current dietary tools. As discussed in the following sections, there is great promise in omics profiling for better assessing risk of CVD and related traits and advancing our understanding of how genetic variation affects diet response and potentially the underlying mechanisms, thus improving our ability to design better targeted interventions. New omics platforms integrated with dietary measures can better quantify biological systems by incorporating not only a single circulating vitamin but also a family of downstream metabolites and other metabolically relevant nutritional factors. Collectively, advances in these areas will bring us closer to individualized lifestyle and pharmacotherapy interventions that are more effective for preventing and treating CVD.

## Genetic Variation

Studies that have focused on identifying the genes and genetic variants associated with the different types of intermediate and CVD phenotypes in humans have been more consistent and successful than studies undertaken to identify genetic variants associated with other complex traits. What may have contributed to this greater success is that the cardiovascular

phenotypes studied, both intermediate (plasma lipid concentrations, blood pressure, etc) and CVD end points (myocardial infarction [MI], stroke, and other CVD), have a standardized clinical definition and are easier to measure than other complex phenotypes.

A 2013 American Heart Association statement[26] supports the notion that for rare and familial forms of CVD, we are identifying single-gene mutations that impart relatively large effects on individual phenotype. For these cases, progress has led to several clinically useful diagnostic tests. However, the prevalence of monogenic disorders typically accounts for only a small proportion of the total CVD observed in the population. There has been less progress in developing genetic testing for complex CVD because individual common variants usually have only a modest impact on risk. Exome sequencing approaches may begin to address this; rare coding mutations in *LDLR* and *APOA5* were found to affect MI risk in the general population through modulation of low-density lipoprotein (LDL) and triglyceride metabolism.[27,28] However, the study of the genomics of complex CVD is further challenged by the influence of environmental variables, phenotypic heterogeneity, and pathogenic complexity.[29]

## Gene-Diet Interactions in Determining CVD Risk in Humans

Multiple gene-environment interactions (GxEs) exist in determining risk of CVD in humans, including factors such as smoking, physical activity, drugs, diet, and social context. An outstanding initiative to unravel this complexity is the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, which was formed to facilitate meta-analyses of genome-wide association studies (GWAS) and replication opportunities among multiple large, population-based cohort studies.[30] While acknowledging the importance of other environmental factors, we focus here on gene-diet interactions because diet is one of the most important exogenous factors that humans are exposed to every day.[31] Gene-diet interactions in CVD have been analyzed for many years, with many reports demonstrating that those interactions have an impact on determining both intermediate and final CVD phenotypes,[32–67] as cataloged in detail.[68] Some of these genetic variants have been highlighted through GWAS. For example, variation in the *TCF7L2* gene, previously implicated in type 2 diabetes mellitus,[69] was shown to interact with diet through intervention with the Mediterranean diet and played a role in determining stroke risk.[34] The effects of other loci such as 9p21 and *FTO*, which are robustly associated with CVD and obesity, respectively, have also been reported to modulate CVD risk through interaction with diet.[44,70] Gene-diet relationships are complex, with multiple dietary components potentially interacting with genotype to determine CVD risk. For example, elevated total homocysteine, a marker of CVD risk,[71] is modulated by dietary folate and alcohol consumption[72,73] and interaction with *MTHFR* genotype.[74] Thus, a better understanding of these gene-nutrient interactions with information on both folate and alcohol intake is essential to understand why total homocysteine levels are elevated (and the underlying reason why CVD risk is elevated).

A comprehensive review of cardiometabolic GxEs from 386 publications,[68] including blood lipids, glycemic traits, obesity anthropometrics, vascular measures, inflammation, and metabolic syndrome, allowed the following conclusions. First, the GxE single-nucleotide

polymorphisms (SNPs) showed little overlap with variants identified by a main-effect GWAS, indicating the importance of environmental interactions with genetic factors on cardiometabolic traits. Second, these GxE SNPs were enriched in adaptation to climatic and geographical features, with implications for energy homeostasis and response to physical activity. Third, a comparison with gene networks responding to plasma cholesterol lowering or regression of atherosclerotic plaques showed that GxE genes have a greater role in those responses, particularly through high-energy diets and fat intake, than do GWAS-identified genes for the same traits. Collectively, these studies demonstrate that SNPs supporting cardiometabolic GxEs often exhibit transcriptional effects or are under positive selection. However, not all SNPs can be assigned potential functional or regulatory roles because data are often lacking in specific cell types.

One limitation in the study of gene-diet interactions is that most of the studies are observational, so they provide a lower level of evidence than experimental studies. In addition, those experimental studies have often had an inadequate sample size. Therefore, it is necessary to increase the level of evidence in support of the gene-diet interactions in CVD. Furthermore, relatively few studies have focused on CVD end points, an area of investigation where future efforts should be focused.[34,57]

### Clinical Application of the Gene-Diet Interactions

Research into gene-diet interactions is crucial to obtain information that will allow us to undertake clinical applications of early genetic diagnosis. If a genetic variant is associated with CVD or an intermediate phenotype (eg, greater risk of hypertension, dyslipidemias, or diabetes mellitus) and it is known that a certain diet can counteract that genetic risk, then one can reason that disease risk could be reduced through prescription of a personalized diet. To date, most studies have focused on primary prevention, but there is also great interest in discovering gene-diet interactions in secondary CVD prevention to provide appropriate dietary recommendations for individuals who have already had a nonfatal CVD event. As next-generation sequencing technologies continue to improve, they will contribute to advancing gene-diet interaction studies in particular and GxE studies in general. The results of these efforts can then provide us with new knowledge to be applied in achieving more efficacious prevention of CVD.

## Nutrient Effects on RNA Expression

We expect that many of the biological effects of diet on cardiovascular risk and outcomes are mediated by changes in gene expression, whether as a result of genetic variation or environmental influences. In this regard, the use of global transcriptional profiling is a powerful tool in nutrigenomic studies. For example, measuring dynamic changes in gene expression before and after a short-term dietary challenge can highlight novel nutrient-responsive genes, and profiling gene expression after a diet intervention can identify genes responsive to the intervention. The overall goal of these studies is to identify novel candidates for cardiometabolic risk.

## Candidate Gene Studies

Some of the best evidence for direct effects of specific nutrients on gene expression comes from studies of orphan nuclear receptors.[75] Of these nutrient-responsive transcription factors, the peroxisome proliferator-activated receptor (PPAR) family has been particularly well studied.[76,77] As lipid-responsive genes, with effects on lipoprotein metabolisms and inflammation, the PPARs have been recognized and extensively studied for their relevance to cardiometabolic disease. SNPs in PPAR genes have been implicated in cardiometabolic risk in gene-diet interaction studies.[78,79] The PPAR family members α, δ, and γ are responsive to specific dietary fatty acids (PUFAs, monounsaturated fatty acids, and SFAs)[76,80] and fatty acid–derived eicosanoids, as well as to physiological states induced by nutrient status (eg, fasting). PPARs are also responsive to a number of synthetic ligands, including fibrates and thiazolidinediones, and thus are attractive drug targets. PPAR agonism is responsible for activating and inhibiting a number of downstream genes, which remain to be fully characterized,[81–83] and may act as a key regulator of hepatic fatty acid metabolism, response to fasting, and inflammatory responses.[84–86] Although PPARα agonism through fenofibrate does not appear to have effects on systemic inflammatory responses in healthy humans,[87] agonism of PPARγ and other targets by n-3 PUFA supplementation has an effect on systemic inflammatory response.[88] PPARγ is crucial for adipose tissue development and adipocyte differentiation and potentially increasing browning of adipose tissue.[89] Thus, PPARγ agonism can increase the lipid storage capacity of adipose tissue while increasing fatty acid oxidation capacity, leading to improvements in insulin sensitivity and cardiometabolic risk. Thiazolidinediones have been used extensively as insulin-sensitizing agents through PPARγ agonism to treat type 2 diabetes mellitus, although concerns have arisen about the safety of this class of drugs, with potential for increased MI and exacerbation of heart failure.[90,91] Given the importance of diet-derived ligands in PPAR agonism, differences in nutrient status may be important in mediating drug effects, with potential differences in the effects of PPAR agonism, through physiological versus pharmacological ligands. These genes thus remain interesting targets for further nutrigenomics study.

In addition to PPARs, there are other clear examples of gene-diet interaction, and similarly, several additional nuclear receptors have been shown to be important nutrient regulators, including the bile acid–responsive farnesoid X receptor (*FXR* or *NR1H4*), which may influence fatty acid and glucose homeostasis[92]; the retinoic acid–responsive retinoid X receptor (*RXR*)[93]; and the oxysterol-responsive liver X receptor (*LXR*α/β, *NR1H3*/2), which may alter atherosclerosis and diabetes mellitus risk.[94] The nuclear receptor superfamily members form both homodimers and heterodimers and likely act cooperatively to regulate nutrient metabolism and cardiometabolic risk.[95] Each of these highly specific receptors has diet-derived ligands; however, how seemingly divergent signals from each of these receptors respond to a meal remains unclear.

## Unbiased Transcriptomics

Although studying candidate gene expression has utility in confirming hypotheses and defining mechanisms, large-scale, unbiased techniques are required to further advance our knowledge. Unbiased approaches to assessing transcriptional changes in response to dietary

intervention have used microarray and RNASeq approaches. These technologies and their application to CVD have been reviewed elsewhere.[96,97] We focus here on how these technologies can be applied to the field of nutrigenomics.

In understanding the interaction between nutritional components and gene expression changes, selecting the relevant cell type is of great importance. The majority of studies in humans have focused on blood-derived samples, for example, whole blood or peripheral blood mononuclear cells (PBMCs), or on adipose tissue, with a smaller number in skeletal muscle. These represent relatively accessible and relevant tissues and give important, albeit incomplete, insight, which leaves other disease-relevant tissues to be studied in animal models. Transcriptomic studies of nutrition have to date mainly focused broadly on dietary patterns such as Mediterranean diets, on macronutrients, or on specific dietary components, primarily fish oil–derived fatty acids and some phytonutrients. These studies are further categorized into those implementing a dietary intervention versus those examining habitual dietary status. Associations between PBMC gene expression patterns and habitual consumption of a prudent versus Western diet were reported in healthy subjects participating in the PREDIMED study (n=30).[98] A Mediterranean diet intervention was also found to alter PBMC expression of genes in cardiovascular pathways.[99] Changes in gene expression in blood and adipose tissue from the same individuals (n=3) were reported after an intervention to alter macronutrient content,[100] with divergent transcriptomic responses in the 2 tissues. Adipose tissue gene expression changes were characterized in response to both overfeeding in healthy subjects (n=6) and caloric restriction in obese subjects (n=18),[101] with >100 genes identified as responding to caloric intake. Several studies have profiled PBMC expression before and after intervention with n-3 PUFA,[102–104] and the adipose tissue transcriptome by n-3 PUFA status has also been studied.[105] Furthermore, the response to an 8-week high-fat diet intervention of SFAs or monounsaturated fatty acids was characterized in adipose tissue from overweight subjects (n=20).[106] Other studies have included additional short-term interventions, which increase the power to detect dynamic metabolically relevant changes. For example, skeletal muscle was profiled in obese subjects with insulin resistance (n=15) at 4 time points after supplementation with n-3 PUFA or n-3 PUFA with fish gelatin, in both cases before and after a euglycemic-hyperinsulinemic clamp.[107] This approach allowed identification of genes that were robustly altered by the clamp and by supplementation itself. This group has also used response to intervention as a tool to understand genetic differences in transcriptomic responses. High and low responders to n-3 PUFA supplementation as defined by change in triglycerides were identified and shown to differ in their transcriptomic responses.[108]

Despite increasing availability of transcriptomic data, many limitations still apply. We expect the transcriptome to vary, depending on time of day; cell type composition; age, race, and sex of the individual; and the health or disease status and habitual diet. Given these many confounders, extracting biologically meaningful data is a challenge. In general, the majority of transcriptomic studies will find statistically significant changes in the expression of some genes or transcripts, even in relatively small numbers, but it is difficult to decipher which of these are truly meaningful and functional. A key constraint is the need to collapse data into intelligible results. To reduce the long lists of genes identified in transcriptomics experiments, common approaches include some sort of pathway analysis and functional

clustering. Although this approach is certainly valid, it is biased toward genes with known functions, meaning that many interesting but unstudied candidates will likely be missed among the vast amount of available data. The use of unbiased methods to construct interaction networks may overcome these limitations.[109] The first step to understanding the health implications of diet-related gene expression patterns on a global scale is to characterize the transcriptome of multiple tissues under different diet and temporal conditions. However, at present, the field is still in a developmental stage in which we are generating data but struggling to obtain meaningful insight. Many studies remain underpowered with small numbers of subjects and many confounders. With decreasing costs, analyzing the transcriptomes of larger numbers of individuals over multiple time points is now feasible. Furthermore, public data repositories and large-scale collaborations are allowing the meta-analysis of multiple data sets,[81] increasing the value of the information that can be extracted from existing data. Thus, the next step for the field will be broad integration of available transcriptomic information with in-depth functional and mechanistic interrogation of novel candidates, as well as increased use of repeated-measures and acute “evoked phenotype” study design interventions. Beyond this, integration of transcriptomic data with other information, both in the reverse direction of genomic and expression quantitative trait locus analysis and in the forward direction toward proteins and metabolites, is crucial to obtain a cohesive view of the metabolic response to nutrients.

### Noncoding RNA

As next-generation sequencing has become increasingly affordable and feasible, our knowledge of noncoding RNA (ncRNA) has improved.[110–113] A large proportion of the transcriptome is not translated into protein yet is functional, with both long ncRNA and small RNAs exhibiting specific functionality.[114] Of particular relevance to nutrigenomics, microRNAs and other classes of small RNA have received particular attention for their possible ability to signal not just across species but across kingdoms. Plant-derived dietary microRNAs may potentially cross the intestinal barrier and not only remain intact as they enter the bloodstream but also retain functionality and regulate host gene expression.[115,116] Although this remains highly controversial,[117–119] host-derived small RNAs are known to regulate many processes of relevance to cardiometabolic risk[120] and to be altered in response to dietary intervention and specific nutrients.[121,122] For example, several microRNAs were reported to be changed in the PBMC transcriptome after 1 year of supplementation with resveratrol-containing grapeseed extract in subjects with type 2 diabetes mellitus.[123] Thus, the potential functional role of diet acting directly or indirectly through small RNA is intriguing.

## Epigenetics

As discussed above, dietary components can directly modify gene expression. However, many of the effects of diet and nutritional status on gene expression and regulation are mediated through epigenetic mechanisms. Dysregulation of epigenetic states plays a major role in disease, including CVD.[96,124] Although our awareness of this role is expanding rapidly as we learn more about the nature of the endogenous epigenetic regulatory machinery and the ways in which it can be perturbed, much remains to be elucidated.

Importantly, the reversible nature of epigenetic mechanisms provides a unique opportunity for the development of treatment measures targeting the perturbed marks or pathways. Although the list of epigenetic mechanisms and their functions continues to grow, those with roles in disease include DNA methylation, the addition of a methyl group ($CH_3$) to the cytosine of a CpG dinucleotide; DNA hydroxymethylation, the presence of a hydroxymethyl group ($CH_2OH$) at the cytosine of a CpG dinucleotide; and posttranslational modifications to histone tails of nucleosomes such as methylation, acetylation, ubiquitination, phosphorylation, sumoylation, and biotinylation. However, our understanding of how these epigenetic mechanisms regulate gene expression and how disruption leads to disease remains incomplete. Major functions include recruitment and accessibility of transcriptional machinery to target genes and in stability and cellular localization of RNA and proteins. Furthermore, studies show an additional role for epigenetic mechanisms in determining genomic stability.[125,126] Although there are seemingly distinct roles for each of these mechanisms acting individually· we more often observe redundant and cooperative functions for which several mechanisms must work together for normal cellular function and development.[127,128] Likewise, multiple mechanisms are simultaneously perturbed in disease states.

## Role of Nutrition in Epigenetic Perturbation

There is some evidence relating diet, including micronutrients and macronutrients and diet composition· to epigenetic changes that may alter cardiometabolic risk. A classic example of a seemingly direct role of nutrients in determining epigenetic states is the role of “methyl-donor” nutrients such as choline, methionine, betaine, folate, vitamin $B_{12}$, and zinc. These dietary components promote the formation of S-adenosyl methionine, a metabolite of the 1-carbon pathway,[129–131] which contributes the methyl group required for methylation of DNA and histones. Bioavailability of these nutrients is a limiting factor in the proper establishment and maintenance of these epigenetic marks. Indeed, in vivo studies show that deficiency in or oversupplementation of these nutrients can result in altered epigenetic states, including changes in DNA methylation, histone modifications, and ncRNA.[132–134] In addition, acetyl-CoA, a byproduct of fatty acid metabolism, acts as a cofactor for histone acetylation carried out by members of the histone acetyltransferase gene family.[135,136] High-fat diet-induced obesity in mice leads to distinct changes in promoter methylation, potentially linked to the downstream health consequences associated with obesity.[137] Similarly, research in nonhuman primates has highlighted a link between diet-induced obesity and epigenetic changes.[138] Such diets have long been linked to CVD, but the finding that they act via epigenetic mechanisms is intriguing and represents an area for future investigation. Several studies have found evidence of epigenetic changes that alter cardiometabolic disease risk,[139–141] including defects in endothelial cell function, abnormal blood flow, inflammation, and plaque formation.[142–147] Identification and characterization of common epigenetic outcomes linked to disease manifestations and their interaction with nutrient status may allow the development of specific treatment and intervention measures.[148–151]

Interestingly, the effect of limited or oversaturated nutrient bioavailability on epigenetic states is complex and not necessarily direct. For example, deficiency of methyl donors

results in hypermethylation at some loci and hypomethylation at others. Furthermore, the contribution of oversupplementation to epigenetic perturbation remains largely unexplained. To fully understand the mechanism(s) of nutrient involvement in epigenetic states, we must take into account the complexity of metabolic pathways that involve nutrients and their metabolites, which often act simultaneously in multiple divergent pathways. Different metabolic pathways playing roles in different cellular functions often use common genetic pathways (eg, metabolic enzymes). These effects highlight the importance of distinguishing the difference between epigenetic responses that result from defective gene expression regulation in the cell and lead to disease phenotypes and epigenetic changes that reflect an adaptive response to insult and are not directly causal. Controlled studies are thus required to elucidate the directionality of effects and to distinguish between causal and reactive changes. Finally, we must also consider the demonstrated role of other environmental influences in epigenetic perturbation and the potential for aggregate effects involving nutrition.[152] These include well-studied epigenetic effects caused by environmental toxicants and less elucidated environmental stimuli such as stress and general socioeconomic factors, which have been shown to influence the risk of CVD.[153] Future research will clarify the overlapping roles that nutrition and other environmental factors play in modulating CVD risk.

## Timing of Epigenetic Perturbation: Developmental, Postnatal, and Transgenerational Origins

Maternal nutritional status has important and direct effects on the offspring in utero. Paternal diet has also been shown to play an important role in epigenetic status of the offspring, although specific links to CVD risk have not yet been determined.[154] Furthermore, grandmaternal nutritional status may also affect subsequent generations of offspring through epigenetic modification of fetal germ cells.[155] Epigenetic programs are especially susceptible to change during fetal development because patterns of epigenetic states required for future development are established during early embryogenesis.[152] Although some epigenetic states change throughout fetal development and during postnatal development and aging, epigenetic states that are programmed during embryonic development set the stage for future epigenetic outcomes.[156,157] Maternal dietary deficiency altering epigenetic programming can result in severe fetal and infant outcomes such as neural tube defects caused by a folic acid deficiency.[158] However, maternal diet may also affect long-term risk of chronic disease development. Notable examples demonstrating maternal undernutrition and disease-relevant epigenetic changes in the resulting offspring include the Dutch Hunger Winter studies.[159] People conceived or born in the Netherlands during the World War II Dutch Hunger Winter (1944–1945) were at increased risk of diseases, including diabetes mellitus and CVD.[160] These diseases were linked to epigenetic changes, supporting the notion that diet-induced epigenetic defects occurring during fetal development or even before conception[161] can alter cardiometabolic disease risk and progression throughout life. Epigenetic perturbation occurring before or during gestation coincides with developmental origins of CVD.[162] Investigators cleverly took advantage of seasonal nutritional changes among pregnant women in The Gambia to demonstrate an association between naturally occurring maternal nutrient metabolite levels and DNA methylation patterns.[163]

Postnatal diet may compensate for some effects occurring in utero. For example, post-weaning supplementation with folate and selenium after a maternal high-fat diet leads to alterations in hepatic methylation.[164] These and other studies demonstrate that postnatal nutrition also plays a critical role in maintaining epigenetic programs and that perturbation of these systems after birth contributes to disease; postnatal supplementation may be used to alleviate these incurred effects.

Because of the development of both somatic and germline epigenetic programs during embryonic development, diet-induced epigenetic perturbations occurring in utero are also implicated in the transmission of disease to successive generations in a multigenerational or transgenerational manner.[165] Although multigenerational transmission of disease is not a novel concept, it has previously been studied mostly with respect to genetic changes in DNA sequence, leaving the role of epigenetic causes largely unexplored. Thus, this major breakthrough unveiled the involvement of nongenetic changes that by definition occur in the absence of changes in DNA sequence, are susceptible to environmental/exogenous perturbation, may increase in severity with age, may be transmitted to successive generations, and may play a significant role in disease. Animal models make up the majority of the body of work demonstrating these changes, but some human studies also support these findings.[124] Little is known about the potential for repeated insult and how that would affect heritable outcomes, and even less is understood about the contributions of effects that are transmitted paternally. It remains difficult to determine causality among nutrition, epigenetic changes, and disease in human studies, given the presence of multiple confounding factors. Thus, animal and cell-based models will play critical roles in identifying the causal mechanisms and characterizing the pathways involved.

## Epigenetic Biomarkers

Epigenetic biomarkers allow the determination of risk of CVD and the diagnostic and treatment purposes. However, accurately characterizing epigenetic biomarkers for any disease requires careful measurements and an acknowledgement of the limitations of their use. One major challenge in human studies is the limited sources of biological materials. Most in vivo human studies are limited to blood or plasma collection, the latter of which is lacking cells and thus is not an option for accurately measuring epigenetic states. Because epigenetic states vary between cell types, without cell sorting, mixed cell types present in the blood may create difficulties in accurately measuring epigenetic changes between individuals. To fill in the gaps in disease pathogenesis in humans, human cell lines or animal models are often substituted to identify tissue-relevant biomarkers of change. In addition, because epigenetic states often retain some level of plasticity within a lineage of cells, studies must measure states along a time course sufficient for determining whether a change is stable or transient, a distinction that is necessary for determining the therapeutic use of the biomarker. Furthermore, it is important to note the distinction between epigenetic biomarkers that are causal to the disease mechanism, epigenetic biomarkers that are byproducts of the disease state itself and thus not causal, and epigenetic biomarkers that are initially byproducts of the disease state but contribute to later stage effects as the disease progresses or even to other unrelated diseases/symptoms. Distinguishing these classes of biomarkers is critical to their accurate use in disease diagnoses and prevention or treatment

of CVD. Many of the epigenetic biomarkers currently identified are epigenetic changes in genes known to play a role in the initiation or progression of CVD, many of which were already identified as mRNA or protein biomarkers.[120,166,167] Alternatively, other biomarkers that are indicative of epigenetic changes may be used as a proxy for changed epigenetic states.[168]

### Therapeutics

Identification of epigenetic perturbations that contribute to CVD provides the potential for gene therapeutic approaches that take advantage of the potentially reversible nature of epigenetic mechanisms. Current studies are investigating the use of therapeutic agents that target histone deacetylases and ncRNA via chemical inhibitors and molecular interference.[169–171] However, given the wide-ranging effects of epigenetic modifications, the potential for off-target effects remains an important concern. Understanding the links between these epigenetic mechanisms and nutrition may allow more effective dietary interventions to address the development and progression of CVD. Although there is excitement about the potential for clinical applications of therapeutic epigenetic remodeling, much research remains to be done before this could realistically be implemented.[172]

## Metabolomics, Lipidomics, and Proteomics

### Metabolomics

Because metabolites and proteins are downstream of genetic variation and transcriptional changes, they are attractive “proximal” reporters of a given metabolic phenotype, particularly because they directly integrate the breakdown products of our dietary intake. Metabolomics offers significant potential to better understand how different dietary patterns or specific foods affect metabolic pathways.[173] Specifically, metabolomics provides important information on perturbations in metabolic pathways that affect disease onset and treatment. In addition, metabolomics may soon be used to identify biomarkers of dietary intake in a way that overcomes some of the shortcomings of diet assessment tools.[173] Although there is significant circadian and day-to-day variation in metabolite profiles, in a reproducibility study from a single blood collection, 90% of 257 metabolites were at least moderately reproducible 1 year later,[174] much better than for nutrients assessed from 2 single days of dietary assessment repeated 1 year apart.[22] Importantly, metabolomics can be used to identify patterns of metabolic profiles among individuals that reflect differences in dietary intake or individual metabolic activity that could explain variation in diet response. Aggregating individuals by differences in their metabolome provides a strategy for evaluating the effects of diet. Metabolites span a variety of compound classes, with significant differences in size and polarity across a wide range of concentrations. As a consequence, no single analytical method is able to accommodate the chemical diversity of the entire metabolome. Although various methodologies have been used, 2 core technologies have prevailed as the workhorses of metabolite profiling: nuclear magnetic resonance spectroscopy and mass spectrometry, the latter coupled to an array of separation techniques, including gas and liquid chromatography. However, with an estimated 5000 currently detectable human serum metabolites (a number likely to increase with advancement in technology), a comprehensive map of the entire metabolome remains an unattained goal.

However, by using a combined analytical approach, one can build a more inclusive picture of the metabolome by overcoming the limitations of individual techniques.

With improved throughput, an increasing number of studies have begun to apply these technologies to large population-based studies to identify novel predictors of cardiometabolic disease. For instance, studies in epidemiological cohorts have demonstrated that selected amino acids and amino acid derivatives are elevated more than a decade before the onset of type 2 diabetes mellitus.[175,176] Some of these metabolites such as 2-aminoadipic acid may directly modulate glucose homeostasis. Furthermore, the experimental demonstration that 2-aminoadipic acid is influenced by both diet and genetic background highlights the potential role for nutrigenomic interventions.[177] It is anticipated that as sufficiently large human data sets are acquired, investigators will begin to be able to parse the relative contributions of diet and genes in this pathway and others in disease development.

Given the possibility of nutritional manipulation of circulating metabolites, it is important to understand which ones have direct causal roles in disease protection or susceptibility rather than simply serving as markers. Mendelian randomization studies offer one approach to investigating causality. Given the independent assortment of alleles, individuals are randomized to carrying the major or minor allele at polymorphic sites. Metabolite concentrations can have a strong heritable component, and it has been shown that common genetic variants explain part of this heritability.[178] If a SNP is associated with levels of a metabolite, then examining the association of this SNP with a downstream clinical trait may be informative in terms of the causal role of the metabolite. For instance, it is known that elevated LDL cholesterol is associated with increased risk of MI. LDL is also a heritable trait with a number of rare and common genetic determinants. Variants that determine LDL would also be expected to relate to MI risk (which they do) if LDL is causal (which it is). Studies testing the causal links of novel metabolites with cardiometabolic diseases are underway but require very large sample sizes given the complex genetic determination of such traits.

## Lipidomics

Lipidomics, closely linked to metabolomics, uses mass spectrometry–based profiling to evaluate the comprehensive lipid profile in a sample[179,180] and is increasingly being applied to cardiometabolic disease studies.[181] Circulating lipids can have complex structures, with multiple different classes, and specific composition. For example, triacylglycerols are composed of a glycerol backbone attached to 3 acyl chains, all of which can vary in length and saturation, making measurement of specific species challenging.[182] Despite the importance of circulating lipids and lipoproteins in cardiometabolic disease, well-known lipid species such as LDL, high-density lipoprotein (HDL), and total cholesterol explain only a small portion of atherogenic risk. The relationship among intake of dietary fat, circulating lipids, and cardiometabolic outcomes is influenced not only by genetically determined host metabolism but also by metabolic action of intestinal microbiota and interaction with other dietary and metabolic components. We have a good understanding of the scientific evidence informing specific dietary guidelines on SFA, monounsaturated fatty

acid, and PUFA intake,[9,183] but questions remain about the functions and interactions of lipid subspecies and metabolites. Thus, whereas triacylglycerols with certain SFAs may be pathogenic in cardiometabolic disease, triacylglycerols with long-chain PUFAs are thought to be protective.[182] However, chain length and saturation may also affect the bioavailability of other nutrients, with SFAs generating smaller micelles with greater bioaccessibility.[184] Profiling the many structurally similar yet biologically distinct lipid subspecies is challenging but is becoming possible through improved lipidomics approaches.[185,186] These newly developed methods facilitate the application of functional lipidomics to fully profile and understand the specific role of each unique lipid subspecies.[187] Application of lipidomics to human plasma has direct utility, with potential to identify novel and predictive biomarkers of disease,[188–191] including coronary disease progression,[192,193] as well as biomarkers of responsiveness to therapeutic intervention.[194,195] As many specific lipid species are being generated in vivo from dietary precursors, lipidomics is a promising avenue for understanding the complex relationship between dietary lipids and cardiometabolic risk and identifying lipid biomarkers of dietary intake.

## Proteomics

Given the complexity of specific dimensional configuration and posttranslational modifications of proteins, accurately profiling the proteome is particularly challenging. Several methods exist for proteomic characterization, including gel based,[196] liquid chromatography–coupled mass spectrometry based,[197] and aptamer based,[198] with broad applicability to a wide variety of sample types, disease states, and desired biomarkers. However, the complexity of data obtained from proteomic studies makes translation of putative biomarkers into clinically useful prognostic tools difficult. As has been reviewed extensively elsewhere, proteomics has been successfully applied as a discovery tool to CVD in plasma, urine, and tissue[199–202] in the context of both animal models aimed at understanding cardiac function and development[203] and human biomarkers of atherosclerosis,[204] dyslipidemia,[205] and cardiometabolic disease.[206] Proteomics has also been applied in the context of nutritional studies to identify biomarkers of diet and nutritional status.[207–209] Although the proteome may be the most complex entity to assay accurately, the ultimate application is similar to other omics. As with metabolomics and lipidomics, increased application of proteomics methodologies will be required to fully understand the relationships between dietary and genetic factors in determining the unique cell, tissue, and circulating profile that results in health or disease. With some reduction in costs and increases in the resolution of instrumentation and methods allowing the increased use of proteomics, perhaps the greatest hurdle remaining will be the informatic integration and analysis of vast amounts of data into intelligible results.

## Limitations of Disease Biomarkers

The measurement of intermediate biomarkers, including metabolites, proteins, and lipids, is a powerful approach both to understand intermediate signaling processes and to estimate cardiovascular risk in the absence of clinical end points. However, the use of biomarkers as surrogates for clinical outcomes is not without limitations. Dissecting causal and bystander effects is particularly challenging, and current measurement approaches may be misleading. For example, HDL cholesterol, originally considered a causal marker of CVD, is now

understood to have a far more complex role in disease pathogenesis.[210] Thus, although HDL function may be a causal mediator of disease risk, measurement of HDL concentration may not be an ideal risk predictor, and interventions aimed specifically at reducing HDL cholesterol concentrations have proven ineffective at reducing cardiovascular risk. Large, long-term, randomized, controlled trials; mendelian randomization approaches; and greater inclusion of both biomarkers and clinical end points may be required to establish the utility of many putative disease biomarkers.

## The Microbiome

The microbiome, in particular the gut microbiome, has been identified as a potential risk factor for susceptibility to several chronic metabolic diseases, including diabetes mellitus,[211] obesity,[212] and CVD.[213,214] Initial studies have focused primarily on inflammation, and a developing body of literature indicates that microbial dysbiosis[215–217] in the digestive tract may also influence systemic inflammation by altering gut permeability and thus increasing circulating lipopolysaccharide,[218–220] a powerful trigger of the immune response. An alternative line of literature is developing that views the microbiome as a metabolically active, complex organ, producing many metabolites that can directly influence host phenotype.

### Inflammation and the Microbiome

Inflammation plays a unifying role in cardiometabolic disease,[221] with inflammatory elements being observed in atherosclerosis,[222] insulin resistance,[223,224] and obesity. Obesity, in turn, is characterized by chronic, low-grade systemic inflammation, with adipocytes serving as key mediators for metabolic and cardiovascular sequelae. In addition, there is growing recognition of the importance of the gut in immune system regulation, with subsequent metabolic effects. A large proportion of quantitative trait locus regions reported to regulate microbial abundance contain genes related to immunity and maintenance of barrier function.[225–227] The influence of immune-related genes is further evidenced by the dramatic effects on microbial community structure caused by mutations in single genes related to host immunity.[228,229] As an example, mice genetically deficient in the gut mucosal expression of innate immune system modulators (Toll-like receptor 5) developed insulin resistance even in the absence of increased obesity,[217] and high fecal calprotectin levels have been found to be indicative of an inflammatory colonic environment.[230] Several taxa such as members of the *Clostridiales* order are known to be decreased in intestinal inflammatory environments,[231] suggesting that differences in immune response and chronic inflammatory disease susceptibility may result from differences in microbiota composition.

### Host Genetics and Microbial Composition

Considering the interindividual variability at the level of the microbiome,[232,233] detailed studies integrating the intestinal microbiome with disease risk complement current GWAS approaches and other efforts seeking to understand heterogeneity in health and disease status. Importantly, understanding how microbial diversity and specific microbial species affect clinical phenotypes and risk of CVD will be beneficial as we begin to focus on personalized approaches to nutrition and medicine. As our interest in the role of the

microbiome role in chronic disease has expanded, so has interest in how host genetics influences microbial diversity. Several groups have reported that enteric microbial composition is a heritable trait,[234,235] although results from twin studies have shown discordant evidence of heritability.[236] However, studies using naturally occurring genetic variation among panels of inbred mouse strains and single gene mutations in genetically modified mice have consistently shown an effect of host genetics on intestinal microbial community structure[225,226,237–240] and may have increased power to detect genotype-driven microbial differences. This is especially relevant because murine studies allow tight control over environmental factors, including diet.[226] For example, numerous genetic studies in mice, including those with using genetic reference panels,[225,226,230,241] have demonstrated an effect of genetic background on microbial diversity. Interestingly, Benson and coworkers[226] demonstrated that multiple taxa can colocalize to a single genetic locus, suggesting that a single genetic locus may regulate the abundance of several taxa. Inbred strain surveys in mice also demonstrate a significant effect of host genetic makeup on microbial diversity,[241] and some of these differences have been linked to cardiometabolic phenotypes.[242]

However, the relative strength of environmental versus genetic signals on microbial regulation is unclear. Much of our knowledge of the environmental effects on the microbiome has been derived from studies in mice.[239] Several studies have shown how the maternal environment, litter effects, cage mates, the location that the mice are housed, and the commercial vendor can influence microbial populations.[226,230,241,243,244] Uterine implantation studies have also shown that mice of different genetic backgrounds have similar microbial composition when reared by the same foster mother, indicating that, in certain circumstances, environmental drivers can overpower genetic influences at least for nonadherent bacterial populations.[243] These studies are further supported by studies that have demonstrated that bacteria from diverse sources can colonize the gut of gnotobiotic mice and compete with “normal” microbiota.[245] Clearly, more work is needed to understand the interactions between host genetics and microbial diversity.

## Effect of Diet

The human microbiome uses both dietary and host-derived nutrients for survival. Thus, changes in diet have a profound impact on the microbiome,[239,246] including altering the overall bacterial composition. Host dietary factors can alter the intestinal environment, promoting a bloom or inhibition of certain taxa, as evident by the dynamic changes in both mouse and human microbial populations in response to dietary intervention.[239] Interestingly, alterations early in life may have long-lasting effects on multiple phenotypes,[247] but it is unclear how these effects influence the regulation of microbial diversity by GxE interactions[237] and subsequent risk of disease.[227,237]

Although the study of GxE interactions influencing the microbiome is relatively new,[248] studies using mouse genetic reference populations[237] or single gene knockout models[249] have demonstrated an interaction between microbiota and diet that is influenced by host genotype. These effects are less clear in humans, and a clinical study reported that, despite retained variation in taxonomy after dietary intervention, microbial gene expression, as

assessed by RNASeq, clustered by diet group and exhibited less between-subject variation than at baseline.[250]

Reports have highlighted interactions between the microbiome and metabolism of dietary components such as phosphatidylcholine and carnitine on modulating CVD risk[251–253] through the metabolite trimethylamine N-oxide (TMAO). Collectively, these studies demonstrated that increased plasma TMAO levels were positively associated with aortic lesion formation in mice and with increased risk of prevalent CVD and incident adverse cardiac events and mortality in humans in the setting of heart failure,[254,255] diabetes mellitus,[256] and chronic kidney disease.[257] TMAO is formed from trimethylamine via hepatic flavin mono-oxygenase 3.[258] Mechanistic studies in mice have identified that modulation of flavin mono-oxygenase 3 levels affect TMAO levels and glucose and lipid metabolism,[259,260] further complicating the identification of the precise mechanism by which TMAO affects CVD. The microbiome plays an obligate role in the formation of trimethylamine (from the trimethylamine-containing nutrients choline and carnitine), and antibiotic knockdown studies clearly show that TMAO is not formed in the absence of the microbiome.[253] Bacterial species harboring putative choline utilization gene clusters (*cut-c*) have been suggested to play a central role in enteric trimethylamine formation[261] (and therefore downstream TMAO production). The specific microbiota capable of generating trimethylamine have not been fully identified, but previous reports have indicated a relationship between plasma TMAO and members of the *Tenericutes phylum*,[242 253] whereas species within the *Desulfovibrio* genus have also been demonstrated to degrade choline to trimethylamine.[261]

Despite the compelling evidence of the microbiome as a critical mediator of CVD risk, we still do not understand the factors responsible. For example, a comparative GWAS approach to discover loci for plasma TMAO levels identified a locus for TMAO levels on mouse chromosome 3 harboring *Slc30a7*, a gene that encodes a zinc transporter.[262] In comparison, no significant loci were identified in a GWAS of ≈2000 subjects undergoing elective cardiac evaluation at the Cleveland Clinic.[262] Notably, similar results were also reported in the population-based Framingham Heart Study.[178] The relatively limited genetic signals observed for TMAO levels, at least in humans, thus far is consistent with the concept that interpersonal differences in diet and the repertoire of gut microbial species, more so than host genetic variants, likely serve as the primary determinants of plasma TMAO levels. Studies in mice have supported that both TMAO levels and atherosclerosis susceptibility are transmittable via the microbiome.[263] Future studies are critical to better understand the relationship among diet, genetics, the microbiome, and ultimately cardiovascular risk.

## Evoked Phenotypes

There are important physiological differences between individuals in the fasted state compared with a prandial or postprandial state or in response to pharmacological or pathogenic challenge. The functional changes that occur in response to a meal or other challenge may be more relevant to disease processes than resting metabolism,[264,265] highlighting the degree of metabolic and phenotypic flexibility of an individual.[266] Thus, although studying individuals in a rested fasting state has important utility in minimizing

noise and improving reproducibility, resting biomarkers may not accurately reflect the physiological milieu of the more relevant dynamic and potentially disease-promoting state. The use of evoked phenotypes as a research tool for understanding dynamic physiology has considerable utility in cardiometabolic disease and is particularly applicable to nutrigenomic studies.

Dietary intervention to evoke phenotypes acutely has long been used in nutrition research, principally in the form of carbohydrate challenge (oral glucose tolerance test, frequently sampled intravenous glucose tolerance test), or fat challenge (oral lipid tolerance test), sometimes in combination with longer-term dietary interventions such as modification of dietary fat intake[267,268] or sodium restriction.[269] The addition of genetic or genomic information such as SNP genotype[270–273] can further increase the utility of these evoked challenge studies by highlighting subgroups of individuals with differing responses. Relatively few studies to date have used other omics approaches in combination with evoked dietary challenge, although the efficacy of the approach has been demonstrated, with examples of transcriptomic,[5,274] metabolomic,[275,276] proteomic,[277] and lipidomic[278] studies highlighting the many powerful potential applications of these approaches.

The effects of longer-term dietary interventions or of habitual dietary patterns are often extremely difficult to detect, with only very subtle changes in resting biomarkers expected from a dietary intervention or supplementation. Thus, even for substances such as n-3 PUFA that are well studied with multiple lines of evidence supporting health effects, detecting biological changes after intervention is difficult. In such studies, additional pharmacological challenges may be required to evoke a measurable and disease-relevant phenotype. The use of evoked endotoxemia (low-dose lipopolysaccharide) as a model of cardiometabolic disease is well documented[279–282] and has shown great utility as a discovery tool both in omic[283,284] and nutritional contexts.[88,285,286] The combination of nutritional and omic profiling in the context of evoked endotoxemia has great promise for understanding nutritional effects on inflammatory responses. Other challenges have also been successfully used in an integrative omic context, for example, the use of vaccination as a model for activation of immune response by Franco et al,[287] which revealed novel genes acting in response to immune activation. Although this study did not include dietary analysis, the design has obvious utility for a nutrigenomic context. As an alternative to a direct pharmacological or acute dietary challenge, the use of repeated measures in longitudinal studies allows natural interventions to provoke phenotypes, including naturally occurring infection. This was highlighted in a single individual in a personalized omic profiling approach by Chen et al,[288] which established a proof of principle that would be extremely valuable to apply to larger numbers of individuals.

Although the use of human evoked phenotypes as models of cardiometabolic disease is still in its infancy, the potential benefits, particularly in the nutritional context, are considerable. Evoked phenotypes not only are more biologically relevant to disease processes but also reveal a greater dynamic range, allowing statistical power for discovery with smaller numbers of individuals. Controlling the provocation can reduce or eliminate the issues of confounding and reverse causation inherent to observational studies. Increased use of phenotype challenges in combination with nutrigenomic approaches is a powerful and

pragmatic approach that can yield disease-relevant data from smaller numbers of individuals. Given the historical difficulties in establishing dietary links with disease processes, in-depth phenotyping of dynamic nutrient-responsive physiology and integration with omics-scale data will likely yield significant advances in cardiometabolic disease research.

## Personalized Nutrition

The ability to use evidence-based personalized or precision medicine through dietary intervention is a worthy healthcare goal with significant potential. Some examples of routine genetics-based dietary modification with large effects exist, for example, in inborn errors of metabolism such as phenylketonuria,[289] mutations in human leukocyte antigen complex and other genes leading to celiac disease or gluten sensitivity,[290] or variants in the *LCT* gene affecting lactase persistence.[291] However, such clear examples do not yet exist for complex cardiometabolic disease. We caution that this area in particular is subject to popular claims that reach beyond the evidence base, with several companies offering direct-to-consumer genetic testing promising nutrigenetics-guided personalized dietary advice. The genetics-based ABO blood group diet[292] became highly popular after its publication in 1996 and claimed to cure or prevent many chronic diseases, but it was not based on scientific evidence.[293] Although the prescribed dietary patterns may be associated with health benefits, these occur independently of ABO blood group status.[294] Although the scientific evidence to make personalized dietary recommendations is not yet convincingly established, there is evidence that consumers are receptive to personalized dietary advice. In a randomized trial of genetic-based personalized nutrition advice, individuals receiving personalized advice were more likely to understand the advice given and to judge it as useful.[295] In this study, with the exception of sodium intake, participants were no more likely to adhere to the advice given compared with general dietary advice, but this was attributable to the fact that participants were already broadly adhering to dietary guidelines at baseline.[296] An intervention to improve diet quality based on personalized advice for genotype at *APOE* found that high-risk individuals who received personalized dietary advice were more likely to make short-term dietary improvements compared with low-risk or control subjects.[297] Although consumers are more engaged when receiving personalized dietary advice, the higher initial motivation may not lead to sustained long-term implementation of dietary changes. However, even if the hurdles of implementation and long-term patient motivation are overcome, the main obstacle to personalized nutrition lies in establishing sufficient scientific evidence to make informed and efficacious recommendations.

Pharmacogenomics trials are starting to study the impact and implementation of personalized drug treatment recommendations based on genotype at known functional variants.[298,299] This approach would also be beneficial to advance the field of nutrigenetics. As discussed earlier, there are published reports of genetic variants that interact with dietary composition to modulate biomarkers and health outcomes, including within the context of randomized trials.[57,300] However, most have not been validated through prospective, genotype-guided, randomized, controlled dietary intervention trials. Historical limitations in nutrition research limited the ability to develop clear evidence-based guidelines; personalized nutrition presents an opportunity to greatly improve on these recommendations

using current standards and technologies. Although some gene-nutrient interaction variants with large effects exist, many of the reported gene-nutrient interaction variants have relatively small individual effects. Genetic risk scores may represent an alternative to single-variant analysis. Such scores have been applied in a predictive capacity to assess disease risk[301–303] and could be useful within the context of a gene-nutrient risk score. In a study assessing the effect on weight loss of genotype-guided nutrigenetics intervention using genotype information from 7 published SNPs,[304] there was no difference in weight loss between the group assigned to personalized diet and the group assigned to a standard balanced diet, although adherence to diet correlated with weight loss in the nutrigenetics-diet group. Although personalized nutrition may prove to become an effective tool in disease prevention and management, current evidence does not yet demonstrate that personalized nutritional advice leads to improved health outcomes compared with following current dietary guidelines. However, the evidence that individuals are both receptive to personalized dietary advice and more motivated to implement personalized recommendations is very encouraging. Many of our existing nutritional guidelines were introduced before stringent standards for level of evidence; personalized nutrition research using optimal current methods allows considerable improvement and refinement of nutritional guidelines on both a personalized and a population level. Large, randomized, controlled trials guided by additional mechanistic research may allow personalized nutrition to become a realistic option for CVD management.

## Limitations and Future Directions

Nutrition is a crucial component in the prevention of cardiometabolic disease, but dietary studies are limited by difficulties in accurately assessing dietary intake in free-living subjects and heterogeneity in habitual diet. Furthermore, the richness of dietary options and vast numbers of possible interactions between dietary components make dissecting relative contributions of various nutrients extremely difficult. Omic profiling represents a feasible albeit challenging method to address these issues, with the potential to use biomarkers coupled with genomic knowledge to obtain accurate and comprehensive assessments of nutritional input. However, to relate nutrient intake to nutritional biomarkers, well-conducted studies are required that use currently available nutritional profiling methods coupled with comprehensive unbiased biomarker profiling to discover and validate markers of metabolically active dietary components. Currently, many human studies of biomarkers and disease do not collect dietary information, and many dietary studies do not have resources for omic profiling. Increased collaboration among researchers with nutritional and omics expertise during planning and development stages would allow the efficient collection of the additional data and samples required to provide maximum benefit and allow nutrigenomics to be applied in human disease studies. An increased awareness of nutrition among cardiometabolic disease researchers would be beneficial to the field. Moreover, the collection of dietary information and additional samples for nutritional profiling does not add substantially to the cost of a human trial. Similarly, increased awareness of important dietary distinctions would be beneficial in rodent models of cardiometabolic disease, in which researchers often disregard the complexity of diet, for example, attributing differences

in a Western diet and chow solely to the higher fat content despite many other differences in nutrient composition, including sucrose and micronutrients.[305]

Limitations in computational approaches remain a major bottleneck in nutrigenomics studies. As data collection becomes less arduous and less expensive, a limitation is the ability to analyze and make sense of the resulting data. Development of improved methods and standardized approaches for data reduction and integrative data analysis is crucial.

Although omics profiling methods will allow efficient discovery of new biomarkers, this approach is biased toward hypothesis generation. Even when biomarkers have direct clinical application, in most cases, focused functional and mechanistic interrogation will be required to fully understand the mechanisms of action. Thus, to avoid a glut of underinterpreted data, the research climate and standards in the field should encourage omics researchers to follow up findings with attempts at functional interrogation and translation.

Despite many challenges and limitations, the application of nutrigenomics approaches should be promoted and encouraged, given the potential for discovery and progress, with direct application to human health. Cooperation among researchers from many different disciplines combining diverse expertise will be required to move toward the common goal of an integrated omics approach to nutrition in cardiometabolic disease.

## Summary and Conclusions

Despite the known importance of genetics in cardiometabolic disease, environment plays a large role in determining to what extent a genetic predisposition to disease will manifest. Although multiple environmental exposures are known to modify risk, diet is one of the most important. Smoking, another key modifiable risk factor, has already demonstrated improvements, with a marked reduction in smoking rates in the United States since the 1960s that has been accompanied by a reduction in cardiovascular events.[306] However, as smoking rates have declined, diet-related obesity has increased. Diet is both essential and directly modifiable, meaning that improved knowledge of optimal nutrition has the potential to improve quality of life and to reduce global disease morbidity and mortality. The use of integrated omics approaches, together with nutritional information, will improve the ability to identify relationships between diet and health, including the interactions among diet, genetic background, and the microbiome that modify these relationships. This will allow the development of new therapeutic approaches, including targeted modification of dietary intake, pharmacotherapies, and new strategies in modulating the microbiome, aimed at the prevention and treatment of cardiometabolic disease.

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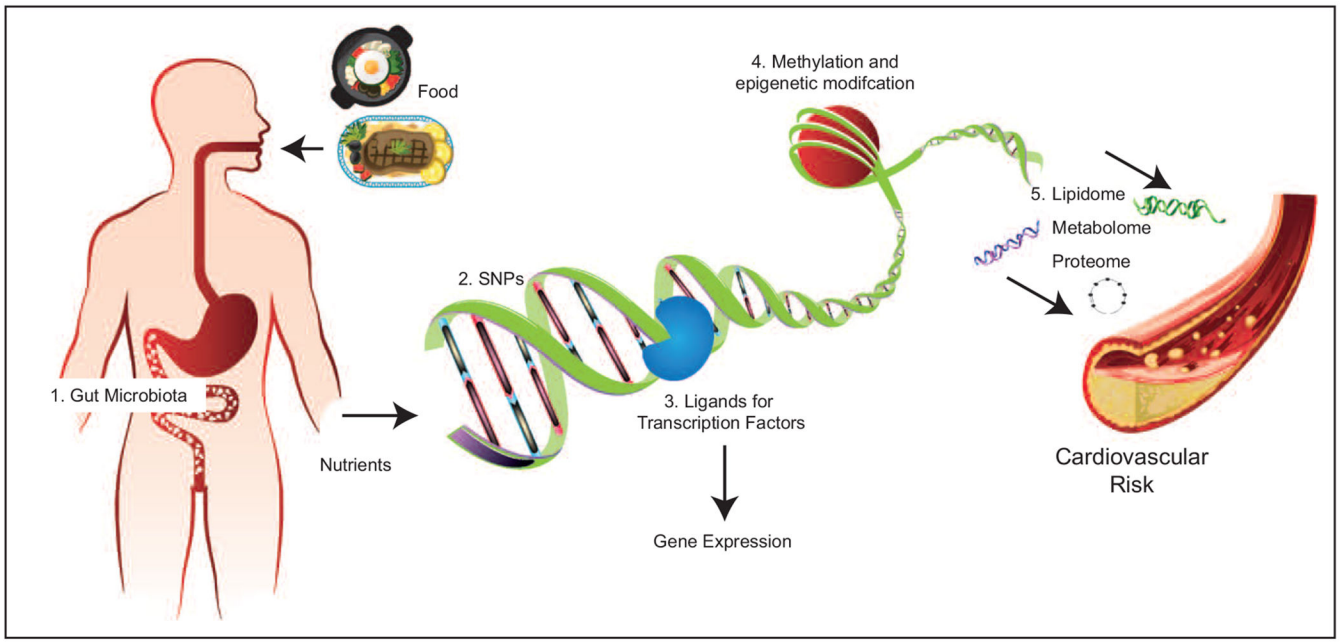


**Figure.**

Potential molecular mechanisms for nutrigenomic/nutrigenetic interactions in cardiovascular disease (CVD) risk. Specific food consumption alters CVD risk through multiple distinct and interrelated mechanisms: (1) differential intestinal metabolism and uptake of nutrients, depending on gut microbiome composition; (2) differential absorption and nutrient binding, depending on individual genotype; (3) modulation of gene expression through specific transcription factor binding; (4) specific effects on methylation and epigenetic modification; and (5) modulation of metabolic signaling through lipids, metabolites, and proteins. SNP indicates single-nucleotide polymorphism.