Nutrigenetic Associations With Cardiovascular Disease

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It is becoming increasingly evident that not all people respond equally to diet. Nutrigenetics and nutrigenomics is the study of how genes affect dietary response or how nutrients affect gene expression. Understanding gene–nutrient interactions has become essential in many areas of study to account for variation in results. Identifying subgroups or individuals who might benefit from more targeted recommendations has also been a result of studying these interactions. This review summarizes findings from genetic polymorphisms in apolipoprotein E, fatty acid desaturase, lipoxygenase-5, peroxisome proliferator-activated receptors, apolipoprotein A1, apolipoprotein A2, apolipoprotein A5, and methylenetetrahydrofolate reductase associated with cardiovascular disease.

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Cardiovascular disease • Genetics • Diet • Nutrigenetics

Death rates from cardiovascular disease (CVD) declined 27.8% from 1997 to 2007, but CVD was still responsible for 33.6% of all deaths in 2007.[1] The goal of the American Heart Association is to improve cardiovascular health and reduce CVD and stroke deaths by 20% by the year 2020. For this to occur, many segments of the population will need to focus on improving cardiovascular health behaviors, particularly those behaviors related to diet and weight status. Data from the National Health and Nutrition Examination Survey 1999-2006 show 100% of those with CVD met three or fewer of the five components of a healthy diet.[1] The five healthy diet components measured included (1) consuming at least 4.5 cups of fruits and/or vegetables per day, (2) eating fish (preferably oily) at least twice per week, (3) eating at least 3 servings of fiber-rich whole grains per day, (4) keeping sodium intake below 1500 mg/d, and (5) keeping sugar-sweetened beverage intake below 36 oz per week. It is also suggested that saturated fat intake be less than 7% of total energy intake, processed meats be eaten at most only twice per week, and at least four servings per week of nuts, legumes, and seeds be included.

Although diet has long been considered a main risk factor for CVD, conflicting ideas presented in the media regarding dietary approaches to ameliorating risk from CVD can be confusing to the general public. Understanding gene–environment interactions, particularly with regard to diet, through the fields of nutrigenetics and nutrigenomics, may help explain the variation in scientific results and reduce public skepticism.

Over the past decade, several studies have been conducted on genetic polymorphisms related to heart disease in an attempt to determine the interaction between diet and polymorphisms. Nutrigenetics is the study of how genes affect the response to diet, whereas nutrigenomics is how nutrients affect gene expression. This review summarizes findings from genetic markers related to CVD and associated gene–diet interactions. Although many genes have been studied in relation to CVD, this review focuses on polymorphisms of the following eight genes: apolipoprotein E (*APOE*), fatty acid desaturase (*FADS*), 5-lipoxygenase (*5-LO*), peroxisome proliferator-activated receptors (*PPARs*), apolipoprotein A1 (*APOA1*), apolipoprotein A2 (*APOA2*), apolipoprotein A5 (*APOA5*), and methylenetetrahydrofolate reductase (*MTHFR*). Variation within genes is most commonly due to single nucleotide polymorphisms (SNPs), wherein a single DNA building block, known as a nucleotide, is replaced by a different nucleotide. For example, if in a strand of DNA, the nucleotide base cytosine (C) replaces tyrosine (T), this is referred to as an SNP and is illustrated as T→C. The two other DNA nucleotide bases referenced herein are guanine (G) and adenine (A). Single nucleotide polymorphisms are common and normal, and usually do not affect health unless they are located within a gene or within a regulatory region near a gene. When this occurs, SNPs can play a more direct role related to disease and may help predict an individual's risk for developing particular diseases.

Nutrigenetics is the study of how genes affect the response to diet, whereas nutrigenomics is how nutrients affect gene expression.

Apolipoprotein E

The most widely studied genetic polymorphisms associated with CVD are linked to *APOE* genotypes. *APOE* has three alleles (E2, E3, E4); more than 60% of the population carries the most common E3 allele, the E4 isoform is the most atherogenic, and the E2 isoform is the least common, and is associated with the lowest low-density lipoprotein (LDL) cholesterol levels but elevated triglycerides (TGs).

APOE *and Cholesterol*

APOE genotypes in relation to LDL cholesterol levels have been well studied; on average, E4 carriers have 31% higher LDL cholesterol concentrations when compared with E2 carriers.[2] When National Cholesterol Education Program (NCEP) recommendations were tested in those with *APOE* genotypes, it was found that men with the E4 allele had a significantly greater reduction in LDL cholesterol levels ($P = .006$) when they followed the prescribed low-saturated fat, low-cholesterol diet than did those with the E3 allele.[3] These results indicate that men with the *APOE4* genotype respond more favorably to Step 1 NCEP diet guidelines than men with other APOE isoforms.

High-density lipoprotein (HDL) cholesterol levels have also been studied in relation to *APOE* genotype and diet. Mosher and colleagues[4] studied the HDL cholesterol response to carbohydrate intake with regard to *APOE* genotype and sex, and found that, independent of *APOE* genotype, men had similar HDL cholesterol decreases with increased carbohydrate intake. In women, however, only participants with the E4 allele had HDL cholesterol reductions under similar conditions. The association between carbohydrate consumption and HDL cholesterol in women with the E4 isoform was highly significant ($P = .0003$), whereas no association existed with other isoforms. These results provide one possible mechanism to explain the sex differences often noted in HDL cholesterol levels. This study was cross-sectional and a subset of the Strong Heart Family Study.

SNPs are the most common type of genetic variation studied. A randomized crossover study by Moreno and colleagues[5] examined the *APOE* gene promoter G→T SNP and the impact of dietary fat on LDL oxidation and lipid response. This SNP has been associated with premature coronary artery disease and increased myocardial infarction (MI) risk. Three diets including a saturated fat-enriched diet (SFA), a carbohydrate-rich diet (CHO), and a monounsaturated fat-rich diet (MUFA)

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were administered to participants for 4 weeks. After consuming an SFA-rich diet, those with the T allele demonstrated higher LDL cholesterol plasma concentrations compared with GG individuals ($P < .05$). Carriers of the T allele also had a significantly greater decrease in LDL cholesterol when switching from the SFA diet to the CHO diet ($P < .05$). This study provides insight into the variability of responses to diet via genetics.

Plasma APOE, Blood Pressure, and Triglycerides

The amount of APOE circulating in plasma may also be an independent risk factor for CVD. APOE plays an important structural role in lipid metabolism as part of several lipoproteins. It promotes uptake of triacylglycerol-rich lipoproteins from circulation and is involved in reverse cholesterol transport. Participants with the *APOE4* genotype had the lowest concentration of plasma APOE in a study by Moreno and associates.[6] After administering an SFA-rich diet, CHO-rich diet, and MUFA-rich diet for 4 weeks, women with the *APOE3/2* and *APOE3/3* types showed a significant decrease in APOE concentrations when shifting from the SFA diet to the CHO or MUFA diets, whereas no differences were observed in those with the *APOE4/3* genotype. Circulating APOE concentrations seem to be determined by sex and *APOE* genotype, and this effect is modulated by amount and type of fat consumed.

Blood pressure and TG levels, other measures of cardiovascular health, also appear to have nutrigenetic influences. In the Quebec Family Study, Robitaille and associates[7] found individuals with the *APOE4* genotype had significantly higher systolic ($P = .001$) and diastolic ($P = .01$) blood pressure with increased fat intake, whereas only a small change in blood pressure was noted in the other *APOE* genotype carriers in response to dietary fat. This study examined 45 different genes associated with cardiovascular risk factors, as well as 10 different metabolic pathways related to CVD. It has also been shown that men with the *APOE4* genotype respond with significantly greater reductions in TG with 0.7 g/d or 1.8 g/d of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) fish oil supplementation.[8]

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Although the E4 allele may be the most atherogenic, individuals with the *APOE4* genotype may be more responsive to dietary therapy (Table 1).

Fatty Acid Desaturase

FADS1 and *FADS2* genes on chromosome 11q are responsible for encoding rate-limiting enzymes involved with polyunsaturated fatty acid (n-3 PUFA and n-6 PUFA) biosynthesis, and converting linoleic acid (LA) into arachidonic acid (AA), and α-linolenic acid (ALA) into EPA (Figure 1). The section of chromosome 11 containing the *FADS* genes is known as the *FADS* gene cluster region and SNPs in this region have been studied in association with cholesterol levels and inflammation. Variants of the *FADS* genotype have been shown to affect the AA to LA ratio, with a higher ratio being a risk factor for coronary artery disease due to the proinflammatory potential of AA.

FADS, Cholesterol, and PUFAs

Variation in the *FADS1* gene may interact with dietary PUFAs to affect plasma cholesterol levels. Lu and colleagues[9] measured dietary PUFA intakes, cholesterol concentrations, and three SNPs in the *FADS* cluster in 3575 participants in the Doetinchem Cohort. Those with high n-3 PUFA intakes (> 0.51% of diet) had significantly higher HDL concentrations than those with low n-3 intakes ($P = .02$). When considering genotype, those with the *rs174546* genotype and C allele had higher total cholesterol with a high n-3 PUFA intake ($P = .006$) and higher HDL cholesterol with high n-6 PUFA intake ($P = .004$). There were no associations with low PUFA intakes. In response to these results, Dumont and coworkers[10] studied the polymorphism with regard to cholesterol and PUFA intake in adolescents. Dietary LA and ALA amounts were measured and used to stratify the sample into high or low LA or ALA intake groups. Similar to the study by Lu and colleagues,[9] and considering the T allele in isolation, only a diet high in ALA (n-3 PUFAs) caused lower total cholesterol ($P = .01$) and non-HDL cholesterol ($P = .02$) concentrations in participants with the *FADS1 rs174546* T allele, whereas no association existed with a low-ALA diet. This provides more evidence for a diet–gene interaction at *FADS1* that could affect CVD risk factors even in participants of a younger age.

5-Lipoxygenase

The 5-LO pathway has also received attention recently for its possible role in CVD. 5-LO is the enzyme responsible for producing

TABLE 1

Gene-diet Interactions Related to CVD Risk Factors

CVD Risk Factor	Gene	Dietary Factor	Results
Inflammation	*PPARA L162V*	6-week fish oil supplementation	162L allele resulted in reductions in CRP levels with supplementation while 162V allele had increased CRP[19]
TG	*PPARA L162V*	High-PUFA (> 8%) or low-PUFA (< 4%) diet	Carriers of 162V had 28% higher TG than 162L carriers with a low-PUFA diet, but had 4% lower TG with a high-PUFA diet[18]
	APOA5 1131T→C	High-PUFA (> 6%) diet	C allele resulted in higher TG only with a high n-6 PUFA diet[26]
	APOE4	0.7 g/d and 1.8 g/d EPA + DHA	Men with APOE4 had significantly higher TG reductions in response to fish oil supplementation compared with other allele carriers[8]
LDL-C	*APOE4*	Low-saturated fat, low-cholesterol diet	Men with *APOE4* allele had a significantly greater reduction in LDL-C levels than those with the *APOE3* allele[3]
	APOE gene promoter G→T SNP	SFA-, CHO-, and MUFA-rich diets	T allele resulted in higher LDL levels following an SFA-rich diet and higher LDL decreases when switching to a CHO-rich diet[5]
	FADS	n-3 PUFA	T allele carriers experienced LDL-C reductions with high n-3 PUFA intake[10]
	PPARA	n-3, n-6 PUFAs	In white subjects G→A SNP associated with lower total and LDL-C with high n-6 intake; in blacks C→T SNP associated with lower total and LDL-C with high n-3 intake[13]
	PPARA 162V	High fat intake (60% fat, 15% PRO, 25% CHO)	162V allele associated with higher fasting LDL-C levels with a high dietary fat intake[16]
HDL-C	*APOE4*	carbohydrates	Only women with the *APOE4* allele had HDL-C reductions in response to increased CHO intake[4]
	FADS	n-6 PUFA	C allele carriers had increased HDL-C with high n-6 intake[9]
	APOA1 G→A SNP	PUFAs	Women with A allele had higher HDL-C with high PUFA intake; HDL-C decreased as PUFA intakes increased with G/G carriers[20]
Blood pressure	*APOE4*	Dietary fat	Only the *APOE4* genotype resulted in significant increases in systolic and diastolic blood pressure as fat intake increased; *APOE2* and *APOE3* carriers only had minor changes[7]
Intima media thickness	*5-LO*	Marine n-3 fatty acids (EPA, DHA)	Carriers homozygous for the variant allele had reductions in intima media thickness with increases in dietary marine n-3 fatty acids[11]
MI risk	*5-LO*	Dietary AA	Less common 3 and 4 alleles resulted in increased MI risk when dietary AA intake was high[12]
Obesity	*APOA2* 265T→C	High-SFA diet	CC genotype associated with increased obesity only in presence of high-SFA diet[22,23]
	APOA5 1131T→C	High-fat diet	TT genotype associated with increased obesity only with high-fat diet; higher-fat diet not associated with obesity in C allele carriers[24,25]

AA, arachidonic acid; CHO, carbohydrate; CRP, C-reactive protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; MUFA, monounsaturated fatty acid; PRO, protein; PUFA, polyunsaturated fatty acid; SFA, saturated fat-enriched; SNP, single nucleotide polymorphism; TG, triglycerides;

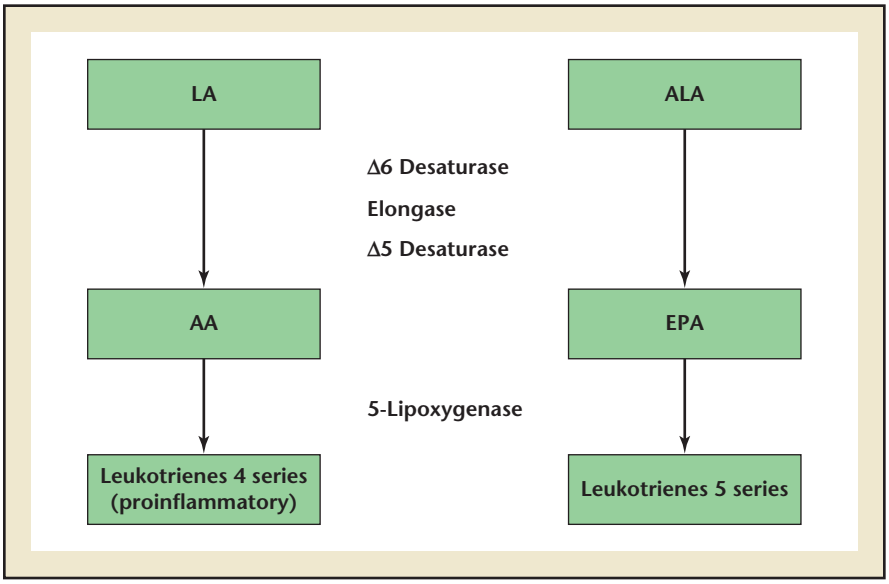

Figure 1. *FADS1* and *FADS2* encode the rate-limiting enzymes Δ6 and Δ5 desaturases in the biosynthesis of long-chain fatty acids AA and EPA from dietary precursors LA and ALA. 5-Lipoxygenase is the enzyme required to convert AA and EPA into leukotrienes. The 4 series produced from AA are proinflammatory whereas the 5 series from EPA have the opposite effect. AA, arachidonic acid; ALA, α-linolenic acid; EPA, eicosapentaenoic acid; LA, linoleic acid.

proinflammatory leukotrienes from the essential AA (Figure 1). Leukotrienes have been implicated in disease states ranging from asthma to atherosclerosis in which inflammation plays a key role.

5-Lipoxygenase and n-3 and n-6 PUFA Intake

Gene–diet interactions associated with 5-LO indicate n-6 fatty acids may promote—whereas n-3 fatty acids may inhibit—inflammation, leading to atherosclerosis in a subpopulation carrying the variant *5-LO* alleles. Dwyer and colleagues[11] measured intima-media thickness in generally healthy men and women across different *5-LO* polymorphisms and found an increase in the mean thickness ($P < .001$) in carriers of two variant alleles compared with those with the common allele. C-reactive protein (CRP) levels were also twice as high in carriers of the two variant alleles. Dietary intakes of fatty acids (AA, LA, EPA and DHA, MUFA, and SFA) were then measured through six 24-hour recalls, a retrospective dietary assessment method commonly used to ascertain intake among populations. Higher amounts of dietary AA ($P < .001$) and LA ($P = .03$) significantly increased the atherogenic effect of the variant genotype. However, an increased intake of marine n-3 fatty acids lessened this effect; an inverse relationship was seen with intima media thickness ($P = .007$) among carriers of the two variant alleles. The marine n-3 fatty acids, DHA and EPA, are substrates also acted upon by 5-LO, but they produce noninflammatory leukotrienes. The significant findings of research involving these competing substrates support the role of leukotrienes in atherogenesis and identify a subgroup that may benefit from marine n-3 fatty acids.

Allayee and associates[12] tested these observations using MI as a more clinically measurable phenotype in 1885 case-control pairs. Risk for MI was higher in the less common *5-LO* alleles (3 and 4) compared with the more common 5 allele when dietary AA intake was high (> 0.25 g/d), and these alleles were associated with a lower MI risk when dietary AA intake was low (< 0.25 g/d; $P = .015$). These genetic variants result in higher 5-LO expression and in the presence of a diet high in AA may increase the risk for CVD or MI.

Peroxisome Proliferator-activated Receptors

PPARs play an important role in fatty acid oxidation and lipid metabolism by binding to lipids and their metabolites and regulating gene expression associated with lipid metabolism and transport. Binding of PUFAs with PPARs can cause changes in gene expression involved with lipid metabolism. Because genetic variations in PPARs can affect CVD risk and PUFAs are ligands of PPARs, it is an area of study for gene–diet interactions. PPAR-α (PPARA) is more often studied in relation to CVD risk factors such as cholesterol, TG, and inflammation, whereas the PPAR-γ (PPARG) variant Pro12Ala is associated with obesity and insulin resistance.

PPARs, Dietary Fatty Acids, and Cholesterol

A large-scale study (10,134 white subjects and 3480 black subjects) using participants from the Atherosclerosis Risk in Communities (ARIC) study considered different *PPARA* genotypes in relation to n-3 and n-6 fatty acid intake and lipid measures.[13] Although no significant associations were found between genotype and lipid measures alone, significant results arose when diet was included. Results indicated a homozygous variant genotype was associated with lower total and LDL cholesterol ($P < .05$) with higher intake of n-6 fatty acids (> 7.99 g/d) in white subjects and

with increased intake of n-3 fatty acids (> 0.32 g/d) among blacks ($P < .05$). Serum HDL concentrations may also be affected by *PPARA* polymorphisms in response to diets high in PUFA, as demonstrated by Chan and associates,[14] who found an association among carriers of the V227A SNP between PUFA intake and HDL levels ($P < .05$). These studies further link *PPARA* with the lipid reductions associated with high PUFA diets and indicate genetic variants in the *PPARA* region may affect lipid response to PUFA intake.

Lipid response related to the *PPARA* L162V polymorphism, as studied by Paradis and coworkers,[15] showed an association with the polyunsaturated to saturated diet ratio (P:S). The L162V SNP was not associated with plasma lipid concentrations until after participants switched from a low P:S diet ratio (P:S = 0.3) to a high P:S diet (P:S = 1.0). The high P:S diet resulted in significant gene diet interactions causing changes in total cholesterol and cholesterol concentrations in small LDL particles ($P < .05$). The minor 162V allele has also been shown to be associated with higher fasting total and LDL cholesterol levels following a high-fat diet (60% fat, 15% protein, 25% carbohydrate).[16] This *PPARA* L162V polymorphism may also contribute to the varying responses seen with n-3 fatty acid supplementation. Rudkowska and colleagues[17] observed a lower gene expression of *PPARA* in carriers of the 162V allele after adding DHA and EPA to macrophages from 12 participating men. This would lead to less favorable lipid improvements in response to n-3 fatty acids for those with the 162V polymorphism.

PPARA *and Other CVD Risk Factors*

Other CVD risk factors such as TG and plasma CRP levels have also been linked to the *PPARA* L162V genotype. Results from participants in the Framingham Heart Study indicate low PUFA intakes (< 4%) caused 28% higher plasma TG levels with the 162V compared with 162L carriers, whereas high PUFA intakes (> 8%) resulted in 4% lower plasma TG in the 162V genotype than the 162L homozygotes ($P < .01$).[18] In another study where subjects followed a low-fat diet for 8 weeks followed by 6 weeks of fish oil supplementation (5 g/d), a significant ($P < .01$) gene–diet interaction was found with the L162V SNP and CRP levels in response to the n-3 PUFAs.[19] Carriers of the 162L allele experienced CRP reductions in response to supplementation, whereas those with the 162V allele had increased levels of CRP. The interaction remained after adjustments for APOE. There was also a reduction of TG with supplementation ($P = .03$) across both genotypes.

Serum HDL concentrations may also be affected by PPARA polymorphisms in response to diets high in PUFA…

APOA1, APOA2, and APOA5

APOA1 is the main protein component (70%) of HDL particles and is essential in reverse cholesterol transport from tissues to the liver. APOA2 is the second most abundant protein in HDL. APOA5 is located in the liver on TG-rich particles, and overexpression of the *APOA5* gene is related to TG reductions.

APOA1

PUFA intake may also modulate *APOA1* gene expression. The common G→A SNP in the promoter region of *APOA1* was studied by Ordovas and associates[20] in relation to dietary fat modulation of HDL cholesterol in 1610 men and women from the Framingham Offspring Study. In women only, the A allele was significantly associated with higher HDL cholesterol levels in response to high (> 8%) PUFA intakes ($P < .05$). When PUFA intakes were low (< 4%), women with the G/G allele had significantly higher HDL cholesterol concentrations than A allele carriers ($P < .05$). In G/G carriers, HDL cholesterol decreased as PUFA intakes increased. In this instance, opposing dietary advice depending on genotype could be more beneficial for women trying to raise HDL levels. More recently, this G→A SNP has also been shown to affect LDL particle size. Participants consumed three diets (high SFA, high CHO, and low-fat, high MUFA) for 4 weeks using a randomized crossover design.[21] Carriers of the GG genotype for *APOA1* showed decreased LDL particle size after consuming a high-CHO diet when compared with the results of high-fat diets ($P < .05$). Carriers of the A allele had decreased LDL size and increased oxidation susceptibility following consumption of a high-SFA diet. Based on these studies, dietary advice for carriers of the G allele would significantly differ from advice given to A allele carriers with regard to achieving higher HDL levels or decreased LDL particle size.

APOA2

The *APOA2* gene has been studied in relation to body mass index (BMI). Corella and colleagues[22] analyzed gene–diet interactions with the 265T→C *APOA2* polymorphism and SFA intake on BMI

in a population of 3462 Americans from the Framingham, Genetics of Lipid Lowering Drugs and Diet Network Study (GOLDS), and Boston-Puerto Rican studies. A significant ($P < .05$) average increase in BMI of 6.2% was noted between the CC and TT+TC genotypes with a high (> 22 g/d) SFA intake, but not with low SFA intake. This was replicated across each population studied. The CC genotype was significantly associated with increased obesity in all populations only in the presence of a high-SFA diet (meta-analysis $P < .0001$) and occurs on average in approximately 10% to 15% of people. This association was substantiated through a cross-sectional study in Mediterranean and Asian populations,[23] with the CC genotype associated with a 6.8% greater BMI ($P = .018$) and more prevalent obesity (BMI > 30; $P = .036$) only with a high SFA intake. In these studies, diet was able to modulate the effects of the 265T→C *APOA2* polymorphism on body weight.

APOA5

Similar to *APOA2*, variations of the *APOA5* gene have been studied in regard to BMI and obesity risks. The 1131T→C SNP showed significant interactions with fat intake and BMI.[24] As total fat consumption increased, BMI also increased only in carriers homozygous for the major T allele, whereas this increase was not detected in carriers of the minor C allele. Again, the *APOA5* C allele carriers were at lower risk for obesity ($P = .032$) and being overweight ($P = .031$) compared with the TT genotype carriers who had a high fat intake (≥ 30% of energy). There was no association when fat intake was low. Approximately 13% of the population studied had the 1131T→C SNP, and the modulation effect of fat intake on body weight was present in both men and women. This effect was replicated in a Spanish population of overweight or obese participants in which the TT genotype was associated with increased obesity as fat intake increased, and higher fat intakes were not associated with obesity in the C allele carriers.[25] Because *APOA5* is also a regulator of plasma TG concentrations, this population was studied for gene–diet interactions affecting TG levels. The minor C allele was associated with higher TG levels. When diet was considered, fat intake was inversely correlated to TG concentrations in carriers of the C allele ($P < .001$), whereas no association existed with the major allele carriers. Due to cultural norms of high olive oil intake, over 50% of the fat energy consumed was from MUFAs. Although in the above studies, the C allele appears almost protective in the face of a high-fat diet, studies show the 1131T→C *APOA5* SNP to be associated with higher TG, higher LDL cholesterol, lower HDL cholesterol, and smaller LDL particles, leading to higher risk of CVD. Because of the more atherogenic lipid profile associated with the *APOA5* C allele carriers, this SNP has also been studied in relation to PUFA intake. Lai and coworkers[26] found the C allele to be associated with higher TG only in participants consuming a high (> 6%) PUFA diet ($P = .002$), showing a dose response effect. The interactions were specific for n-6 fatty acids (and not n-3). When PUFA intake was low, carriers of the C allele and TT homozygotes had similar TG concentrations. Results differed from the study by Sánchez-Moreno and associates,[25] and it should be noted that the majority of the fat consumed in that study came from MUFAs, whereas the present study only measured PUFA intake, not total fat.

Methylenetetrahydrofolate Reductase

MTHFR is an enzyme encoded by the *MTHFR* gene necessary for homocysteine to be converted to methionine. Folate, vitamin B_6, and vitamin B_{12} are also required for proper homocysteine metabolism. Although hyperhomocysteinemia is an independent risk factor for heart disease, lowering homocysteine levels does not necessarily reduce CVD risk. *MTHFR* genetic polymorphisms have been implicated in conditions such as homocystinuria, anencephaly, and spina bifida, and identified as possible risk factors for heart disease, hypertension, stroke, and glaucoma.

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MTHFR *and LDL Oxidation*

Although *MTHFR* polymorphisms are often studied in relation to homocysteine levels, they have also been associated with increased oxidation of LDL. The diet–gene interaction of a Mediterranean diet and the *MTHFR* C677T mutation was studied in 574 men and women from Greece. Adherence to the Mediterranean diet (primarily a diet rich in plant foods, whole grains, and fats from nuts, olives, and olive oil) was inversely associated with LDL oxidation levels ($P < .001$).[27] When adding genotype to the analysis, it was discovered that diet adherence was only associated with lower LDL oxidation in variant alleles, but not in

individuals with the homozygous CC genotype.

MTHFR *and Homocysteine*

Another study on these same individuals from the ATTICA study measured homocysteine concentrations related to Mediterranean diet adherence and the *MTHFR* C677T mutation.[28] Individuals were generally healthy (no CVD or other chronic illness) with genotypes 41% homozygous normal (CC), 48% heterozygous (CT), and 11% homozygous mutant (TT). Homocysteine levels were higher in those with the TT genotype ($P < .001$), and those with the CT and TT genotypes had significant homocysteine reductions with adherence to a Mediterranean diet ($P = .002$) compared with those with the CC genotype. In a large-scale prospective study (24,968 participants), healthy white American women were followed for 10 years; although the TT genotype resulted in higher homocysteine levels, neither the *MTHFR* 677C→T mutation or the intake of folate or B vitamins modulated CVD incidence.[29] Higher intakes of folate and B vitamins did reduce homocysteine levels in this study, but did not significantly affect incident CVD. An association existed between homocysteine levels and CVD at baseline, but as adjustments for CVD risk and socioeconomic status were incorporated, the association was weakened and became nonsignificant. A recent meta-analysis on the *MTHFR* C677T polymorphism, folate status, and stroke risk indicated that populations with lower folate intakes experienced larger effects on homocysteine in response to the C→T SNP than in those regions employing folate fortification.[30] The odds ratio for stroke was higher in the low folate population. Future studies on the *MTHFR* C677T mutation and homocysteine effects on CVD or stroke need to be conducted in low folate regions.

Conclusions

Replication of studies is necessary before recommendations can be made. Variation in results between studies often occurs, which can confuse the public and affect their willingness to follow dietary guidelines. This review evidences how gene–diet interactions significantly impact CVD risk and accounts for some of the variation between studies. Understanding how genetic polymorphisms and diet interact to affect CVD risk will aid in providing more targeted prevention and treatment modalities. Studying combinations of SNPs from different genes and their specific interactions with diet may be useful in providing more individual recommendations and care to persons with identified CVD phentoypes.

Genotypes conferring greater CVD risk appear to respond more favorably to healthy dietary habits, diminishing the difference and risk between the common and variant types (eg, *APOE4*, *5-LO*, *PPARA* with triglyceride, *APOA2*, *MTHFR*). Persons with these genotypes may benefit from individualized nutritional recommendations. In other instances, such as with *APOA1* G→A SNP, diet can have opposing effects on the common and variant alleles, which delineate subgroups

MAIN POINTS

- The most widely studied genetic polymorphisms associated with cardiovascular disease (CVD) are linked to *APOE* genotypes. *APOE* has three alleles (E2, E3, E4); more than 60% of the population carries the most common E3 allele, the E4 isoform is the most atherogenic, and the E2 isoform is the least common, and is associated with the lowest low-density lipoprotein cholesterol levels but elevated triglycerides. The amount of *APOE* circulating in plasma may also be an independent risk factor for CVD.
- Variation in the *FADS1* gene may interact with dietary polyunsaturated fatty acids (PUFAs) to affect plasma cholesterol levels.
- A large-scale study considered different *PPARA* genotypes in relation to n-3 and n-6 fatty acid intake and lipid measures; although no significant associations were found between genotype and lipid measures alone, significant results arose when diet was included. Serum high-density lipoprotein concentrations may also be affected by *PPARA* polymorphisms in response to diets high in PUFAs.
- Understanding how genetic polymorphisms and diet interact to affect CVD risk will aid in providing more targeted prevention and treatment modalities. Genotypes conferring greater CVD risk appear to respond more favorably to healthy dietary habits, diminishing the difference and risk between the common and variant types. Persons with these genotypes may benefit from individualized nutritional recommendations.

that respond less favorably to typical dietary advice. Arkadianos and colleagues[31] showed that using genetic information to personalize a calorie-controlled diet resulted in better compliance and longer-term BMI reduction. The area of nutrigenetics and nutrigenomics is still in its infancy, but with continued methodologically rigorous study, investigations could provide recommendations regarding early prevention and control of CVD through diet. ■

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