

SYNTHESIS ARTICLE



APOE4 AND CARDIOVASCULAR DISEASE: INTERPLAY OF DIETARY FATS IN MODULATING LDL LEVELS

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ABSTRACT

Introduction

Apolipoprotein E (APOE) gene significantly affects lipid metabolism and CVD susceptibility, with its isoforms exerting different effects on cholesterol levels and cardiovascular health. Of particular concern is the APOE4 allele, which is linked to dyslipidemia, elevated LDL-C levels, and increased oxidative stress, thereby heightening the risk for coronary artery disease (CAD) and stroke. This review explores the complex relationship between APOE genotypes, lipid metabolism, and CVD risk, with a specific focus on the APOE4 allele.

Materials and methods

This review followed a systematic literature review (SLR) methodology in accordance with PRISMA guidelines. Implementing a pre-defined eligibility and screening criteria, 48 studies were included in the review.

Results

It highlights the influence of dietary fat intake on lipid profiles and the potential for targeted nutritional interventions in individuals carrying the APOE4 allele to mitigate genetic risk. Despite evidence linking APOE4 to impaired lipid clearance and cardiovascular pathology, research examining the interplay of genetics, nutrition, and metabolism in CVD remains limited.

Conclusions

This paper emphasizes the importance of personalized dietary strategies tailored to an individual's APOE genotype to improve lipid metabolism, reduce CVD risk, and enhance overall cardiovascular health. By better understanding the genetic-nutritional relationship, clinicians and researchers can design more effective preventive and therapeutic strategies for individuals at higher genetic risk for CVD.

Keywords

Cardiovascular Disease (CVD), Apolipoprotein E (APOE), LDL Cholesterol, Lipid Metabolism, APOE4 Genotype, Dietary Intervention.

APOE4 ȘI BOLILE CARDIOVASCULARE: INTERACȚIUNEA GRĂSIMILOR ALIMENTARE ÎN MODULAREA NIVELURILOR DE LDL

Introducere

Gena apolipoproteinei E (APOE) influențează semnificativ metabolismul lipidic și susceptibilitatea la bolile cardiovasculare (BCV), iar izoformele sale exercită efecte diferite asupra nivelurilor de colesterol și asupra sănătății cardiovasculare. Un interes deosebit îl prezintă alela APOE4, asociată cu dislipidemia, creșterea nivelurilor de colesterol al lipoproteinelor cu densitate joasă (LDL-C) și intensificarea stresului oxidativ – factori care determină un risc crescut de boală coronariană (BC) și de accident vascular cerebral (AVC). Această revizuire analizează relația complexă dintre genotipurile APOE, metabolismul lipidic și riscul de BCV, cu accent deosebit asupra alelei APOE4.

Materiale și metode

Lucrarea reprezintă o revizuire sistematică a literaturii (Systematic Literature Review – SLR), în conformitate cu recomandările PRISMA. Prin aplicarea unor criterii predefinite de eligibilitate și selecție, au fost incluse pentru analiză 48 de studii.

Rezultate

Studiul relevă influența consumului de grăsimi alimentare asupra profilului lipidic și potențialul intervențiilor nutriționale ținute la purtătorii alelei APOE4 pentru atenuarea efectelor riscului genetic. Deși există dovezi care asociază APOE4 cu afectarea clearance-ului lipidic și dezvoltarea patologiei cardiovasculare, cercetările privind interacțiunea dintre factorii genetici, nutriție și metabolism în apariția bolilor cardiovasculare rămân incomplete.

Concluzii

Lucrarea subliniază importanța strategiilor alimentare personalizate, adaptate genotipului APOE individual, pentru optimizarea metabolismului lipidic, reducerea riscului de boli cardiovasculare și îmbunătățirea sănătății cardiovasculare generale. O mai bună înțelegere a relației dintre factorii genetici și nutriționali ar putea facilita dezvoltarea de către clinicieni și cercetători a strategiilor preventive și terapeutice mai eficiente pentru persoanele cu predispoziție genetică la bolile cardiovasculare.

Cuvinte-cheie

Boli cardiovasculare (BCV), apolipoproteina E (APOE), colesterol LDL, metabolism lipidic, genotip APOE4, intervenție nutrițională.

INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading cause of death worldwide, accounting for an estimated 19.8 million fatalities globally (representing approximately 32% of all global deaths), with heart attacks and strokes responsible for 85% of these deaths (1). Over three-quarters of CVD-related deaths occur in low- and middle-income countries (1). Among premature deaths (under 70 years of age) attributed to non-communicable diseases, CVDs contribute to at least 38% (1). CVD refers to a group of conditions affecting the heart and blood vessels that include coronary artery disease (CAD), which can cause chest pain (angina) and heart attacks, as well as irregular heartbeats (arrhythmias), heart failure, and problems with heart valves. The development of atherosclerotic plaque in the coronary arteries results in inadequate blood and oxygen delivery to the myocardium and other regions of the body, posing it one of the most complex diseases with high morbidity and mortality worldwide (2). Cholesterol is widely recognized as a significant risk factor for atherosclerosis and cardiovascular diseases (CVD). Among the different forms of cholesterol, low-density lipoprotein cholesterol (LDL-C) is most closely linked to an elevated risk of coronary artery disease (CAD) and stroke. High levels of LDL-C contribute to the accumulation of cholesterol in arterial walls, resulting in plaque formation and vascular complications (3). The role of cholesterol in CVD is further influenced by dietary lipid intake, food choices, and overall lifestyle habits.

Research suggests that dietary components, such as specific fats, carbohydrates, fiber, antioxidants, and micronutrients, can influence lipid profiles and potentially be linked with CVD risk in APOE4 carriers. Body fat distribution is a better measure of disease risk than BMI (Body mass index), as central adiposity is associated with dyslipidemia and insulin resistance (4). Emerging evidence supports the integration of targeted dietary interventions, focusing on reducing LDL-C levels and improving lipid metabolism, to address the heightened susceptibility in this population (5,6). The literature indicates that preventing obesity and heart disease depends on diet, with the type of fat being more important than the amount. Dietary lipids enhance the taste, texture, and energy content of food while serving vital roles in the body, including providing energy, forming cell membranes, acting as precursors for signaling molecules, aiding the absorption of fat-soluble vitamins, and influencing cardiovascular health, as saturated fats raise LDL-C levels, whereas omega-6 polyunsaturated fatty acids lower total and LDL-C levels, with replacing saturated fats with omega-6 consistently shown to improve cholesterol profiles (7). Saturated fatty acids (SFA) found in common foods such as milk, butter, cheese, and various meats elevate LDL-C and high-density lipoprotein cholesterol (HDL-C). The rise in LDL-C occurs due to reduced hepatic clearance and increased production of LDL, a process associated with a decline in LDL receptor activity in the liver (5). Therefore, dietary fats play a potential role in lipid metabolism, which can contribute to the development of heart disease.

In addition to lifestyle factors, genetics plays a pivotal role in the risk of CVD and CAD. The Apolipoprotein E (APOE) gene, which encodes a 34 kDa glycoprotein composed of 299 amino acids primarily produced in the liver, is a critical player in lipid metabolism and disease pathophysiology (8). APOE is a ligand for LDL receptors, mediating the transport and clearance of cholesterol and triglyceride-rich lipoproteins. Its isoforms APOE2, APOE3, and APOE4 exert varying effects on plasma lipoproteins and LDL levels, significantly influencing the risk of atherosclerosis and related conditions (9). The APOE4 allele is strongly associated with dyslipidemia, elevated LDL-C levels, and increased oxidative stress, making it a key genetic determinant of CAD and CVD risk. Studies indicate that carriers of the APOE4 allele have impaired lipid clearance, heightened oxidative stress, and disrupted lipid metabolism,

which collectively contribute to the pathogenesis of CAD (10,11). Furthermore, APOE4 is implicated in the onset of neuropathological lesions associated with Alzheimer's disease, highlighting its broad impact on lipid metabolism and systemic health (12,13).

Moreover, the APOE protein facilitates reverse cholesterol transport by forming high-density-like lipoproteins in macrophages, which are then transported to the liver. This function is critical for maintaining lipid homeostasis and underscores the significant influence of APOE on cardiovascular and systemic health (14). Advances in computational and bioinformatics studies further highlight the linear association of APOE4 with CAD, offering novel insights into the gene's role in disease progression and paving the way for future research (15-17). The interaction between the APOE4 genotype and dietary factors underscores the importance of personalized nutritional strategies to mitigate genetic risk.

The interplay between APOE4, lipid metabolism, and lifestyle factors presents an avenue for the development of targeted interventions. This study aims to systematically evaluate the interplay between the APOE4 genotype, dietary fat intake, and lipid metabolism in modulating LDL cholesterol levels and cardiovascular disease risk. Very limited and fragmented studies are present to elucidate and understand the genetic, nutritional, and metabolic relations in CAD which can guide for proper therapeutic development. By understanding the genetic underpinnings and nutritional modulations of APOE4-associated CVD risk, researchers and clinicians can design personalized approaches to reduce disease burden and improve outcomes in genetically susceptible populations. Further investigation into gene-nutrition interactions will be essential for advancing preventive strategies against CAD and CVD.

MATERIALS AND METHODS

Study Design

This review followed a systematic literature review (SLR) methodology to synthesize and critically appraise existing evidence on the relationship between the APOE4 genotype, lipid metabolism, dietary factors, and cardiovascular disease (CVD) outcomes. The study was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure methodological rigor and transparency.

Search Strategy

A comprehensive literature search (1990-2024) was conducted using the following electronic databases: PubMed, Scopus, and Web of Science. Searches were performed using a combination of Medical Subject Headings (MeSH) and free-text terms. The search terms included: "APOE4", "lipid metabolism", "dietary intervention", "LDL cholesterol", "cardiovascular disease", "dietary fats", "genetic polymorphism", and "lipoprotein particles".

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria adopted for the selection of studies in this systematic review are summarized in Table 1.

Table 1. Defined Eligibility Criteria Guiding Study Inclusion and Exclusion in This Review

Criteria Type	Inclusion Criteria	Exclusion Criteria
Study Design	Peer-reviewed original research articles, systematic reviews, and meta-analyses	Editorials, letters, conference abstracts, and case reports
Language	Published in English	Published in non-English languages
Population	Human participants with reported APOE genotypes (specifically APOE4)	Animal studies, in vitro studies
Focus Area	Studies examining the link between APOE4, lipid metabolism, dietary intake, and cardiovascular outcomes	Studies focusing only on neurological outcomes (e.g., Alzheimer's disease)
Outcomes Reported	Includes at least one outcome related to LDL-C, HDL-C, VLDL, triglycerides, or CVD	No outcomes related to lipid metabolism or cardiovascular health
Intervention	Studies reporting dietary or pharmacological interventions relevant to lipid modulation in APOE4 carriers	Studies not discussing any dietary, genetic, or pharmacological intervention

Data Collection

Data collection for this systematic review was conducted through a structured screening and extraction process. After identifying relevant articles through comprehensive searches of PubMed, Scopus, and Web of Science, two independent reviewers screened all titles and abstracts for initial relevance. Full-text articles were then assessed based on the predefined inclusion and exclusion criteria. For each eligible study, key information was systematically extracted using a standardized data extraction form. The variables collected included study characteristics (authors, publication year, location), study design, sample size, participant demographics, APOE genotypes (particularly $\epsilon 4$ allele presence), lipid profile outcomes (such as LDL-C, HDL-C, VLDL, triglycerides), dietary interventions or patterns, and any pharmacological treatments evaluated. Additional data on cardiovascular outcomes, follow-up duration, and gene-diet interactions were also recorded where available. Any discrepancies between reviewers during data extraction were resolved through discussion or consultation with a third reviewer to ensure consistency and minimize bias.

Quality Assessment

The methodological quality of the included studies was evaluated using the QUADAS-2 tool across four domains. As shown Figure 1, most studies showed a low risk of bias in the index test domain due to validated lipid and genotyping methods. However, some concerns were noted in patient selection and reference standards, particularly in observational designs and studies using indirect measures. The flow and timing domain revealed the highest risk, often due to unclear follow-up durations and unreported attrition. Overall, most studies were rated as having some concerns, with a few showing high risk, highlighting the need for cautious interpretation of findings.

	RISK OF BIAS DOMAINS				
	D1	D2	D3	D4	Overall
[35, 36]	+	-	-	-	-
[37]	×	-	+	×	×
[47]	-	+	-	×	-
[43, 44]	-	+	-	×	×
[45, 46]	+	+	-	-	-
[51-53]	-	+	×	×	×
[50]	+	+	+	-	-
[57-59]	+	+	+	-	+
[34, 61]	-	-	-	×	×
[62]	-	-	+	-	-
Domains:	D1: Patient selection D2: Index test D3: Reference standard D4: Flow & timing		Judgement:	× High - Some concerns + Low	

Figure 1. Risk of Bias Summary Based on QUADAS-2 Assessment.

RESULTS

Study Selection Process and Screening Flow

The comprehensive search strategy initially identified 1,186 records. After the removal of duplicates (n = 432), 754 articles were screened based on titles and abstracts. From these, 142 studies were selected for full-text review. Applying the predefined inclusion and exclusion criteria, a total of 48 studies were retained for the final synthesis. The detailed selection process is visually summarized in the PRISMA flow diagram, Figure 2.

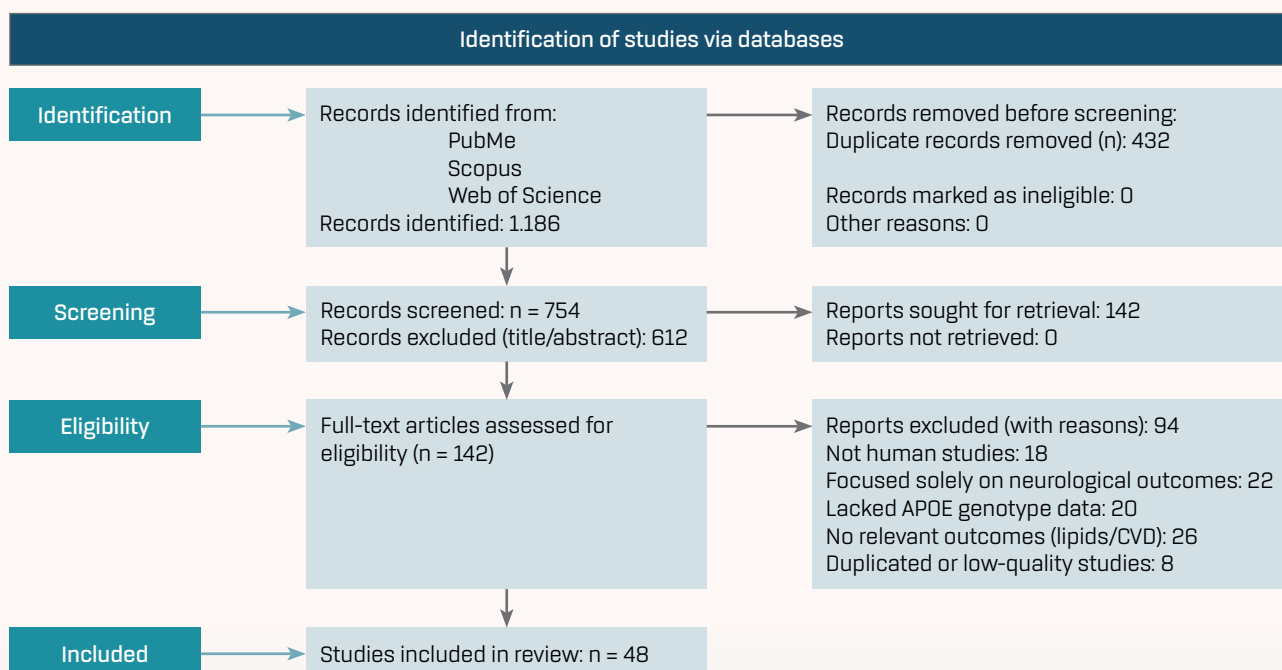


Figure 2. PRISMA 2020 Flow Diagram Illustrating the Systematic Study Selection Process.

Characteristics and Scope of Included Studies

The 48 studies included in this review were published between 1990 and 2024, encompassing research across a broad range of ethnically diverse populations from North America, Europe, Asia, and Latin America. Most studies focused on adult populations aged 18–75 years. Notably, approximately 70% of the included studies stratified outcomes based on APOE genotypes, with a particular emphasis on individuals carrying the ε4 allele.

To provide further insight into the research landscape, the year of publication of the included studies was analysed. The included studies cover a period of over 30 years, with a relatively low number of studies published before 2000, a slow increase in the early 2000s, and a significant rise after 2010. Peak numbers of studies were found from 2015 to 2024, suggesting a surge of interest in the effect of the interaction between APOE genotype and diet on cardiovascular risk. This reflects the growing awareness of the role of nutrigenomics and precision medicine in cardiovascular disease. Table 2 provides a comprehensive overview of the most relevant findings across multiple populations, linking APOE4 to lipid regulation and cardiovascular outcomes.

Table 2. Consolidated Evidence of APOE4-Linked Lipid Dysregulation, Dietary Interactions, and Cardiovascular Risk Across Populations.

Finding	Study/Population	Key Outcome
APOE4 associated with elevated LDL-C and TGs levels	Indian and Mexican populations (Das et al., 2008; Cahua-Pablo et al., 2022)	APOE4 linked to increased LDL-C and triglyceride concentrations in ethnically diverse populations
Preferential binding of APOE4 to VLDL leads to more efficient conversion into LDL	Gregg et al., 1986; Feingold, 2024	APOE4 enhances hepatic uptake of VLDL remnants and accelerates LDL production
Saturated fat intake increases LDL-C in APOE4 carriers	Sydney Diet Heart Study (1966–1973)	High SFA diets lead to adverse CVD outcomes in APOE4 individuals despite lowering total cholesterol
PUFA and MUFA intake reduce LDL-C, especially in APOE4 carriers	Observational and interventional dietary studies	Replacing SFA with PUFA/MUFA significantly improves lipid profiles
Trans fats increase LDL-C and decrease HDL-C, aggravating risk in APOE4 carriers	Meta-analyses and cohort studies	TFA intake linked to heightened cardiovascular risk due to its dual impact on LDL and HDL
Phytosterols lower LDL-C but may interfere with fat-soluble vitamins and have potential adverse effects	Animal and human studies	Plant sterols effectively reduce cholesterol but may have risks for red blood cell integrity and hormone regulation
Fiber reduces LDL-C by interrupting intestinal absorption and enhancing LDL receptor expression	Dietary intervention studies	Soluble and insoluble fiber intake improves lipid profiles and reduces CVD risk
Pharmacological agents like statins, ezetimibe, and PCSK9 inhibitors show varying efficacy in APOE4 carriers	Clinical trials and pharmacogenetic reviews	Statins are generally effective; PCSK9 inhibitors and ezetimibe provide additive benefits, especially where statin tolerance is low
APOE4 genotype modifies individual response to dietary and pharmacological interventions	Multiple studies in nutrigenomics	Highlights the importance of personalized nutrition and pharmacogenetics
Obesity exacerbates APOE4-mediated dyslipidemia by disrupting cholesterol absorption and insulin sensitivity	Epidemiological data and mechanistic studies	Visceral fat impacts lipid metabolism pathways, increasing CVD risk in APOE4 carriers

When it comes to study design, the evidence was a combination of observational, interventional and mechanistic studies. Most of the evidence came from observational studies (cross-sectional, case-control, and cohort designs) due to the novelty of the gene-diet interaction in population-based studies. A minority of the studies included randomized controlled trials (RCTs), which mainly involved dietary interventions and blood lipids. Moreover, a few mechanistic, experimental and pharmacogenetic studies were also included to understand the mechanisms of APOE4-related lipid metabolism. This mix suggests that although there is a large amount of associative evidence, there is relatively little high-quality randomized evidence (tab. 3).

Table 3. Distribution of Included Studies by Study Design.

Study Design Category	Description	Approximate Representation
Observational Studies	Cohort, case-control, cross-sectional	Majority
Randomized Controlled Trials (RCTs)	Dietary or pharmacological interventions	Limited
Mechanistic/Experimental Studies	Molecular, in vitro, or metabolic pathway studies	Moderate
Reviews/Meta-analyses (if included)	Secondary evidence synthesis	Minor

DISCUSSION

The findings of this review underscore the critical role of the APOE4 genotype in lipid metabolism, particularly its association with elevated LDL cholesterol levels and increased cardiovascular disease risk. Furthermore, the interplay between dietary fat intake and APOE4-mediated lipid regulation highlights the need for targeted nutritional interventions in genetically susceptible individuals.

Understanding the APOE Gene: Role in CVD

The APOE gene (3598 bp) maps to chromosome 19, and codes for APOE protein, a glycoprotein containing 299 amino acids of molecular weight 34 kDa, associated with lipid particles, that mainly functions in lipoprotein-mediated lipid transport between organs via the plasma and interstitial fluids (18). The protein involves three APOE variants (isoforms) in human lipid homeostasis and mediates the binding of VLDL and IDL to LDL-R and LDL receptor-related proteins (19,20). The single locus on chromosome 19 that produces three isoforms are APOE2, APOE3, and APOE4 from three alleles viz, epsilon 2 (ϵ 2), epsilon 3 (ϵ 3), and epsilon 4 (ϵ 4) and the difference among them is due to amino acid substitution at positions 112 and 158 (21). Among the three, APOE3 is the most prevalent form which has cysteine residue at 112 and arginine at 158, whereas APOE4 has arginine at both 112 and 158 positions, and APOE2 has cysteines at both the sites, making them contribute significantly to coronary artery disease (CAD) and atherosclerosis (22) (tab. 4).

Table 4. Summary of the Differences among APOE Isoforms.

Differences	APOE4	APOE3	APOE2	References
Sequence Difference	112: Arg	112: Cys	112: Cys	(21,23-25)
	158: Arg	158: Arg	158: Cys	
Domain Interaction	Ionic interaction between Arg-61 and Glu-255	Absent	Absent	(26)
Binding Affinity	APOE4 binds to large LDL and VLDL	APOE3 and APOE2 bind to small HDL		(27, 28)
Prevalence (Allelic Frequency)	14%	78%	7%	(29, 30)
Disorders	CAD; CVD; AD	Normal	Type-III hyperlipoproteinemia	(31-33)
CAD = coronary artery disease; CVD = cardiovascular disease; AD = Alzheimer's disease.				

However, not all studies demonstrate a consistent magnitude of effect between APOE4 and lipid levels, and in some cases, differences in LDL receptor affinity or plasma clearance rates are marginal. These discrepancies suggest that additional mechanisms beyond lipoprotein binding, such as hepatic lipid regulation or inflammatory pathways, may be more central to APOE4's atherogenicity.

The amino acid differences in the three APOE isoforms result in distinct structural properties that influence their functions, such as domain interaction and protein stability (molten globule formation). Studies have shown that replacing cysteine with arginine at position 158 in APOE2 significantly reduces its ability to bind to LDL receptors, while a similar substitution at position 112 in APOE3 does not affect its binding activity compared to APOE4 (25). The unique structure of APOE4 plays a key role in atherosclerosis, although the exact mechanism of how it interacts with LDL receptors and triggers structural changes remains unclear (32). Studies reported that the receptor-binding activity of APOE4 is thought to contribute to its association with a higher risk of CAD, linked to its role in cholesterol metabolism (15,17). Additionally, its unique domain interaction and protein stability further distinguish APOE4 from APOE3, contributing to its role in disease development. Literature has increasingly highlighted the APOE4 variant is strongly linked to higher risks of CVD, Alzheimer's disease, and cognitive decline, with individuals carrying one or two copies of the allele being more susceptible to these conditions (34).

APOE4 in Modulating LDL-C Levels

Several studies conducted across diverse populations have reported a correlation between the ApoE4 isoform and elevated lipid levels. For instance, Das et al., (2008) (35) observed increased levels of LDL-C and triglycerides (TG) in the Indian population, while Cahua-Pablo et al., (2022) (36) found similar trends among Mestizo women from Southwestern Mexico. These findings suggest a consistent association between the ApoE4 allele and dyslipidemia across different ethnic groups (35,36). However, these studies often lack stratified clinical outcomes or adjustments for confounding variables like obesity, physical activity, or co-medications, limiting their generalizability.

Though APOE4 is thought to promote more efficient conversion of VLDL remnants into LDL, some studies report minimal genotype-based differences in hepatic clearance rates. This variability may reflect population-specific factors, such as metabolic status or background diet, which are rarely controlled for uniformly (37-39).

With regards to lipid transport and atherosclerosis, studies discussed how cholesterol and triglycerides, being water-insoluble, are transported in the blood via lipoproteins such as LDL, HDL, VLDL, with some promoting plaque buildup in arteries (pro-atherogenic) and others helping to remove cholesterol (anti-atherogenic). The body uses two main pathways – the exogenous (from dietary fats) and endogenous (from the liver) – to move these lipids around. HDL, in particular, plays a protective role by helping remove excess cholesterol from tissues and transporting it back to the liver, a process that helps prevent atherosclerosis (40). Another study assigned participants to a dietary intervention group (n=221) and a control group. The intervention, which increased the intake of triglyceride-rich lipoproteins such as chylomicrons and VLDL, resulted in a higher concentration of ApoE per lipoprotein particle. This elevated ApoE per TAG-rich lipoprotein may enhance competition with LDL for LDL receptor-mediated clearance, potentially leading to increased circulating LDL-C levels (41).

As illustrated in Figure 3, the ApoE4-mediated pathway of VLDL metabolism demonstrates a preferential binding affinity of ApoE4 to VLDL particles, which influences their hepatic processing and subsequent conversion into IDL and LDL, thereby impacting plasma LDL-C concentrations ⁵.

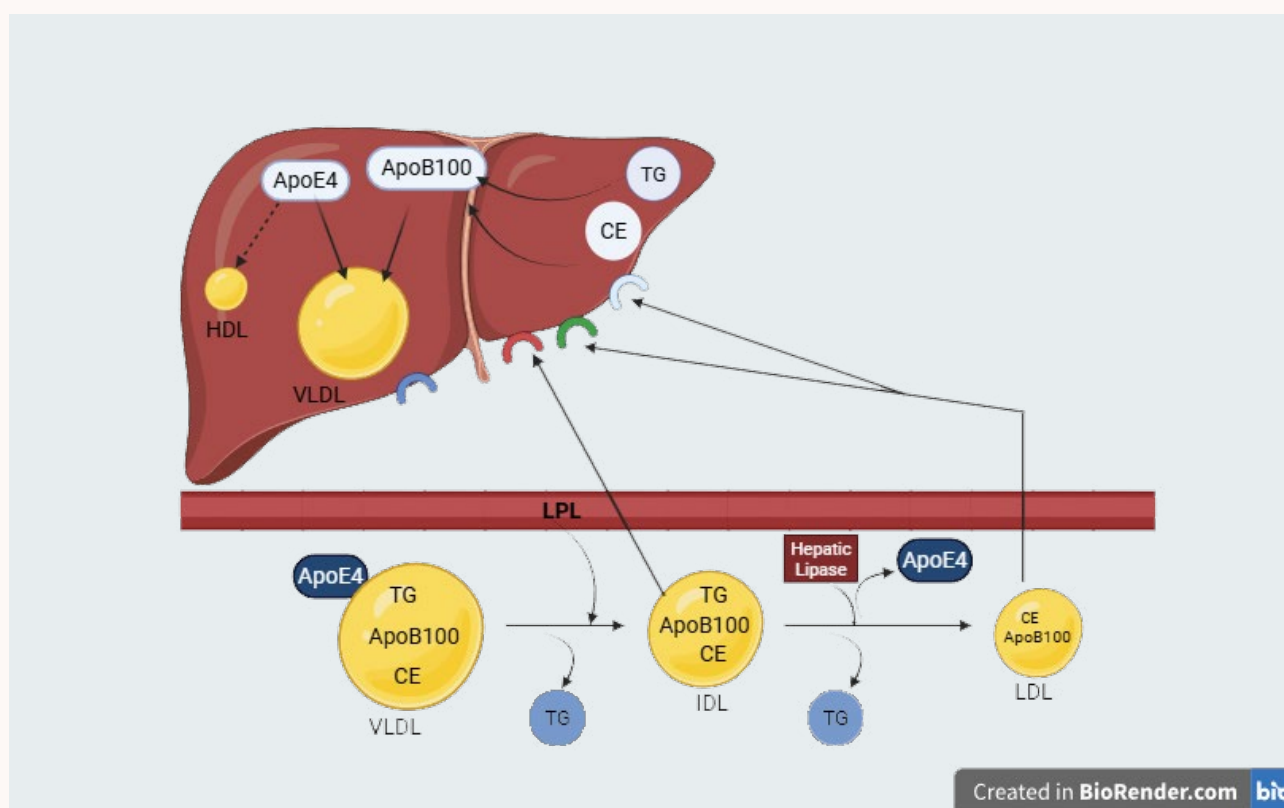


Figure 3. ApoE4 mediated VLDL-Metabolism.

In the liver, cholesterol esters and triglycerides are packaged with ApoB-100, a key structural component of VLDL and a ligand for the LDL-R, thereby facilitating the clearance of circulating lipoproteins. Newly synthesized ApoE4 exhibits a preferential binding affinity for VLDL particles. These VLDL particles are secreted into circulation and deliver triglycerides to peripheral tissues, a process mediated by lipoprotein lipase (LPL)-induced hydrolysis. This enzymatic removal of triglycerides leads to the conversion of VLDL into IDL. ApoE present on IDL enables recognition and uptake by receptors such as LDL-R and LRP1, promoting their clearance from the bloodstream. However, a subset of IDL particles undergoes further triglyceride hydrolysis, facilitated by hepatic lipase, leading to the formation of LDL (Feingold, K. R., 2024). The resulting LDL particles can then interact with various hepatic receptors, including LDL-B, LDL-E, etc. CE- Cholesterol ester, LDL-R- LDL Receptor, LPL- Lipoprotein Lipase, IDL- Intermediate-Density Lipoprotein, LRP-1- LDL Receptor Related Protein 1. (The ApoE4-mediated VLDL metabolism in the above figure emphasizes the preferential binding of ApoE4 to VLDL).

Understanding the Diet: Role in CVD

The role of lipids and lipoproteins in cardiovascular disease (CVD) is well established. Saturated Fatty Acids (SFA) are found in foods like butter, cheese, and red meat. They increase LDL cholesterol (LDL-C), which is a risk factor for CVD. Additionally, they modestly increase HDL cholesterol (HDL-C), which is considered protective, but the overall effect leans towards a negative impact due to the pronounced LDL-C rise (42). Monounsaturated and Polyunsaturated Fatty Acids (MUFA and PUFA) are fats, found in olive oil, nuts, and fatty fish, and are beneficial as they reduce LDL-C levels. PUFAs, particularly omega-3 fatty acids, also have anti-inflammatory properties, making them heart-protective. Replacing SFAs with MUFAs and PUFAs is a key dietary recommendation for lowering CVD risk (43). Trans Fatty Acids (TFA), primarily from partially hydrogenated oils and processed foods, increase LDL-C and decrease HDL-C. This dual negative effect makes TFAs particularly harmful, and their consumption is strongly linked to an increased risk of CVD. Observational studies have consistently shown that higher dietary intake of trans fats (TFA) increases the risk of cardiovascular disease (CVD) (44). A study summarizing the links between fatty acids and coronary disease found that saturated, monounsaturated, and omega-3 and omega-6 polyunsaturated fats showed little to no strong association with coronary risk, while trans fats were linked to a higher risk. The findings suggest limited support for current guidelines promoting high polyunsaturated fat intake and low saturated fat intake for heart health (45).

Similarly, another most discussed dietary factor is cholesterol. Dietary cholesterol, present in egg yolks and shellfish, increases LDL-C levels, though the effect is modest and varies among individuals. Some people, known as hyper-responders, experience a more significant rise in LDL-C. Current recommendations focus on moderating cholesterol intake rather than strict avoidance (5). The Sydney Diet Heart Study, a randomized controlled trial conducted from 1966 to 1973, evaluated the effects of replacing dietary saturated fats with polyunsaturated fats in men aged 30 to 59 years with a history of coronary artery disease. Participants were randomized into two groups: an intervention group (n=221) that received dietary instructions to substitute animal fats, butter, traditional margarines, and shortenings with safflower oil and safflower oil-based polyunsaturated margarine, and a control group (n=237) that received no specific dietary advice. The dietary intervention aimed to increase polyunsaturated fatty acid (PUFA) intake to approximately 15% of total energy, reduce saturated fat (SFA) intake to below 10%, and limit dietary cholesterol to less than 300 mg per day. Additionally, liquid safflower oil was provided as a dietary supplement. At baseline, serum cholesterol

levels in both groups were approximately 280 mg/dL. After the intervention, cholesterol levels decreased to 267 mg/dL in the control group and to 244 mg/dL in the intervention group. Despite these improvements in lipid profiles, the intervention group demonstrated higher rates of all-cause mortality (17.6% vs. 11.8%; $P=0.051$), cardiovascular mortality (17.2% vs. 11.0%; $P=0.037$), and coronary heart disease mortality (16.3% vs. 10.1%; $P=0.036$) over the five-year follow-up period. The paradoxical increase in mortality observed in the intervention group, despite favorable changes in cholesterol levels, raises important concerns. One possible explanation involves the use of safflower oil-based margarine, which may have contained trans fatty acids – a byproduct of partial hydrogenation processes common at the time. Trans fats have since been recognized as detrimental to cardiovascular health, potentially offsetting the anticipated benefits of reduced saturated fat intake (46). These findings underscore the complexity of dietary fat modification strategies and highlight the need for careful consideration of the type and source of fats used in dietary interventions.

Carbohydrates (CHO) are the simple sugars and low-quality carbohydrates that contribute to an increase in triglycerides (TGs). High triglyceride levels are associated with a greater risk of metabolic disorders. Complex carbohydrates like whole grains and legumes are preferred as they have a neutral or beneficial impact on lipids. Trials replacing saturated fat with mainly carbohydrates did not lower CVD risk. However, these carbohydrates were often unspecified and included sugars and refined carbs. Observational studies show that whole-grain carbohydrates can reduce CVD risk when they replace saturated fat (47,48). Dietary fiber consists of non-digestible carbohydrates such as non-starch polysaccharides, cellulose, pectins, hydrocolloids, fructo-oligosaccharides, and lignin. Soluble forms of fiber are found in fruits and vegetables, and insoluble fiber is found in cereals and whole-grain products and helps lower LDL-C by reducing intestinal cholesterol absorption, leading to improved lipid profiles and a reduced risk of CVD. Studies discussed that it reduces cholesterol absorption in the small intestine, which lowers cholesterol in chylomicrons and reduces the amount delivered to the liver. This decrease in liver cholesterol boosts LDL receptors, leading to lower LDL-C levels in the blood (49).

Similarly, phytosterols are naturally present in plant-based foods. Plant sterols and stanols (phytosterols/phytosterols) are known to lower LDL cholesterol levels. Foods with these compounds are commonly used to reduce cholesterol and the risk of atherosclerosis (50). Studies suggest that phytosterols and phytosterols regulate cholesterol metabolism through genes like ABCA1, ABCG5/G8, SREBP-2, and LXR. These genes are involved in LDL cholesterol regulation, which is linked to cardiac diseases. Despite the absence of ABC transporters, phytosterols can still inhibit cholesterol absorption, affecting processes like cholesterol esterification, lipoprotein assembly, and synthesis (50). Phytosterols raise safety concerns beyond cardiovascular effects. Studies have shown that phytosterol-rich vegetable oil can make red blood cells less flexible, shortening rat lifespan, and leading to a ban on such foods in Canada in 2003 (51). In vivo studies also suggest phytosterols may negatively affect hormonal and reproductive systems in rats and goldfish, though this has not been proven in humans. To investigate the effects of lipid-soluble (pro) vitamins, a study on 185 healthy volunteers was conducted, but found no impact on reproductive hormones after a year of phytosterol consumption (52). Additionally, phytosterols may interfere with the absorption of fat-soluble vitamins like vitamin E and β -carotene, prompting recommendations to use natural sources of β -carotene (53). Table 5 outlines the effects of various dietary constituents on lipid and lipoprotein levels, highlighting their roles in cardiovascular health.

Table 5. Summary of the effect of dietary constituents on Lipid and Lipoproteins (5)(Feingold, 2021).

Sl. No.	Diet constituents	Effect on the Lipid and Lipoproteins
1	SFA	Increase LDL-C and modest increase HDL-C
2	MUFA and PUFA	Decrease LDL-C
3	TFA	Increase LDL-C and decrease HDL-C
4	Cholesterol	Increase LDL-C
5	Carbohydrates	Increase TGs particularly simple sugars
6	Fiber	Decrease LDL-C
7	Phytosterols	Decrease LDL-C
SFA = saturated fatty acids; MUFA = Monounsaturated Fatty Acids; PUFA = Polyunsaturated Fatty Acids		

Dietary guidelines consistently recommend reducing saturated fat (SFA) intake due to its association with cardiovascular disease (CVD) in observational studies. However, meta-analyses show mixed results, suggesting the impact depends on what replaces SFA in the diet. Replacing SFA with polyunsaturated fats (PUFA) reduces CVD risk, while replacement with carbohydrates generally shows no benefit unless they are high-quality carbohydrates. Additionally, the source of SFA matters, with SFA from meat linked to increased CVD risk, but SFA from dairy shows a protective effect (54,55).

Pharmacological Interventions

In addition to dietary strategies, various pharmacological agents are employed to manage lipid levels in individuals with elevated CVD risk, including those with the APOE4 genotype. Statins (e.g., atorvastatin, simvastatin) inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis, leading to reduced LDL-C levels (56). There are cholesterol management guidelines that recommend using two additional medicines besides statins to further lower LDL cholesterol and reduce the risk of heart disease. One is ezetimibe, which blocks cholesterol absorption and helps reduce LDL levels when used with statins, without major safety concerns. It is also helpful for people who have side effects from statins, like muscle pain, as it can be combined with a lower statin dose. The other option includes proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors like alirocumab and evolocumab, which are approved to lower LDL cholesterol effectively (57). Ezetimibe inhibits intestinal cholesterol absorption by targeting the Niemann-Pick C1-Like 1 (NPC1L1) protein. PCSK9 inhibitors (e.g., evolocumab, alirocumab) enhance LDL receptor recycling, significantly lowering plasma LDL-C. Omega-3 fatty acid formulations (e.g., icosapent ethyl) are also used to modulate triglyceride levels. These agents may have varying efficacy in ApoE4 carriers due to altered lipoprotein processing, underscoring the importance of integrating pharmacogenetic data into treatment plans (58,59). Studies on pharmacological interventions are still evolving, and more research is needed to fully understand the underlying mechanisms. However, the pharmacological interventions, through targeted drugs and their specific mechanisms of action, effectively modulate key biological processes to treat various conditions, offering tailored therapeutic benefits.

Linking APOE Genotype and Diet in Cardiovascular Health

Diet fatty acids and cholesterol are major targets for reducing plasma total and LDL cholesterol as a strategy to decrease cardiovascular disease risk. Individuals with the APOE4 allele show a more significant reduction in LDL-C levels in response to lower dietary fat and cholesterol intake compared to those with the APOE3 or APOE2 alleles (60). Similarly, genetic polymorphisms in other genes can influence how lipids and lipoproteins respond to dietary changes. Clinical conditions also play a role; for instance, the lipid-lowering effects of a low-cholesterol, low-SFA diet are less pronounced in obese individuals (61). Therefore, dietary effects vary among individuals, and clinicians must monitor each patient's response to tailor dietary recommendations.

Research suggests that tailoring diets based on an individual's APOE genotype can significantly improve health outcomes. For APOE2 carriers, a heart-healthy diet with healthy fats, lean proteins, and plenty of fruits and vegetables, along with omega-3-rich foods like fatty fish and walnuts, may offer cardiovascular benefits. APOE3 carriers, with a neutral risk profile, can optimize health through a balanced, nutrient-dense diet that includes lean proteins, whole grains, and colourful fruits and vegetables, while avoiding processed foods. APOE4 carriers, at higher risk for cognitive decline, may benefit from a brain-boosting diet with antioxidant-rich foods and omega-3s to protect against neurodegeneration (34).

Nutrigenomics, the study of how nutrition interacts with genetics, plays a key role in personalized diets. This field explores the complex relationship between genetics and nutrition, highlighting how specific APOE genotypes can influence cardiovascular health and how tailored diets can optimize heart health outcomes. Importantly, gene-environment interactions encompassing dietary patterns, physical activity, and lifestyle choices play a crucial mediating role in determining individual susceptibility and metabolic outcomes in APOE4 carriers. To create a genotype-specific diet plan, routine genetic testing for APOE allele status is required as an initial diagnostic step. Following APOE status identification, specific blood biomarkers including total cholesterol, LDL-C, HDL-C, triglycerides, apolipoprotein B (ApoB), high-sensitivity C-reactive protein (hs-CRP), and markers of oxidative stress should be systematically monitored over time to evaluate treatment efficacy, track longitudinal metabolic trajectories, and dynamically adjust personalized dietary and pharmacological interventions.

In addition to the genetic factors influencing cholesterol metabolism, lifestyle factors such as obesity play a significant role in how the body processes LDL cholesterol. Obesity, particularly abdominal fat, can disrupt hormonal balance and alter gut microbiota, leading to impaired cholesterol absorption and processing. By reducing abdominal fat, individuals can improve insulin sensitivity, reduce inflammation, and enhance the body's ability to process cholesterol more effectively. This not only helps manage cholesterol levels but also makes dietary interventions, such as those tailored to specific APOE genotypes, more impactful. Therefore, combining weight management with personalized dietary strategies is essential for optimizing cholesterol regulation and overall heart health.

Clinical Relevance and Limitations of Evidence

Although numerous observational and mechanistic studies suggest that APOE4 carriers may respond differently to specific dietary interventions, particularly reductions in saturated fat intake, robust clinical trial evidence supporting genotype-based dietary recommendations remains limited. Most existing studies are either cross-sectional, of short duration, or lack genotype stratification with sufficient power to detect meaningful gene-diet interactions.

Furthermore, while this review highlights promising avenues for personalized nutrition, the current evidence base is insufficient to support formal clinical guidelines targeting APOE4 individuals. The Sydney Diet Heart Study, for instance, found paradoxical increases in cardiovascular mortality despite lipid improvements, underscoring that biomarker modulation does not always translate to improved clinical outcomes. These inconsistencies reflect the complex interplay between diet, genotype, and comorbidities, factors often inadequately controlled in many studies.

Therefore, until large-scale, genotype-stratified randomized controlled trials (RCTs) are conducted, recommendations for APOE4-specific dietary modifications should be viewed as hypothesis-generating rather than practice-defining. This limitation must be acknowledged when interpreting the translational significance of current findings.

CONCLUSIONS

The APOE4 allele is a major genetic determinant of cardiovascular disease, being associated with elevated LDL-C levels, increased oxidative stress, and a higher risk of coronary artery disease and stroke. Current evidence demonstrates a clinically significant interaction between APOE genotypes, particularly APOE4, and dietary factors that influences cardiovascular risk. Consequently, personalized nutritional interventions tailored to the APOE4 genotype represent a promising approach for improving lipid profiles and reducing cardiovascular risk. However, further research is needed to better understand gene–nutrient interactions and to strengthen the evidence supporting the routine clinical implementation of genotype-based dietary recommendations. Integrating personalized nutrition into clinical practice may improve preventive and therapeutic strategies for individuals with increased genetic susceptibility to cardiovascular disease.

CONFLICT OF INTEREST The authors declare that they have no conflicts of interest.

ETHICAL APPROVAL This manuscript is a systematic literature review based on the analysis of fully anonymized, publicly available, peer-reviewed data and secondary research sources. Because no animal or human subjects were directly involved, animal clinical case guidelines do not apply, and institutional ethical approval and written participant consent were not required.

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