THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Apolipoprotein E: A Genetic Bridge Between Premature Atherosclerosis and Alzheimer Disease

EDITORIAL COMMENT

Apolipoprotein E (*APOE*) represents one of the most important common genetic determinants linking coronary artery disease (CAD) and neurodegeneration. ApoE links lipid metabolism, vascular health, and brain function. The three common *APOE* alleles, ε2, ε3, and ε4, encode functionally different isoforms with important cardiovascular and neurological consequences.[1,2] Table 1 depicts the ApoE alleles and related clinical consequences.

Peripheral and brain ApoE biology should be considered separately. In the circulation, ApoE is present mainly on triglyceride-rich lipoproteins and their remnants and on a subset of high-density lipoprotein (HDL) particles. It facilitates receptor-mediated lipoprotein clearance and influences plasma lipid concentrations. Large-scale human data show a graded relationship between *APOE* genotype, low-density lipoprotein (LDL) cholesterol, and coronary risk; ε2 is generally associated with lower LDL-cholesterol and lower coronary risk, whereas ε4 is associated with higher LDL-cholesterol and a modest increase in coronary risk across the genotype spectrum.[1,2]

In this issue, Dogsom et al[3] report an exploratory hospital-based case-control study of 63 Mongolian patients with angiographically confirmed CAD and 61 controls. The study provides data from a population poorly represented in cardiovascular genetic research. The strongest finding was lower odds of CAD among individuals with the ε2/ε3 genotype (OR 0.29, 95% CI 0.12-0.71). Although ε4/ε4 was more frequent among cases, its association with CAD was not statistically significant (OR 2.68, 95% CI 0.68-10.55). Thus, the study does not establish ε4 as a CAD risk factor specifically in Mongolians, but provides hypothesis-generating data requiring confirmation.[3] The small genotype groups also limit multivariable precision and preclude important sex-specific analyses. In addition, non-HDL-cholesterol or ApoB would also have provided a more complete assessment of atherogenic lipoprotein burden.

Population-specific evaluation is particularly important for *APOE*. Allele frequencies and effect sizes vary across ancestries. In Alzheimer disease (AD), the effect associated with ε4 differs substantially across ancestry groups and is influenced by global and local genetic ancestry and gene-environment interactions.[4] This supports generating *APOE* data from Mongolian and other understudied populations.

The study also illustrates why lipid values obtained after CAD has developed require cautious interpretation. Total cholesterol and triglycerides were lower among cases, while LDL-cholesterol was higher.[3] Detailed lipid-lowering treatment data were unavailable, so these differences should not simply be attributed to therapy. More importantly, a single lipid value does not represent lifetime exposure. This is relevant in premature atherosclerosis, where cumulative atherogenic exposure and inherited susceptibility are central considerations.[5]

Meral Kayikcioglu

Department of Cardiology, Faculty of Medicine, Ege University, İzmir, Türkiye

Corresponding author:
Meral Kayikcioglu
✉ meral.kayikcioglu@gmail.com

Available Online Date: September 28, 2026

Cite this article as: Kayikcioglu M. Apolipoprotein E: A genetic bridge between premature atherosclerosis and Alzheimer disease. *Anatol J Cardiol.* 2026;XX(X):X-X.

DOI: 10.14744/AnatolJCardiol.2026.7025

Table 1. Cardiovascular and Neurological Effects of Common APOE Alleles

Feature	*APOE* ε2	*APOE* ε3	*APOE* ε4
Peripheral lipid phenotype	Generally lower LDL-C; altered remnant lipoprotein metabolism	Reference phenotype	Generally higher LDL-C and total cholesterol
Coronary atherosclerosis	Generally lower coronary risk than ε3; ε2/ε2 may predispose to dysbetalipoproteinemia in susceptible individuals	Reference phenotype	Modestly higher coronary risk in large population studies
Premature CAD	Possible protective association, but evidence is limited	Reference phenotype	ε3/ε4 associated with increased premature CAD risk in a recent observational case-control study
Brain ApoE and lipid transport	ApoE-containing HDL-like particles participate in CNS cholesterol transport; isoform-specific effects differ	Reference ApoE function	Altered ApoE lipidation and cellular cholesterol handling
Alzheimer disease	Associated with lower AD risk than ε3	Reference phenotype	Strongest common genetic risk allele for late-onset AD; clear gene-dose effect
Selected brain effects	Generally associated with lower AD risk; mechanistic effects remain context dependent	Reference phenotype	Amyloid-β pathology, altered astrocyte lipid handling, microglial lipid accumulation, neuroinflammation, BBB dysfunction, and tau-related pathways
Effect of ancestry	Allele frequency and effect size vary among populations	Allele frequency varies among populations	Allele frequency varies across populations; APOE-related AD risk is strongly modified by global and local genetic ancestry, while cardiovascular associations also show population heterogeneity
Clinical interpretation	Context dependent; generally associated with lower LDL-C and AD risk, but ε2/ε2 may predispose to dysbetalipoproteinemia	Most common reference isoform	Risk allele, not a deterministic diagnosis; effect depends on ancestry and other risk factors

AD, Alzheimer disease; ApoE, apolipoprotein E protein; *APOE*, apolipoprotein E gene; BBB, blood–brain barrier; CAD, coronary artery disease; CNS, central nervous system; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol.

The relationship between *APOE* ε4 and premature CAD also deserves attention. Li et al[6] reported that ε3/ε4 was independently associated with premature CAD in a case-control study. This is consistent with broader evidence linking ε4 to higher LDL-cholesterol and coronary risk.[1,2] *APOE* genotyping is not part of routine premature CAD assessment, but unexpectedly early or severe atherosclerosis should prompt evaluation for inherited lipid disorders and other genetic contributors.[5]

Brain cholesterol metabolism is largely compartmentalized from plasma lipoprotein metabolism. Under physiological conditions, ApoE is produced predominantly by astrocytes and secreted in HDL-like lipoprotein particles that redistribute cholesterol and phospholipids among brain cells.[1,7]

The ε4 allele alters several aspects of central nervous system lipid homeostasis. Human induced pluripotent stem cell-derived astrocytes carrying ε4/ε4 show altered ApoE lipidation and reduced neurotrophic support.[8] *APOE* ε4 has also been associated with blood-brain barrier dysfunction and pericyte injury.[9] Human brain and cellular studies have identified an *APOE4*-associated microglial phenotype characterized by triglyceride-rich lipid-droplet accumulation and enhanced inflammatory and neurotoxic responses.[10] These findings connect disturbed lipid handling, inflammation, and neurodegeneration.

Clinically, *APOE* ε4 is suggested as the strongest common genetic risk allele for late-onset AD, with a clear gene-dose effect.[4] Fortea et al[11] showed that ε4 homozygotes have a highly predictable age-related pattern of AD biomarker abnormalities and proposed that ε4 homozygosity may represent a distinct genetic form of AD. This does not mean that every ε4 homozygote will inevitably develop clinical dementia.

Thus, *APOE* links cardiovascular and neurological disease through parallel, tissue-specific pathways rather than through a simple sequence in which atherosclerosis causes AD (Figure 1). For cardiologists, the practical message remains prevention. Genetic susceptibility conferred by *APOE* is lifelong, while many cardiovascular risk factors are modifiable. Early and sustained control of LDL cholesterol and other atherogenic lipoproteins, blood pressure, and diabetes, together with smoking avoidance, weight management, and regular physical activity, remains fundamental to the prevention of premature atherosclerosis. Whether these interventions specifically attenuate *APOE4*-related AD risk remains uncertain. Importantly, higher physical activity has been associated with lower AD risk across *APOE* ε4 carrier status and polygenic risk levels, suggesting that lifestyle remains relevant even with increased genetic susceptibility.[12]

The study by Dogsom et al[3] opens a broader discussion than its modest size might suggest. *APOE* is not simply another

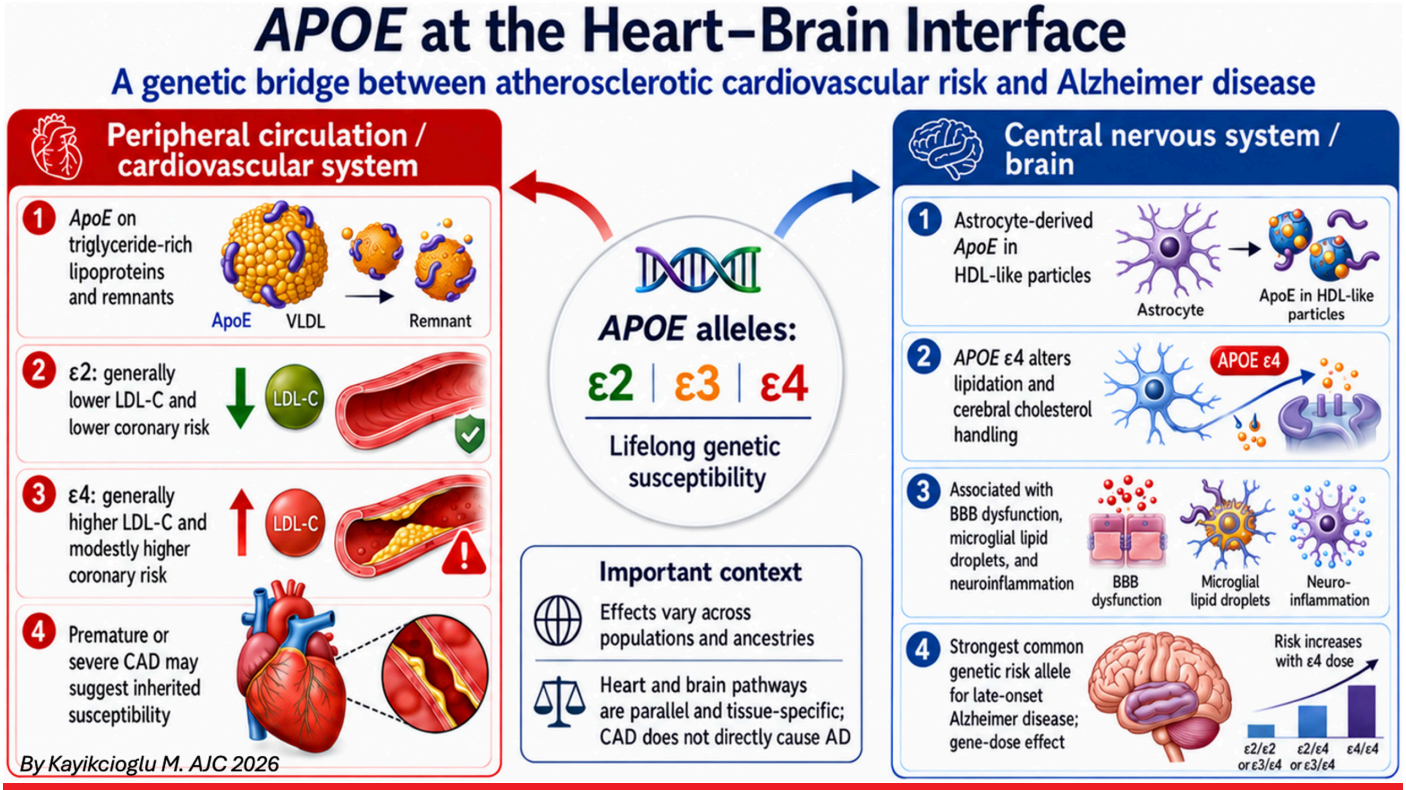

Figure 1. *APOE* **at the heart-brain interface. APOE influences cardiovascular and neurological risk through distinct but partly overlapping pathways. In the circulation, APOE-related differences in lipid metabolism may promote atherosclerosis and premature CAD. In the brain, APOE4 is associated with impaired lipid homeostasis, amyloid-β handling, neuroinflammation, blood-brain barrier dysfunction, and tau pathology.**

lipid-related gene; it is a biological link between lifelong lipid metabolism, premature atherosclerotic susceptibility, brain lipid homeostasis, and neurodegeneration.

Declaration of Interests: MK received research grants, honoraria for consultancy or lectures/speaker's bureau from Abbott, Abdi-Ibrahim, Amgen, Chiesi, Astra-Zeneca, Daiichi-Sankyo, Ionis pharmaceuticals, Medpace, Lib-therapeutics, Lilly, MSD, Novartis, NovoNordisk, Pfizer, Recordati, Servier, and Ultragenyx.

REFERENCES

1. Alagarsamy J, Jaeschke A, Hui DY. Apolipoprotein E in cardiometabolic and neurological health and diseases. *Int J Mol Sci*. 2022;23(17):9892. [CrossRef]
2. Bennet AM, Di Angelantonio E, Ye Z, et al. Association of apolipoprotein E genotypes with lipid levels and coronary risk. *JAMA*. 2007;298(11):1300-1311. [CrossRef]
3. Dogsom O, Punsaldulam A, Dogsom O, et al. Apolipoprotein E genotype and coronary heart disease in a Mongolian cohort: an exploratory case–control study. *Anatol J Cardiol*. 2026. [CrossRef]
4. Jackson RJ, Hyman BT, Serrano-Pozo A. Multifaceted roles of APOE in Alzheimer disease. *Nat Rev Neurol*. 2024;20(8):457-474. [CrossRef]
5. Kayikcioglu M, Ozkan HS, Yagmur B. Premature myocardial infarction: a rising threat. *Balk Med J*. 2022;39(2):83-95. [CrossRef]
6. Li Y, Zhong W, Huang C, Peng J, Li H. Apolipoprotein E E3/E4 genotype is associated with an increased risk of premature coronary artery disease. *BMC Cardiovasc Disord*. 2024;24(1):353. [CrossRef]
7. Fagan AM, Holtzman DM, Munson G, et al. Unique lipoproteins secreted by primary astrocytes from wild type, apoE (-/-), and human apoE transgenic mice. *J Biol Chem*. 1999;274(42):30001-30007. [CrossRef]
8. Zhao J, Davis MD, Martens YA, et al. APOE ε4/ε4 diminishes neurotrophic function of human iPSC-derived astrocytes. *Hum Mol Genet*. 2017;26(14):2690-2700. [CrossRef]
9. Montagne A, Nation DA, Sagare AP, et al. APOE4 leads to blood–brain barrier dysfunction predicting cognitive decline. *Nature*. 2020;581(7806):71-76. [CrossRef]
10. Haney MS, Pálovics R, Munson CN, et al. APOE4/4 is linked to damaging lipid droplets in Alzheimer's disease microglia. *Nature*. 2024;628(8006):154-161. [CrossRef]
11. Fortea J, Pegueroles J, Alcolea D, et al. APOE4 homozygozity represents a distinct genetic form of Alzheimer's disease. *Nat Med*. 2024;30(5):1284-1291. [CrossRef]
12. Na S, Muir K, Lophatananon A, Huang Y, Lee J. Physical activity and Alzheimer's disease risk across genetic susceptibility: a prospective UK Biobank study using accelerometer data. *J Neurol*. 2026;273(1):1. [CrossRef]