Research article

Association between apolipoprotein E gene polymorphisms and serum lipid indicators and Alzheimer's disease risk

Journal of Alzheimer's Disease
1–9

DOI: 10.1177/13872877261416064
journals.sagepub.com/home/alz

Honghai Chen[1], Huiming Zhang[2], Miaomiao Yang[3], Qianyun Xie[3] and Lin Zhu[4,5]

Abstract

Background: Apolipoprotein E (*APOE*) polymorphisms, particularly the *APOE4* genotype, are established genetic risk factors for Alzheimer's disease (AD). However, the clinical utility of combining *APOE* genotypes with serum lipids and blood-based AD biomarkers remains incompletely defined.

Objective: To investigate the association between *APOE* gene polymorphisms, serological indicators, and the occurrence of AD.

Methods: Blood samples of 109 patients with AD and 85 non-AD participants were used to detect *APOE* genotypes. Serum levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), amyloid-β 1–42 ($A\beta_{1-42}$), and p-tau-181 were measured. Receiver operating characteristic analysis was performed in an independent validation set of 82 cases.

Results: The frequency of the *APOE4* genotype was significantly higher in the AD group compared with the non-AD group, whereas *APOE2* and *APOE3* genotypes showed no significant differences. TC, HDL-C, and LDL-C levels were significantly elevated in the AD group compared with the non-AD group, while TG, $A\beta_{1-42}$, and p-tau-181 levels did not differ significantly. Among patients with AD carrying the *APOE4* genotype, TC and LDL-C levels were significantly higher than those in non-AD *APOE4* carriers. Further, within the AD group, *APOE4* carriers had a significantly higher proportion of elevated TC and LDL-C levels than non-*APOE4* carriers. Validation experiments revealed that the combination of *APOE4* genotype with elevated TC and LDL-C demonstrated greater diagnostic efficacy for AD.

Conclusions: *APOE4* genotype combined with elevated TC and LDL-C levels strongly correlate with AD onset and may be valuable auxiliary biomarkers for AD diagnosis and treatment.

Keywords

Alzheimer's disease, apolipoprotein E gene polymorphisms, diagnosis, serological indicators

Received: 18 September 2025; accepted: 9 December 2025

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder, clinically manifested by memory impairment, executive dysfunction, loss of the ability to perform activities of daily living, and is often accompanied by emotional and behavioral disturbances.[1] According to the World Alzheimer Report 2018, approximately 50 million people worldwide lived with dementia in 2018, with the number projected to increase to 152 million by 2050.[2] Additionally, the global cost of dementia is estimated to reach US$2 trillion by 2030, more than twice the expenditure in 2018. As the most populous country facing accelerated aging, China now considers AD to be a critical public health challenge. However, the pathophysiological mechanisms underlying

[1]Department of Molecular Biology Laboratory, Shenyang Fifth People's Hospital, Shenyang, Liaoning, China
[2]College of Biomedical and Chemical Engineering, Liaoning Institute of Science and Technology, Benxi, Liaoning, China
[3]Pathology and Pathophysiology, School of Basic Medicine, Shenyang Medical College, Shenyang, Liaoning, China
[4]Department of Biochemistry and Molecular Biology, School of Basic Medicine, Shenyang Medical College, Shenyang, Liaoning, China
[5]Liaoning Province Key Laboratory for Phenomics of Human Ethnic Specificity and Critical Illness, Shenyang Medical College, Shenyang, Liaoning, China

Corresponding author:
Lin Zhu, Department of Biochemistry and Molecular Biology, School of Basic Medicine, Shenyang Medical College, 146 Huanghe North Street, Yuhong District, Shenyang, Liaoning, 110034, China.
Email: zhulin@symc.edu.cn

AD remain incompletely understood. Current research highlights the amyloid cascade hypothesis and tau protein pathology as the predominant pathological theories.[3]

Apolipoprotein E (ApoE) is a polymorphic protein that plays a critical role in lipid transport and metabolism in vivo. Studies have shown that *APOE* gene polymorphisms are of substantial relevance to human health and disease, owing in particular to their strong association with AD, making ApoE the most prominent genetic risk factor for AD prognosis.[4] The *APOE* gene is located on the long arm of human chromosome 19 (19q13.2) and encodes a glycoprotein rich in arginine (Arg). There are three common *APOE* alleles, namely *E2*, *E3*, and *E4*, and their combinations give rise to six distinct genotypes. In our study, three *APOE* genotype groups were used for analysis: *APOE2* (*E2*/*E2* and *E2*/*E3*), *APOE3* (*E2*/*E4* and *E3*/*E3*), and *APOE4* (*E3*/*E4* and *E4*/*E4*).[5] These alleles differ at codons 112 and 158. The *E3* allele encodes cysteine (Cys) at codon 112 and Arg at codon 158. The *E2* allele encodes Cys at both positions. The *E4* allele encodes Arg at both positions. Despite these seemingly minor amino acid substitutions, they result in significant alterations in ApoE protein structure and physicochemical properties, ultimately impacting its biological function.[6]

ApoE acts as a key ligand for members of the low-density lipoprotein receptor (LDLR) family, facilitating receptor-mediated uptake and catabolic processing of triglyceride (TG)-rich lipoprotein remnants and low-density lipoprotein (LDL).[7] ApoE3 exhibits a high binding affinity for LDLR, efficiently promoting lipoprotein metabolism and clearance, thereby maintaining normal plasma lipid levels. In contrast, ApoE2 displays a reduced LDLR-binding affinity, leading to diminished efficiency in lipoprotein metabolism, elevated plasma total cholesterol (TC) and TG concentrations, and consequently an increased risk of atherosclerosis.[8] Although ApoE4 maintains a high LDLR binding affinity, it may pursue abnormal metabolic pathways in cells, which can also adversely affect lipid metabolism.[8] In the nervous system, ApoE is engaged in multiple physiological processes essential for neuronal growth, repair, and survival. By binding to neuronal surface receptors, ApoE facilitates the transport of TC and other lipids, providing essential biochemical components for neuronal membrane repair and synaptogenesis.

The various *APOE* isoforms exhibit differential neurobiological functions. The *E3* isoform demonstrates relatively superior neuroprotective and neurorestorative effects. In contrast, the *E4* isoform is associated with increased neuronal damage and apoptosis, potentially inducing neurodegeneration through multiple mechanisms, including enhanced tau protein phosphorylation, Aβ aggregation and deposition, and disrupted intracellular signal transduction.[9] Accordingly, *APOE* polymorphism constitutes a major genetic risk factor for AD. The *APOE4* genotype is a well-established genetic determinant of AD, with carriers exhibiting markedly increased risk and earlier disease onset compared with non-carriers.[10] Studies have shown that ApoE4 contributes to the pathogenesis of AD through multiple mechanisms, including promoting Aβ aggregation, inducing neuro-inflammatory responses, disrupting mitochondrial function, and impairing neuronal repair and regeneration.[11] These multifaceted effects underscore the central role of ApoE4 in AD progression.

Currently, the clinical diagnosis of AD relies primarily on neuroimaging techniques. However, these methods detect AD only at the middle-to-late stages, thus failing to achieve prevention or early diagnosis. Additionally, neuropsychological assessments also exhibit limited sensitivity for early detection of AD-related pathological changes, and the high rates of misdiagnosis and missed diagnosis affect the early intervention and treatment of patients. Emerging evidence indicates that serum metabolic profiles in patients with AD are closely associated with disease progression.[12] Compared with other diagnostic approaches, blood-based biomarker assays offer distinct advantages, including minimal invasiveness, operational simplicity, and suitability for continuous monitoring, making them particularly suitable for large-scale screening and long-term surveillance of patients.[13] However, the integration of blood biomarker analysis with serum metabolic indicators has not yet been incorporated into standardized AD screening protocols.

This study investigated the relationship between blood biomarkers and serum metabolic indicators in the pathogenesis of AD and evaluated their diagnostic utility. Through systematic evaluation of these parameters, we aimed to establish an early screening approach for AD to enable timely clinical intervention for prevention and mitigation of disease progression.

Methods

Study population

A total of 194 patients were retrospectively enrolled for this study from Shenyang Fifth People's Hospital, Liaoning, China, between August 1, 2022, and August 25, 2024, including 109 patients with AD (AD group) and 85 non-AD controls (non-AD group). The patient selection flowchart is presented in Figure 1.

An additional validation cohort of 82 patients was recruited from the same institution between August 26, 2024, and July 11, 2025, to evaluate the diagnostic efficacy of *APOE4* genotype occurrence in combination with serum levels of elevated TC and low-density lipoprotein cholesterol (LDL-C) in patients with AD.

This retrospective study was approved by the Ethics Committee of Shenyang Fifth People's Hospital, Liaoning, China (NO. S2024-001-01).

Materials

The following items were employed in this study: Aβ1–42 kit and p-tau-181 kits (Fujian Yitong Biotechnology Co,

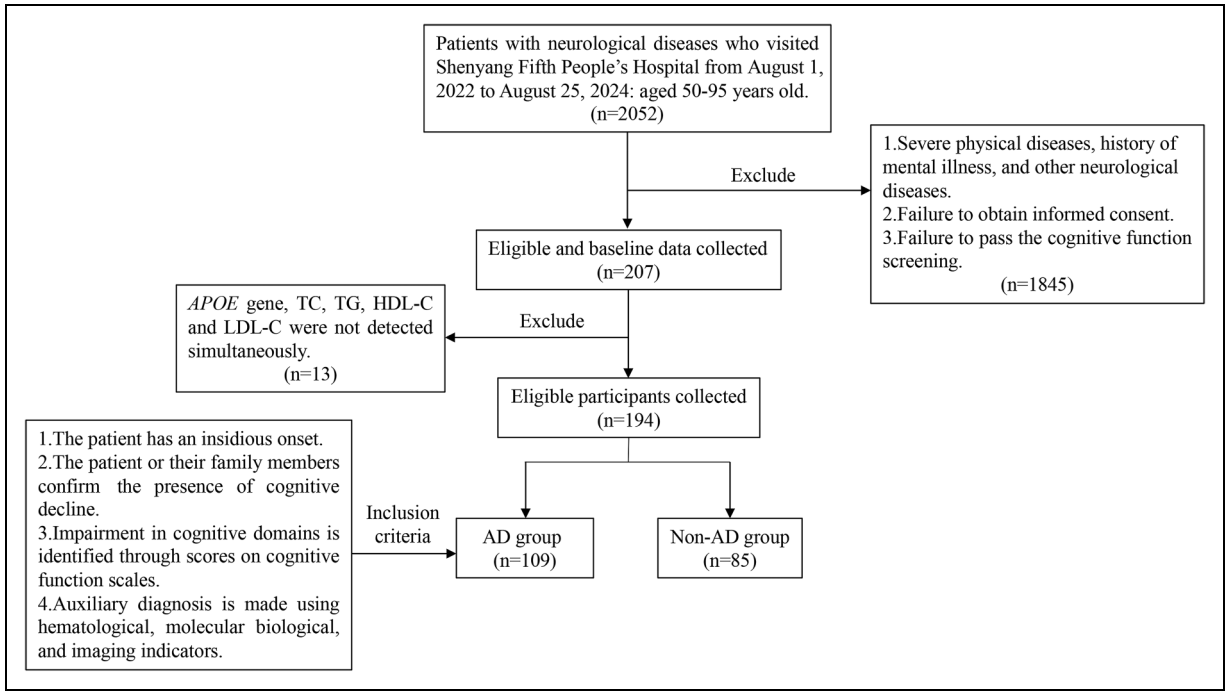

Figure 1. Screening process for patients in the AD and non-AD groups.

Ltd); TG kit, TC kit, high-density lipoprotein cholesterol (HDL-C) kit, and LDL-C kit (Beckman Coulter, Inc.); *APOE* diagnostic kit (Tianlong Technology Co, Ltd).

Beckman AU5800 automatic biochemical analyzer (Beckman Coulter, Inc.); Fascan48E instrument (Tianlong Technology Co, Ltd); microplate reader (Tecan Group Ltd).

Detection of the APOE genotype

Venous blood (2–3 mL) samples were collected from each participant into collection tubes containing anticoagulant. The anticoagulant was thoroughly mixed with the venous blood, and 10 μL of the mixture was added to the universal sample diluent. A 2 μL aliquot of each sample was dispensed into an 8-well strip, incubated at 37°C for 3 min, followed by immediate centrifugation at 6000 rpm for 40 s. After gentle mixing, samples were centrifuged again at 6000 rpm for 5 s, and subsequently analyzed using the Fascan48E sequencing instrument. The assay was considered valid when the SNP-U24 positive control signal value was ≥1 and the negative control signal value was <1. Sample signal values ≥1 were classified as positive, while values <1 were classified as negative. Genotype determination at the target SNP loci was subsequently performed based on these classifications.

Detection of serological indicators

Detection of serum lipid levels. Fasting venous blood samples (5 mL) were collected from the antecubital vein of patients in the morning using tubes containing anticoagulant. The samples were then centrifuged at 3000 rpm for 15 min to separate the serum. The levels of TC, TG, HDL-C, and LDL-C were detected using a Beckman AU5800 automatic biochemical analyzer.

The normal reference range of values was as follows: TC (3.1–5.17 mM); TG (0.4–1.8 mM); HDL-C (1.29–1.55 mM); LDL-C (2.7–3.36 mM).

Detection of serum $A\beta_{1-42}$ and p-tau-181 levels. Samples containing tau and Aβ proteins were centrifuged at 3000 rpm for 15 min. The supernatant was collected and added to the microplate, followed by incubation for 1–2 h. After incubation, the solution was decanted from the wells, and each well was washed 3–5 times with washing buffer. Enzyme-labeled secondary antibody was added to each well and incubated for 60 min. After washing again, substrate solution was added to each well. The microplate reader was used to detect the protein concentration.

A blank control was used to create a no-substrate reference value in the instrument at a wavelength of 450 nm, and measurements were acquired at dual wavelengths of 450/630 nm to determine the optical density value of each well. The concentrations of tau and Aβ proteins in the samples were calculated using the standard curve method.

The following normal reference range of values were employed: $A\beta_{1-42}$ (0–110 pg/mL); p-tau-181 (0–30 pg/mL).

Identification of characteristic indicators

The diagnostic efficacy of various factors relevant to AD was evaluated using the area under the curve (AUC) of

Table 1. Analysis of gender, age, and use of lipid-lowering drugs in enrolled patients.

	Gender (%)		Age (%)			
	Male	Female	40–60 years	61–80 years	81–100 years	Lipid-lowering medication use (%)
AD (n = 109)	34.5	65.5	14.5	61.8	23.7	3.6
Non-AD (n = 85)	48.2	51.8	18.8	70.6	10.6	2.4
χ^2	3.7287		5.6449			0.1397
p	0.0535		0.0595			0.7086

the receiver operating characteristic (ROC) curve. The diagnostic efficacy of AD was analyzed in *APOE4* genotype-positive individuals displaying elevated TC and LDL-C levels, as well as in those with the *APOE4* genotype alone.

The judgment criteria were as follows: Outstanding discrimination (AUC > 0.9); Excellent discrimination (0.8 < AUC ≤ 0.9); Acceptable discrimination (0.7 < AUC ≤ 0.8); Poor discrimination (0.5 < AUC ≤ 0.7); No discrimination (AUC = 0.5).

Statistical methods

All statistical analyses were conducted using GraphPad Prism software (version 8.0). Continuous variables are presented as the mean ± standard deviation (SD) and were compared between two groups using an independent samples t-test. Categorical data are presented as counts and percentages (n, %) and were analyzed using the χ^2 test. A p-value < 0.05 was considered statistically significant.

Results

Baseline patient information

This study included participants recruited from Shenyang Fifth People's Hospital, China, between August 1, 2022, and August 25, 2024. Clinical data, including *APOE* genotypes and lipid profiles, were collected. The final analysis included 109 patients with AD and 85 non-AD controls who met the inclusion criteria and had complete *APOE* genotyping and lipid profile data. A comparison of the baseline characteristics between the AD and non-AD groups revealed no statistically significant differences in sex, age, or the use of lipid-lowering medications (Table 1). This comparability suggests that these variables are unlikely to confound the subsequent analyses.

The role of APOE gene polymorphism and serological indicators in AD diagnosis

Distribution of APOE genotypes and serological indicators in AD and non-AD groups. ApoE, a plasma transport glycoprotein involved in cholesterol metabolism, is widely expressed in both peripheral tissues and the central nervous system. Among its isoforms, *APOE4* has been consistently identified as the strongest genetic risk factor for late-onset AD.[14] In our present study, we first compared the distribution of *APOE* genotypes between AD and non-AD groups. Our results showed that the frequency of occurrence of the *APOE4* genotype was significantly higher in the AD group, whereas the distributions of *APOE2* and *APOE3* genotypes did not differ significantly between AD and non-AD groups (Table 2). These findings suggest that carriers of the *APOE4* genotype may have a higher risk of developing AD compared with *APOE2* or *APOE3* carriers, which is consistent with previous studies, and highlights the pivotal role of *APOE4* in AD pathogenesis.

With respect to peripheral lipid metabolism, we observed that serum levels of TC, HDL-C, and LDL-C were significantly higher in the AD group compared with the non-AD group (Figure 2A). These alterations suggest that dyslipidemia may play an important role in the pathogenesis and progression of AD. In particular, elevated LDL-C levels may exacerbate AD pathology through mechanisms such as promoting neuro-inflammation, and blood-brain barrier (BBB) dysfunction.[15] Conversely, serum levels of TG, $A\beta_{1-42}$, and p-tau-181 showed no significant differences between the AD and non-AD groups (Figure 2A and B). Collectively, these findings further emphasize the importance of the *APOE4* genotype as a genetic risk factor for AD and suggest that abnormalities in serum lipid markers (TC, HDL-C, LDL-C) may be closely associated with the development of AD.

Serological indicator levels in APOE4 genotype carriers between AD and non-AD groups. To further explore more accurate auxiliary diagnostic criteria for AD, we conducted a stratified analysis specifically on patients carrying the *APOE4* genotype.

Table 2. Comparison of *APOE* genotypes [n (%)].

Group	*APOE2*	*APOE3*	*APOE4*
AD (n = 109)	6 (5.5%)	64 (58.7%)	39 (35.8%)
Non-AD (n = 85)	6 (7.1%)	63 (74.1%)	16 (18.8%)
χ^2	0.1753	1.0362	3.853
p	0.7683	0.3598	0.0497

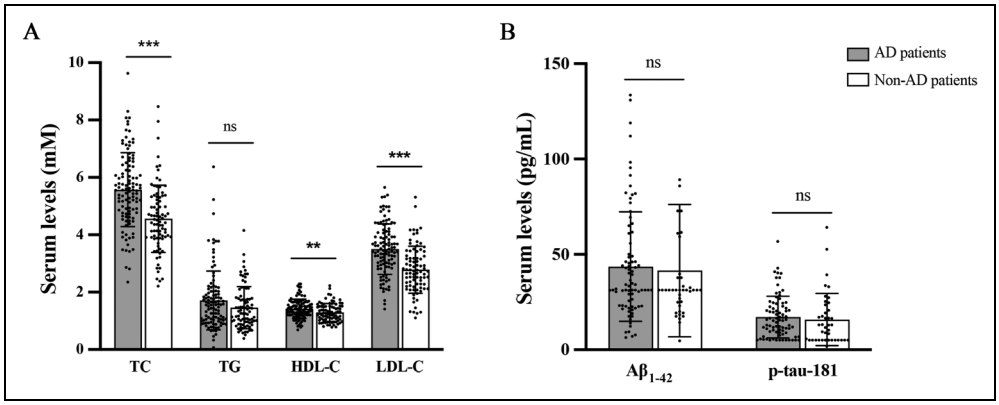

Figure 2. Comparison of serum indicator levels in patients with AD. (A) Serum levels of TC, TG, HDL-C, and LDL-C in AD and non-AD patients. AD patients, n = 109; non-AD patients, n = 85. (B) Serum levels of $A\beta_{1-42}$ and p-tau-181 in AD and non-AD patients. AD patients, n = 81; non-AD patients, n = 41. Values are expressed as mean ± SD and ***$p < 0.001$; ns: not significant.

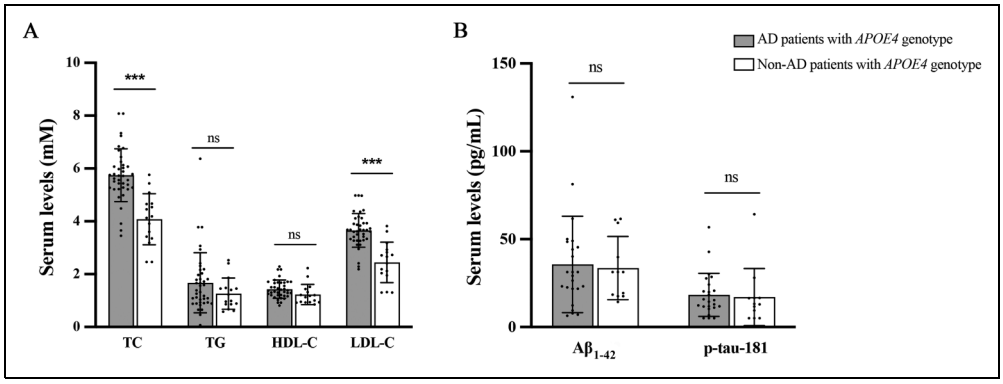

Figure 3. Comparison of serum indicator levels between AD and non-AD patients carrying the *APOE4* genotype. (A) Serum levels of TC, TG, HDL-C, and LDL-C in AD and non-AD patients with *APOE4* genotype. AD patients, n = 39; non-AD patients, n = 16. (B) Serum levels of $A\beta_{1-42}$ and p-tau-181 in AD and non-AD patients with *APOE4* genotype. AD patients, n = 24; non-AD patients, n = 12. Values are expressed as mean ± SD and ***$p < 0.001$; ns: not significant.

The results revealed that serum levels of TC and LDL-C were significantly higher in *APOE4* carriers with AD compared to *APOE4* carriers without AD (Figure 3A). In contrast, no significant differences were observed in serum TG, HDL-C, $A\beta_{1-42}$, or p-tau-181 levels between *APOE4* carriers in the AD and non-AD groups (Figure 3A and B). These findings suggest that elevated serum TC and LDL-C levels may be closely associated with the occurrence of AD in the context of the *APOE4* genotype. This observation provides a novel perspective on the interaction between *APOE4* and lipid metabolism in AD pathogenesis.

Serological indicator levels in patients with AD: comparison between the APOE4 and non-APOE4 genotypes. Further analysis within the AD group revealed that the proportion of patients carrying the *APOE4* genotype with elevated serum TC and LDL-C levels was significantly higher than that of non-*APOE4* carriers exhibiting increased levels of these serological indicators (Table 3). These findings indicate that the *APOE4* genotype and elevated TC and LDL-C levels may exert a synergistic effect, thereby increasing the risk of AD. This result provides novel evidence for the interaction between genetic susceptibility and lipid metabolism, offering a potential theoretical basis for precision prevention strategies in high-risk populations.

Association of APOE4 genotype with elevated serum TC and LDL-C levels and AD diagnosis

APOE4 genotype with increased serum TC and LDL-C levels in AD diagnosis. To investigate the association between the *APOE4* genotype, serum levels of TC, LDL-C, and the occurrence of AD, *APOE* genotyping was performed in 82 patients recruited from Shenyang Fifth People's Hospital, China, between August 26, 2024, and July 11, 2025. The results demonstrated that the rate of AD diagnosis was significantly higher among *APOE4* carriers

Table 3. Comparison of serum TC and LDL-C levels between patients with *APOE4* genotype and non-*APOE4* genotype in the AD group [n (%)].

Genotype	Elevated TC and LDL-C	TC, LDL-C other levels
APOE4	27 (69.2%)	12 (30.8%)
non-*APOE4*	33 (47.1%)	37 (52.9%)
χ^2	4.938	
p	0.0292	

Table 4. Ad diagnosis status among *APOE4* carriers [n (%)].

Genotype	Diagnose AD	Not diagnosed with AD
APOE4 (n = 19)	12 (63.2%)	7 (36.8%)
non-*APOE4* (n = 63)	4 (6.3%)	59 (93.7%)
χ^2	29.9967	
p	<0.001	

Table 5. Ad diagnosis status among *APOE4* carriers with elevated TC and LDL-C levels [n (%)].

APOE4 genotype	Diagnose AD	Not diagnosed with AD
Elevated TC and LDL-C levels (n = 11)	10 (90.9%)	1 (9.1%)
Other levels of TC and LDL-C (n = 8)	2 (25%)	6 (75%)
χ^2	8.6467	
p	0.0063	

compared with non-*APOE4* carriers (Table 4). These findings suggest that the *APOE4* genotype confers an increased risk for AD, consistent with its established role as a major genetic susceptibility factor.

Further analysis of the combined effect of the *APOE4* genotype and elevated serum lipid levels revealed that *APOE4* carriers with elevated TC and LDL-C concentrations had a significantly higher rate of AD diagnosis compared with *APOE4* carriers with normal lipid levels (Table 5). These findings indicate that, in addition to genetic susceptibility, dyslipidemia (particularly elevated TC and LDL-C concentrations) may further contribute to AD risk among *APOE4* carriers, highlighting the potential value of a comprehensive assessment that integrates both genetic and lipid profiles.

Diagnostic efficacy of APOE4 genotype with serum TC and LDL-C in AD. To further evaluate the diagnostic value, we employed ROC curve analysis to show the diagnostic performance of a single genetic indicator (*APOE4* genotype alone) and a combined genetic and metabolic indicator (*APOE4* genotype with elevated serum TC and LDL-C levels). Our results demonstrated that the combined model (*APOE4* genotype with elevated TC and LDL-C levels) achieved an AUC value of 0.8742, indicating high diagnostic accuracy, whereas the *APOE4*-only model yielded an AUC value of 0.8244, indicating moderate diagnostic performance (Figure 4). These findings revealed that incorporating elevated serum TC and LDL-C levels into the *APOE4* genotype-based risk assessment increased diagnostic performance, with a smaller standard error and a higher upper Confidence Interval limit (Table 6). Our data indicate that a combination of the *APOE4* genotype and elevated serum TC and LDL-C levels provides higher sensitivity and accuracy for early detection of AD, as well as providing a potential reference for personalized screening and precision intervention.

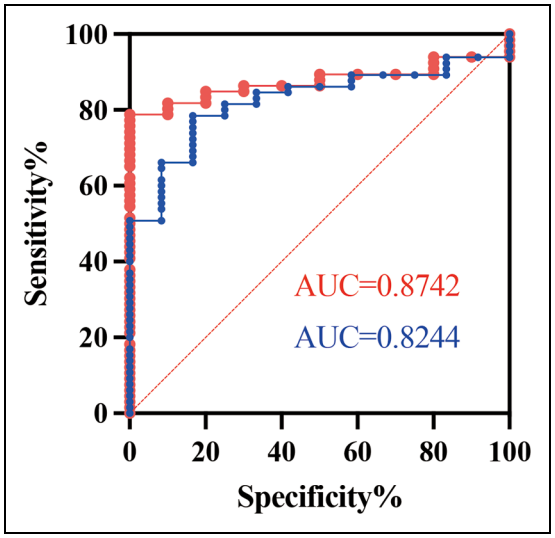

Figure 4. ROC analysis of the diagnostic efficacy for AD. Blue: *APOE4* genotype. Red: *APOE4* genotype with elevated TC and LDL-C levels.

Discussion

AD, a common neurodegenerative disorder, accounts for approximately 60–80% of dementia cases. Reportedly, an estimated 15.07 million individuals aged 60 years and older are living with dementia in China, of whom 9.83 million are affected by AD.[16] AD imposes a substantial burden on patients, families, and society, representing a major global public health challenge. The disease onset is insidious, with early symptoms often being subtle, leading to diagnosis at the middle-to-late stages. Therefore, the identification of reliable biomarkers for early diagnosis is crucial to reducing incidence, slowing progression, and mitigating the associated societal and familial burden of this disease.

The precise etiology of AD remains incompletely understood. Current hypotheses suggest that its pathogenesis may

Table 6. Evaluation of diagnostic efficacy for AD.

	APOE4 genotype with elevated TC and LDL-C levels	*APOE4* genotype
AUC	0.8742	0.8244
Std. Error	0.0391	0.0507
95%CI	0.7977–0.9508	0.7250–0.9237
p	<0.001	<0.001

involve Aβ deposition, and neurofibrillary tangles resulting from tau hyperphosphorylation.[17] However, our study found no significant differences in serum levels of $A\beta_{1-42}$ and p-tau-181 patients with AD patients and non-AD controls. The reason for this could be that Aβ and p-tau are primarily generated in the brain, and their transfer into the peripheral circulation is limited by the BBB.[18] Consequently, serum levels of Aβ and p-tau may inadequately reflect the pathological changes occurring in the brain, thereby limiting the diagnostic sensitivity and specificity of these biomarkers. Currently, the genetic predisposition to *APOE* polymorphism is a well-established contributor to AD.[19,20] The *APOE4* genotype is recognized as the strongest genetic susceptibility factor for late-onset AD, which exhibits a 3- to 4-fold increased risk relative to the general population.[21] Consistent with previous findings, our study demonstrated that the frequency of *APOE4* carriers was significantly higher in the AD than the non-AD group. ApoE is also a crucial protein involved in regulating lipid metabolism and cholesterol homeostasis. Notably, we observed that serum levels of TC, HDL-C, and LDL-C were significantly elevated in patients with AD. The increase in HDL-C levels, which has been regarded as a "beneficial cholesterol" due to its role in promoting reverse cholesterol transport, was unexpected in AD.[22] This phenomenon warrants further investigation and may be associated with compensatory regulation, alterations in lipoprotein subclasses, or dysregulation of lipid transport within the brain.

The transport of lipids across the BBB relies on ApoE-mediated mechanisms. Disruption of this process can impair the delivery of essential lipids to neurons, thereby compromising membrane integrity, synaptic function, and overall brain homeostasis.[23] Furthermore, ApoE4 exhibits a lower binding affinity to LRP1 on the luminal side of brain endothelial cells compared with ApoE3. This reduced affinity diminishes the efficiency of cholesterol transport into the brain parenchyma.[24] Compared with *APOE3* and *APOE2*, *APOE4* is also less efficient in promoting cholesterol efflux from neurons, leading to intracellular cholesterol accumulation.[25] Our current study found that serum levels of TC and LDL-C were significantly higher in *APOE4* carriers compared with non-*APOE4* carriers in the AD group. Additionally, among patients with AD, the proportion of patients carrying the *APOE4* genotype with elevated TC and LDL-C levels was significantly higher than those without the *APOE4* genotype but with elevated TC and LDL-C levels. These findings suggest that the combination of the *APOE4* genotype and elevated TC and LDL-C levels may be closely associated with AD. Beyond its role in lipid dysregulation, ApoE4 can also activate the cyclophilin A-matrix metalloproteinase-9 pathway in pericytes and endothelial cells, causing damage to BBB integrity.[26] Additionally, ApoE4 modulates inflammatory pathways and promotes microglial activation, fostering a neurotoxic environment in the brain.[27]

Current clinical imaging techniques, such as positron emission tomography and magnetic resonance imaging, enable the visualization of pathological changes during AD progression. However, this approach often detects AD only at the middle-to-late stages, making it difficult to achieve early diagnosis and effective prevention. Our current findings suggested that the potential utility of combining the *APOE4* genotype with elevated TC and LDL-C levels for early screening and stratified management of individuals at high-risk for AD in clinical practice. To quantify this effect, ROC curve analyses were used to evaluated diagnostic performance. Our analyses confirmed that the model incorporating both the *APOE4* genotype and elevated TC and LDL-C levels achieved superior predictive accuracy for AD. Importantly, these findings suggest that, among *APOE4* carriers, dynamic monitoring of lipid profiles should be strengthened. Early and targeted interventions, including dietary modifications, a structured exercise regimen, and pharmacological treatment should be implemented to manage dyslipidemia, which may delay or reduce the risk of developing AD.

By integrating specific serological markers with *APOE* gene polymorphism and comprehensively analyzing their synergistic role in AD risk, this study reveals that the *APOE4* genotype combined with elevated TC and LDL-C levels may be closely associated with AD. This approach overcomes the limitations of single-factor studies, enabling a more precise and comprehensive understanding of disease risk. It addresses a key gap in the field, reinforces the evidence supporting early clinical diagnosis and intervention, and advances the development of strategies for the prevention and treatment of AD.

Specifically, our analyses focused only on *APOE* polymorphisms and a limited set of serum biomarkers, and that we did not assess other AD-related genes (e.g., *APP*, *PSEN1*, and *PSEN2*) or systematically distinguish familial, early-onset, or atypical AD subtypes. Therefore, larger multicenter studies with broader genetic panels and detailed phenotyping are needed to clarify how *APOE* interacts with other mutations and sporadic risk factors in AD.

Ethical considerations

All study procedures and experimental protocols were approved by the Ethics Committee of Shenyang Fifth People's Hospital (NO. S2024-001-01).

Consent to participate

The informed consent was obtained from all patients.

Author contribution(s)

Honghai Chen: Data curation; Formal analysis; Methodology; Writing – original draft.
Huiming Zhang: Data curation; Methodology; Software.
Miaomiao Yang: Funding acquisition; Software.
Qianyun Xie: Investigation; Software.
Lin Zhu: Conceptualization; Methodology; Writing – review & editing.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The work was supported by the Graduate Science and Technology Innovation Fund Project of Shenyang Medical College (Y20240517).

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

Individual-level data are not publicly available due to participant privacy and ethical restrictions. Aggregated data and de-identified data may be made available from the corresponding author upon reasonable request, subject to approval by the relevant ethics and data governance requirements.

ORCID iD

Lin Zhu https://orcid.org/0000-0002-3955-1489

References

1. Knopman DS, Amieva H, Petersen RC, et al. Alzheimer disease. *Nat Rev Dis Primers* 2021; 7: 33.
2. Patterson C. *World Alzheimer Report 2018. The state of the art of dementia research: New frontiers*. London, UK: Alzheimer's Disease International, 2018.
3. Qiu T, Liu ZQ, Rheault F, et al. Structural white matter properties and cognitive resilience to tau pathology. *Alzheimers Dement* 2024; 20: 3364–3377.
4. Jiang X, Lacey C, Paterson T, et al. Impact of APOE-ε alleles on brain structure and cognitive function in healthy older adults: a VBM and DTI replication study. *PLoS One* 2024; 19: e0292576.
5. Long L and Sun Q. Analysis of APOE and SLCO1B1 gene polymorphism and correlation with dyslipidemia in China. *Clin Lab* 2022; 68: 220143.
6. Otmane A, Makrelouf M and Zenati A. Apo E gene polymorphism (C112r, R158c) and lipid profile in hypertensive patients. *J Hypertens* 2022; 40: e226.
7. Marais AD. Apolipoprotein E in lipoprotein metabolism, health and cardiovascular disease. *Pathology* 2019; 51: 165–176.
8. Johnson LA, Olsen RHJ, Merkens LS, et al. Apolipoprotein E-low density lipoprotein receptor interaction affects spatial memory retention and brain ApoE levels in an isoform-dependent manner. *Neurobiol Dis* 2014; 64: 150–162.
9. Shafagoj YA, Naffa RG, El-Khateeb MS, et al. APOE Gene polymorphism among Jordanian Alzheimer's patients with relation to lipid profile. *Neurosciences* 2020; 23: 29–34.
10. Lin Y-T, Seo J, Gao F, et al. APOE4 Causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types. *Neuron* 2018; 98: 1294.
11. Wadhwani AR, Affaneh A, Van Gulden S, et al. Neuronal apolipoprotein E4 increases cell death and phosphorylated tau release in Alzheimer disease. *Ann Neurol* 2019; 85: 726–739.
12. Gao F, Lv X, Dai L, et al. A combination model of AD biomarkers revealed by machine learning precisely predicts Alzheimer's dementia: China aging and neurodegenerative initiative (CANDI) study. *Alzheimers Dement* 2022; 19: 749–760.
13. Ruan T, Ling Y, Wu C, et al. Abnormal epigenetic modification of lysosome and lipid regulating genes in Alzheimer's disease. *J Alzheimers Dis* 2025; 104: 1185–1200.
14. Zhao J, Fu Y, Yamazaki Y, et al. APOE4 Exacerbates synapse loss and neurodegeneration in Alzheimer's disease patient iPSC-derived cerebral organoids. *Nat Commun* 2020; 11: 5540.
15. Lin H, Pan T, Wang M, et al. Metabolic asymmetry relates to clinical characteristics and brain network abnormalities in Alzheimer's disease. *J Alzheimers Dis* 2023; 93: 1395–1406.
16. Jia L, Du Y, Chu L, et al. Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: a cross-sectional study. *Lancet Public Health* 2020; 5: e661–e671.
17. Tao B, Gong W, Xu C, et al. The relationship between hypoxia and Alzheimer's disease: an updated review. *Front Aging Neurosci* 2024; 16: 1402774.
18. Tang Y, Song X, Xiao M, et al. Inhibition of Aβ aggregation and tau phosphorylation with functionalized biomimetic nanoparticles for synergic Alzheimer's disease therapy. *ACS Appl Mater Interfaces* 2024; 16: 61774–61786.
19. Lou T, Tao B and Chen M. Relationship of apolipoprotein E with Alzheimer's disease and other neurological disorders: an updated review. *Neuroscience* 2023; 514: 123–140.
20. Martens YA, Zhao N, Liu C-C, et al. Apoe cascade hypothesis in the pathogenesis of Alzheimer's disease and related dementias. *Neuron* 2022; 110: 1304–1317.
21. Bailey M, Ilchovska ZG, Hosseini AA, et al. Impact of apolipoprotein E ε4 in Alzheimer's disease: a meta-analysis of voxel-based morphometry studies. *J Clin Neurol* 2024; 20: 469–477.

22. Rohatgi A, Westerterp M, von Eckardstein A, et al. HDL In the 21st century: a multifunctional roadmap for future HDL research. *Circulation* 2021; 143: 2293–2309.
23. Husain MA, Laurent B and Plourde M. APOE And Alzheimer's disease: from lipid transport to physiopathology and therapeutics. *Front Neurosci* 2021; 15: 630502.
24. Blanchard JW, Bula M, Davila-Velderrain J, et al. Reconstruction of the human blood-brain barrier in vitro reveals a pathogenic mechanism of APOE4 in pericytes. *Nat Med* 2020; 26: 952–963.
25. Asante I, Louie S and Yassine HN. Uncovering mechanisms of brain inflammation in Alzheimer's disease with APOE4: application of single cell-type lipidomics. *Ann N Y Acad Sci* 2022; 1518: 84–105.
26. Montagne A, Nation DA, Sagare AP, et al. APOE4 Leads to blood-brain barrier dysfunction predicting cognitive decline. *Nature* 2020; 581: 71–76.
27. Victor MB, Leary N, Luna X, et al. Lipid accumulation induced by APOE4 impairs microglial surveillance of neuronal-network activity. *Cell Stem Cell* 2022; 29: 1197–1212.e1198.