Received: 6 December 2022 | Accepted: 5 August 2023

DOI: 10.1111/bpa.13208

REVIEW

Brain Pathology

Alzheimer's disease phenotype based upon the carrier status of the apolipoprotein E ϵ4 allele

Xiao-Yu Ji[1,2] | Xin-Yuan Peng[1] | Hai-Liang Tang[3] | Hui Pan[4] | Wei-Tang Wang[1] | Jie Wu[1,2] | Jian Chen[1] | Nai-Li Wei[1]

[1]Department of Neurosurgery, The First Affiliated Hospital of Shantou University Medical College, Guangdong, China

[2]Brain Function and Disease Laboratory, Shantou University Medical College, Guangdong, China

[3]Fudan University Huashan Hospital, Department of Neurosurgery, State Key Laboratory for Medical Neurobiology, Institutes of Brain Science, Shanghai Medical College-Fudan University, Shanghai, China

[4]Shantou Longhu People's Hospital, Shantou, Guangdong, China

Correspondence
Jian Chen and Nai-Li Wei, Department of neurosurgery, The First Affiliated Hospital of Shantou University Medical College, Guangdong, 515041, China.
Email: drchen@stu.edu.cn and nlwei@stu.edu.cn

Funding information
National Natural Science Foundation of China, Grant/Award Numbers: 82201629, 82001447; Natural Science Foundation of Guangdong Province, Grant/Award Numbers: 2214050005144, 2022A1515010687; Guangdong Special Funds for Science and Technology, Grant/Award Numbers: STKJ2021077, STKJ2021075; Guangdong Basic and Applied Basic Research Foundation, Grant/Award Number: 22202104030000234; First Affiliated Hospital of Shantou University Medical College Supporting Funding, Grant/Award Number: 202003-29; 2020 Li Ka Shing Foundation Cross-Disciplinary Research, Grant/Award Numbers: 2020LKSFG01A, 2020LKSFG11C

Abstract

The apolipoprotein E *ϵ4* allele (*APOE4*) is universally acknowledged as the most potent genetic risk factor for Alzheimer's disease (AD). *APOE4* promotes the initiation and progression of AD. Although the underlying mechanisms are unclearly understood, differences in lipid-bound affinity among the three APOE isoforms may constitute the basis. The protein APOE4 isoform has a high affinity with triglycerides and cholesterol. A distinction in lipid metabolism extensively impacts neurons, microglia, and astrocytes. *APOE4* carriers exhibit phenotypic differences from non-carriers in clinical examinations and respond differently to multiple treatments. Therefore, we hypothesized that phenotypic classification of AD patients according to the status of APOE4 carrier will help specify research and promote its use in diagnosing and treating AD. Recent reviews have mainly evaluated the differences between *APOE4* allele carriers and non-carriers from gene to protein structures, clinical features, neuroimaging, pathology, the neural network, and the response to various treatments, and have provided the feasibility of phenotypic group classification based on *APOE4* carrier status. This review will facilitate the application of *APOE* phenomics concept in clinical practice and promote further medical research on AD.

KEYWORDS
Alzheimer's disease, apolipoprotein E, lipid metabolism, phenotype

1 | INTRODUCTION

Alzheimer's disease (AD) is a common neurodegenerative disease in elder people with progressive cognitive decline and psychobehavioral abnormalities [1]. It is also the primary type of dementia, occupying 60%–80% of all cases [2]. It affects 6.5 million Americans aged 65 and older today. By 2060, this number could reach 13.8 million without medical breakthroughs in preventing, curing, or slowing AD [2]. Despite advancements in clinical examination, multi-omics, and experimental techniques, the exact pathogenic mechanisms are not

Xiao-Yu Ji, Xin-Yuan Peng and Hai-Liang Tang are Co-first authors

fully understood. Both epidemiological research and genetic studies have proved that the apolipoprotein E *ϵ4* allele (*APOE4*) exhibited the most potent genetic risk factor for AD with a dose-dependent manner [3]. Apolipoprotein E (APOE) is the principal triglyceride and cholesterol (CL) carrier and plays a primary role in lipid metabolism and homeostasis in the blood and central nervous system (CNS) [4]. It has three protein isoforms (APO-E2, E3, and E4) encoded by corresponding allelic variants (*APOE-ϵ2*, *ϵ3*, and *ϵ4*) [5]. Compared to the most frequent allele *APOE3*, the carrier status of *APOE4* can greatly increase the risk of AD by 3–4 times in heterozygotes and 15 times in homozygotes, while *APOE ϵ2* can reduce the risk by 40% [6, 7]. Furthermore, *APOE4* drives pathogenesis involving both amyloid plaques (Aβ) and abnormal phosphorylation of Tau proteins [8]. Considering its detrimental effects, therapeutic approaches based on *APOE4* status are advocated [3].

Significant and extensive differences exist among APOE isoforms carrying status in clinical features, including neuroimaging, pathogenesis, inflammation, and lipid metabolism. Studies on the impact of APOE genotype on AD phenome have made great progress. Integrating the specific role of *APOE4* in AD development, this review summarizes recent progress and discusses the feasibility of phenotypic group classification using *APOE4* carrier status.

2 | STRUCTURE AND FUNCTION

2.1 | Synthesis and degradation of APOE

APOE can be synthesized in various organs, including the liver, brain, spleen, and kidneys. The brain possesses the second most APOE production in the whole body [9]. Various cells in the brain can secrete APOE, which are mainly astrocytes [10]. Neurons in the hippocampus and cortex can also synthesize APOE under injury or stress [11].

The molecular structures and functions of APOE isoforms vary because of different *APOE* genotypes. The protein APOE consists of 299 amino acids (aa), of which N-terminal domain (1–167 aa) and C-terminal domain (206–299 aa) are connected by hinges (Figure 1) [5]. The two domains are responsible for the function of APOE, with 135–150 aa being the low-density lipoprotein receptor (LDLR)-binding domain and 244–272 aa being the lipid-binding domain (Figure 1) [5]. The structures of the two domains lead to functional differences among the three isoforms. In APOE3, Cys-112 approaches Glu-109 in helix bundle 3 and Arg-61 in helix bundle 2, affecting ionic bonding in the two helix bundles [12]. Compared to APOE3, Cys-112 is replaced by Arg-114 in APOE4, which destroys the ionic effect between Glu-109 and Arg-61. The side chain of ARG-61 is removed from the

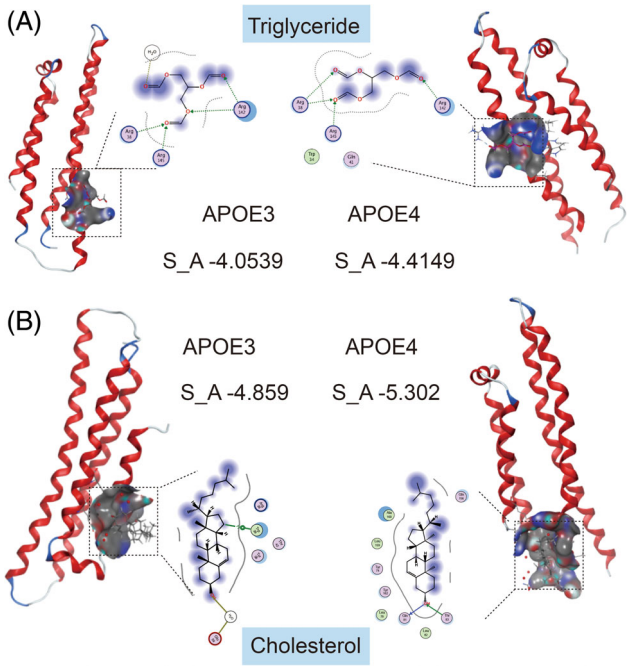

FIGURE 1 Molecular docking results indicate that the binding affinity of APOE4 with triglycerides (A) and cholesterol (B) is higher than that of APOE3.

helical bundle, and a salt bridge is formed between Arg-61 and Glu-255, thus forming an interaction between the domains and lowering the ability of APOE4 to bind to lipids (Figure 1) [5, 12]. In addition, a salt bridge exists between Asp-154 and Arg-158 in APOE3 and APOE4. In contrast to APOE3 and APOE4, with Arg-158 substituted by Cys-158, a salt bridge is formed between Asp-154 and Arg-150 in APOE2, which may separate the side chain of Arg-150 from LDLR binding domain, influencing the ability of APOE2 to bind to LDLR [5, 12]. Meanwhile, mutagenesis of aa could also affect the stability of the protein (APOE4 < APOE3 < APOE2) [13].

Apolipoprotein E undergoes proteolytic cleavage in response to many enzymes in CNS, generating truncated fragments that can be associated with neurofibrillary tangles (NFT) and mitochondrial damage [14]. The fragmentation pattern varied between isoforms, indicating different degrees of damage caused by fragmentation. Therefore, APOE4 is more likely to degenerate than APOE3, and 25 kDa N-terminal fragment in APOE4 is reduced by half compared to APOE3 brains [15]. However, a discrepancy also exists between the fragments generated by APOE3 and APOE4 [15–17]. APOE 22 kDa in the N-terminal domain can bind with their cell surface receptors and induce calcium influx and neurotoxicity. The 22 kDa fragment produced by APOE4 displays higher toxicity than APOE3 [18, 19]. Meanwhile, fragment 1–271 aa in APOE can induce NFT formation in neuronal cells in a manner of APOE4 greater than APOE3 [20, 21]. Furthermore, APOE4 fragment 1–271

aa causes AD-like Tau pathology and behavioral deficits [17], while fragment 1–272 aa promotes mitochondria dysfunction [21]. Fragments 1–185 can induce IL-1β and decrease IL-10 expression, ultimately causing an MMP9/TIMP1 imbalance [22]. In addition, increased intracellular accumulation of Aβ42, which generates reactive oxygen species (ROS) by fragment 1–165 aa, can only be found in APOE4 but not APOE3 [22, 23]. Similarly, only fragments 1–151 aa generated by APOE4 can be trafficked to the nucleus to increase cell death [24]. In brief, proteolytic APOE4 fragments may cause Tau protein phosphorylation, neurofibrillary tangles, cytoskeletal changes, and impairment of mitochondrial function, which may explain why *APOE4* has a higher risk of AD pathogenicity than *APOE3*.

2.2 | APOE and cholesterol metabolism in the brain

Cholesterol (CL) is a fundamental necessary substance for developing synapses and plays a significant role in synaptogenesis and synaptic stability [25]. CL overload often occurs in adult neurons (Table 1) because they primarily rely on exogenous CL from astrocytes [26]. In addition, CNS has a CL redistribution pathway mediated by APOE because of the presence of a blood-brain barrier [27]. Briefly, APOE is an important regulatory factor of CNS-CL metabolism.

The regulation efficiency encoded by APOE isoforms executes diversely in CL synthesis and redistribution. Multiple microRNAs of astrocytes play a role in regulating CL synthesis in neurons by increasing histone acyl-coenzymes and stimulating CL metabolism [28]. However, miRNA levels in *APOE4* carriers are much lower than those in *APOE3* carriers, which leads to higher CL levels in *APOE4* carriers [28]. Furthermore, compared to *APOE3*, the synthesis and secretion of CL decrease in *APOE4* overexpressed epithelial cells and increases in lysosomes; hence, CL produced by *APOE4* carriers is degraded more easily [29]. Additionally, poorly lipidated APOE is more likely to be decomposed [30]. As for the different domain interactions, APOE3 binds to small HDLs, whereas APOE4 prefers large VLDLs [31]. Consequently, APOE4 can degenerate more easily than APOE3, which negatively affects lipid metabolism in CNS and can eventually cause neural damage.

3 | APOE AND AD PATHOLOGY

3.1 | APOE and Aβ

Extracellular amyloid plaques are one of the pathological hallmarks of AD, which are formed by amyloid-β (Aβ) accumulation, oligomerization, and deposition. Derived from the sequential proteolytic processing of the amyloid precursor protein (APP), Aβ contributes to neurotoxicity after deposition. An autopsy cohort study reported that relative to *APOE3* homozygotes, *APOE4* is associated with more Aβ plaques and cerebral amyloid angiopathy (CAA), while *APOE2* displayed lower Aβ plaques burden and CAA [32]. Consistent with this result, another research revealed that *ApoE4* carriers had the highest percentage of Aβ lesions at all ages, and *APOE4* carriers demonstrated Aβ deposits in their 40s [33]. APOE is associated with neuroinflammatory amyloid plaques [34, 35]. Unlike ApoE3, the basement membranes formed by APOE4 astrocytes favor the aggregation of Aβ [36]. APOE isoforms differentially mediate Aβ deposition, resulting in an isoform-dependent effect on AD progression. The mechanism can be divided into APP synthesis and formation and clearance of Aβ.

APOE promotes amyloid plaque generation by increasing the synthesis of APP (rank APOE4>APOE3>APOE2) [37]. The primary mechanism is that the process of APOE binding to its receptors activates the signal of APP transcription. First, APOE binding to its receptors causes a 2–4-fold increase in the level of dual leucine zipper kinase (DLK) [37]. DLK is highly expressed in neurons and plays a part in axon growth, apoptosis, and neuron degeneration [38]. Increased DLK levels lead to phosphorylation of MKK7 (a member of the MAPK signaling pathway); then, phosphorylated MKK7 motivates phosphorylation of extracellular signal-regulated kinase (ERK1/2), ultimately stimulating transcription factor AP-1 in the nucleus [37]. Importantly, AP-1 can mediate the stimulation of APP transcription by APOE and promote a 2–6-fold increase in c-Fos phosphorylation, resulting in enhanced APP synthesis [37]. Supported by both in vivo and in vitro experiments, the same isoform-specific differences (APOE4 > APOE3 > APOE2) were observed in each of the above processes [37], proving the significant role of APOE4 in AD pathogenesis.

In addition, these three isoforms function differently in the formation and clearance of Aβ. The inhibitory effect of APOE4 on Aβ peptide formation is worse than that of APOE3 [39, 40]. In addition, studies on mice demonstrated that APOE4 could decrease Aβ clearance compared to APOE3 [41, 42]. An in vitro trial also found that ApoE4 impaired autophagy in astrocyte cultures, and this effect was associated with a reduced capacity to clear Aβ plaques [43]. Furthermore, lipid-free APOE3 and APOE4 can bind to Aβ and form stable complexes that obstruct the degeneration of Aβ so that Aβ binds more rapidly and effectively with APOE4 [44, 45]. Therefore, APOE contributes to AD in an isoform-specific way.

3.2 | APOE and the Tau protein

Microtubule-associated proteins and tubulin comprise the microtubule system, which is an essential component of the neuronal cytoskeleton. Tau protein is tubulin with

TABLE 1 Clinical features between *APOE4* carriers and non-carriers.

Study (years)	Nubmers of patients (n = *APOE4* carriers; % = *APOE4* carriers of total patients)	To investigate the impact of *APOE* genotype on clinical features	Findings
Cognitive behavior			
D. X. Rasmusson, et al. (1996)	157 AD patients (n = 112; 71.3%)	Verbal deficits (MMSE, BNT)	*APOE4* allele was related to the impairment of global cognition but not language [163].
M. Lehtovirta, et al. (1996)	58 AD patients (n = 37; 63.8%) and 16 control elder people (n = 3, 18.75%).	Neuropsychological characteristics (MMSE, Webster score, Hamilton score, Brief Cognitive ranking score)	AD patients with two ϵ4 alleles are characterized by more severe memory loss and earlier age of onset than those without the ϵ4 allele [164].
M. J. Finton, et al. (2003)	200 AD patients (n = 104; 52%)	Cognitive asymmetries (nonverbal ability and verbal cognitive ability)	*APOE4* allele carriers have relatively worse nonverbal as compared to verbal cognitive ability [165].
W. S. Houston, et al. (2005)	52 healthy older participants (n = 24; 46.15%)	Cognitive asymmetries (nonverbal ability and verbal cognitive ability)	*APOEϵ4* allele carriers demonstrated a greater frequency of cognitive asymmetric profile than non-carriers [166].
B. D. Hoyt, et al. (2005)	151 AD patients (n = 104; 68.87%)	Global and specific measures of cognitive and functional abilities (MMSE, ADAS, IADL)	*APOE*ϵ4 homozygote is associated with global cognitive functioning and functional abilities [167].
X. Wang, et al. (2015)	42 AD patients (n = 16; 38.09%)	Role of *APOE4* in cognitive profiles in AD (COMT, MMSE, CASI C-2. CERAD)	*APOEϵ4*+ exhibited poorer performance on recognition performance, but performed better on the late item generation of the verbal fluency task [168].
U. Saeed, et al. (2018)	250 AD patients and 48 DLB patients	Learning, and memory (MMSE, DRS, CVLT)	APOEϵ4+ performed worse on long-delay free word recall [169].
Neuropsychology behaviors			
C. G. Lyketsos, et al. (1999)	158 AD patients (n = 108; 68.35%) and 73 control elder people (n = 3, 27.40%)	Depression, delusions, and hallucinations in AD (BRDS, MMSE, past medical history, clinical evaluations)	Prevalence of the various psychiatric disturbances did not differ significantly in AD patients with different *APOE* genotypes [170].
C. Holmes, et al. (1998)	103 depressed AD patients (n = 30, 33%), 107 non-depressed AD patients (n = 30, 28%) and 74 elder depression patients (n = 9, 12%)	Depressive symptomatology (DSM-IV criteria, SADS-L, TICS)	The presence of the *APOE* epsilon 2 allele delayed the process of depressive illness [171].
N. Scarmeas, et al. (2002)	87 AD patients (n = 48; 55.17%)	Psychiatric symptomatology incident (CUSPAD)	*APOE4* heterozygote carried a 2.5-fold risk, whereas the homozygote carried a 5.6-fold risk for development of delusions [172].
M. W. Bondi, et al. (2003)	81 AD patients (n = 44; 54.32%) and 79 control (n = 29, 36.71%)	Neuropsychological deficits associated with age: (1) Language: Boston Naming Test, Letter and Category Fluency, and WAIS–R vocabulary; (2) executive functions: modified WCST categories and perseverative errors, trailmaking test Part B; (3) Visuoconstructive and psychomotor skills: WISC–R Block design, WAIS–R digit symbol, trailmaking test part A; (4) Immediate recall: CVLT Trials 1–5 total recall, WMS–R logical memory immediate recall; (5) Delayed recall: CVLT long-delay	Age related neuropsychological deficits with the disproportionate saliency of episodic memory and executive function deficits [173].

TABLE 1 (Continued)

Study (years)	Nubmers of patients (n = *APOE4* carriers; % = *APOE4* carriers of total patients)	To investigate the impact of *APOE* genotype on clinical features	Findings
		freeand cued-recall, WMS–R logical memory delayed recall, and (6) Recall savings: CVLT percent long-delay savings, WMS–R percent delayed recall savings.	
J. B. Chang, et al. (2004)	135 AD patients (n = 59; 43.70%)	Incidental hallucinations and delusions (CASI, CDR, SCID)	The presence of the *APOE*ϵ4 allele carried a 19.0-fold risk for developing hallucinations and a 3.4-fold risk for delusions [174].
Neuroimage			
M. Lehtovirta, et al. (1996)	58 AD patients (n = 59; 63.79%) and 34 control subjects	Relation between SPECT and MRI and apolipoprotein ϵ4 allele in AD	*APOE*ϵ4 homozygous seem to have severe damage in the medial temporal lobe structures early in the disease process and differ from the AD patients with one or no epsilon 4 alleles [175].
M. Yasuda, et al. (1998)	178 AD patients (n = 112; 65.17%)	Relationship between the *APOE* epsilon 4 allele and whole brain atrophy (MRI)	*APOE*ϵ4 alleles aggravated brain atrophy [176].
A. Fleisher, et al. (2005)	193 MCI patients (n = 112; 65.17%)	Association of sex, *APOE*ϵ4 status, and hippocampal volume in MCI (MRI)	The *APOE*ϵ4 genotype status appears to have a greater deleterious effect on gross hippocampal pathology and memory performance in women than in men [177].
L. A. van de Pol, et al. (2007)	323 MCI patients	Hippocampal atrophy rate in 2 years of follow-up (MRI)	The *APOE* epsilon 4 allele were associated with higher hippocampal atrophy rates [178].
Saira Saeed Mirza, et al. (2011)	28 AD patients (n = 14; 50%) and 28 control subjects	Hippocampal atrophy (MRI)	*APOE*ϵ4 alleles aggravated brain atrophy [179].
S. S. Mirza, et al. (2019)	289 SDC patients (239 AD+ 50 DLB; n = 167, 57.79%)	Association of *APOE4* and white matter hyperintensities	Greater WMH volume was associated with worse attention/executive functions, learning/memory, and language in *APOEε4* carriers) [180].
X. Wang, et al. (2015)	42 AD patients (n = 16; 38.09%)	Hippocampal volume, and resting-state functional connectivity in AD (MRI)	*APOE4* allele carriers exhibited smaller left hippocampal volumes compared to non-carriers and decreased their amplitude of low-frequency fluctuations in the left hippocampus [168].
U. Saeed, et al. (2018)	250 AD patients and 48 DLB patients	Hippocampal volume (MRI)	Hippocampal volumes were smaller with increasing *APOEε4* dosage [169].
M. M. Dunk and I. Driscoll (2022)	297 AD patients (n = 202, 68.01%), 539 Late MCIs (n = 287, 53.25%); 249 Early MCIs (n = 122, 43.15%); 404 controlss (n = 109, 26.98%).	Total cholesterol and APOE-related risk for AD	Total cholesterol was higher in *APOE4*+ compared to *APOE3* and *APOE2*+ ($ps < 0.04$) carriers [181].
H. Barthel, et al. (2011)	81 AD patients (n = 32; 39.51%) and 69 non-demented controls (n = 12; 17.39%)	The positive ratio of florbetaben (^{18}F) PET finding.	*APOE ε4* was more common in participants with positive PET images compared with those with negative scans [182].

(Continues)

TABLE 1 (Continued)

Study (years)	Nubmers of patients (n = *APOE4* carriers; % = *APOE4* carriers of total patients)	To investigate the impact of *APOE* genotype on clinical features	Findings
EEG			
M. Lehtovirta, et al. (1996)	58 AD patients (n = 287, 58.54%) and 18 control	Relationship of EEG and *APOE* polymorphism in AD	*APOE* ϵ4 allele carriers showed a tendency towards more pronounced EEG slowing in AD patients [99].
V. Jelic, et al. (1997)	41 AD patients (n = 24, 53.25%) and 34 control	The ratio of alpha and theta absolute power and EEG coherence in alpha frequency band	*APOE*ϵ4 does not influence EEG slowing, but may be associated with selective decreases in functional connectivity as assessed by EEG coherence [183].
C. Babiloni, et al. (2006)	89 MCI subjects (n = 32; 35.96%), 103 AD patients (n = 52; 50.49%)	Relationships between the *APOE*ϵ4 allele and EEG rhythmicity	Amplitude of alpha 1 and 2 sources in occipital, temporal, and limbic areas was lower in subjects carrying the ϵ4 allele than in ϵ4 non-carriers, which was true for both MCI and AD [103].
N. V. Ponomareva, et al. (2008)	50 AD patients, and 95 their unaffected relatives and unrelated individuals.	Relationship of EEG alterations in non-demented individuals and *APOE* genotype and risk of AD	Patients carrying the *APOE*ϵ4 allele the decrease in alpha power was higher than in ϵ4 non-carriers [102].
L. Canuet, et al. (2012)	125 AD patients (n = 60; 48%) and 60 elderly controls (n = 12; 20%)	Spectral density for six frequency bands and resting-state oscillations and functional connectivity	The decrease in interhemispheric alpha connectivity in frontal and parieto-temporal regions was APOE-4-related [184].
V. Gutierrez-de Pablo, et al. (2020)	46 healthy control subjects (n = 6; 13.04%), 39 MCI (n = 10;25.64%), 122 AD (n = 50; 40.98%)	Lempel-Ziv complexity	*APOE*ϵ4 allele could modify the EEG complexity patterns in different brain regions, as the temporal lobes [101].
Gait			
R. K. MacAulay, et al. (2016)	299 non-demented older adults (n = 75; 25.08%)	Gait characteristics	APOE-ϵ4 was linked to shorter stride length and greater dual-task related disturbances in stride length [128].
H. E. Whitson, et al. (2018)	29 older adults with normal cognition	Gait-cognition dual-task performance	*APOE*ϵ4 carriers tended to exhibit greater dual-task interference [185].
Biomarkers (*Aβ1-42*; *p-Tau*; *NFL*)			
T. Lehtimäki, et al. (1995)	83 AD patients and 164 non-demented controls	*APOE* concentrations in the cerebrospinal fluid in Finnish patients with Alzheimer's disease	CSF *APOE* concentrations did not vary in different phenotype groups [186].
Y. Liu, et al. (2016)	336 AD patients (n = 223; 66.37%); 866 MCI patients (n = 436; 50.35%); 561 controls (n = 147; 28.49%)	Impact of ε4 dose on cerebrospinal fluid (CSF) levels' Abeta1-42 (Aβ1-42), tau, p-tau; cortical amyloid deposition (Florbetapir-PETAV45)	*APOEε4* was associated with decreased CSF Aβ1-42 and increased cerebral Aβ deposition, increased CSF tau, p-tau and cerebral hypometabolism, hippocampal atrophy, and cognition decline [35].
M. Mandecka, et al. (2016)	85 SCD (n = 28; 32.94%), 87 MCI (n = 28; 32.18%), and 80 AD-D (n = 43; 53.75%)	CSF biomarkers	The levels of T-tau and P-tau were significantly higher in the APOEϵ4+ than in the noncarriers, but only in the MCI patients ($p < 0.05$) [50].

TABLE 1 (Continued)

Study (years)	Nubmers of patients (n = *APOE4* carriers; % = *APOE4* carriers of total patients)	To investigate the impact of *APOE* genotype on clinical features	Findings
J. K. Morris, et al. (2017)	213 non-demented controls (n = 54; 25.35%), 125 AD patients (n = 78; 62.4%)	Metabolic biomarkers	APOE4 carriers with AD exhibited lower FFA levels [187],
Neuroinflammation			
Y. Y. Fan, et al. (2017)	185 AD patients, and 190 healthy individuals	TNF-α, IL-6, and IL-1β.	The *APOE4* ε4 allele carriers have higher level of increased levels of TNF-α, IL-6, and IL-1βin AD [86].
Qiushan Tao, et al. (2018)	3130	Study the interaction between the apolipoprotein E (ApoE) genotype and chronic low-grade inflammation and its association with the incidence of AD.	*APOE4* coupled with chronic low-grade inflammation was associated with an increased risk of AD [87].
John M Ringman, et al. 2012	33 FAD patients (n = 21; 63.63%)	Plasma inflammatory factors.	The *APOE* genotype was related to the levels of the inflammatory markers I-309, IL-1, IL-3, IL-7, IL-12p40, IL-13, and IL-15 [82].

the highest content, which can promote protein assembly, stabilize and polymerize microtubules, and participate in neurite growth and axonal transport [46]. In brains suffering from AD, Tau is hyperphosphorylated and is associated with neuronal degeneration and loss [47], which are the main pathological features of AD [16]. The degree of Tau phosphorylation varies with APOE isoforms; for instance, *APOE4* knock-in (KI) mice generated more Tau phosphorylation than *APOE3* KI mice [47, 48]. Furthermore, these isoform-dependent differences vary with neuron type. In *APOE4* KI mice, Tau phosphorylation was increased in neurons, whereas there was no significant change in astrocytes [16, 49]. In addition, clinical researches also reported a higher level of T-tau and P-tau in APOE4 carriers in mild cognitive impairment (MCI) and prodromal AD stage patients [35, 50]. Although the mechanism of cell type-specific phosphorylation is unclear, it provides strong evidence for differences in neural function among various APOE genotypes.

3.3 | Lipid metabolism

Aging is a significant risk factor in AD, in addition to genetic and lifestyle factors [51]. Accumulated evidence indicates dysregulated lipid homeostasis that related to aging plays an important role in the development of AD [52]. Genetic variations in APOE genotype affected lipid metabolism and neurological development (Figure 2). Lipid and sterol synthesis and metabolism pathways are downregulated in *APOE4*-carrying astrocytes but upregulated in those expressing APOE2 and APOE3 [29]. The total content of CL, cellular CL, and secreted CL were all decreased in *APOE4*-carrying astrocytes (level E2 = E3 > E4 = KO) in APOE knock-out (KO) mice [29]. Additionally, for proteins that play a vital role in lipid metabolism, western blot analysis has confirmed that Farnesyl-Diphosphate Farnesyltransferase 1 (FDFT1) (squalene synthase) and ATP Binding Cassette Subfamily A Member 1 (ABCA1) are medicated in an APOE isoforms-dependent way (E2 > E3 > E4) [29]. Cellular cholesterylester decreased significantly only in *APOE4*, whereas cellular triacylglycerol (TAG) increased in all APOE genotypes, and cellular phosphatidylethanolamines (PEs) increased only in *APOE2* and *APOE4* cells. Both exhibited an isoform-dependent increase (E4 > E3 > E2 = KO) [29]. Moreover, *APOE4*-expressing cells exhibit enhanced inflammatory signaling and decreased β-amyloid uptake [29].

Genetic variations in *APOE* genotype lead to different fates in neurons. Lipid homeostasis can affect many cellular functions, including membrane synthesis, vesicle transport, protein transformation, and cell proliferation. *APOE4* KI mice revealed a decreased phagocytic capacity in astrocytes and increased senescent synapses compared with other isoforms in KI mice [53]. With decreasing CL secretion in astrocytes, the mice depicted fewer synaptic vesicles, more immature synapses, and less

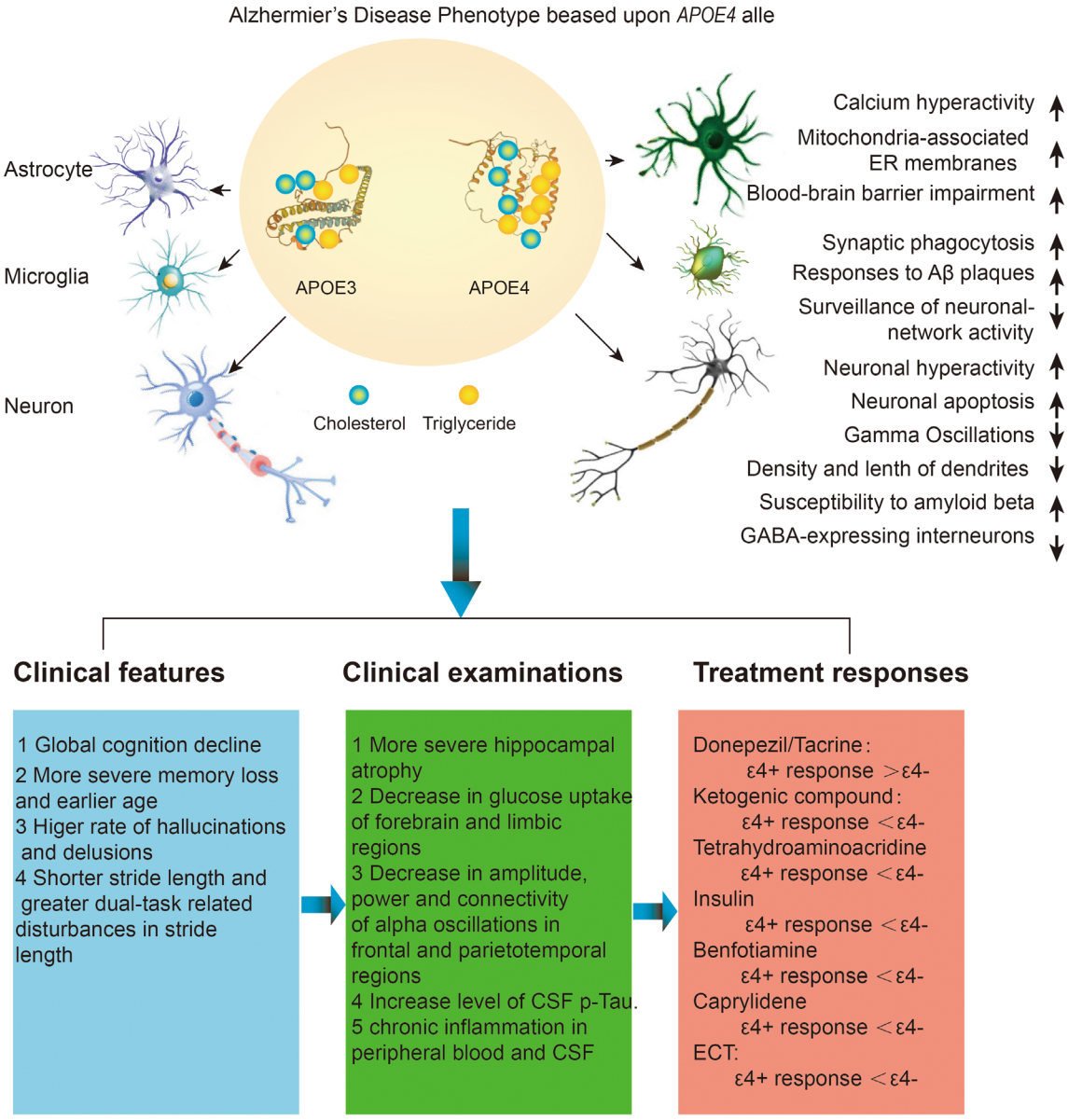

FIGURE 2 Genetic variation in the APOE genotype affects lipid metabolism and neurological development and producing relative isoform-dependent changes of neurons, astrocytes, and microglia. These structural and neurophysiological changes form the basis of the clinical phenotype are defined by the carrier status of the apolipoprotein E ϵ4 allele.

presynaptic synaptosomal nerve-associated protein 25 (SNAP-25) in the hippocampus [54]. In neurons, lipid metabolism is genotype dependent. Among the alleles, *APOE4* encodes the worst efficiency in lipid transport and lipid droplet accumulation [55]. In contrast, human *APOE2* and *APOE3* alleles can functionally replace the glial lazarillo (Glaz) loss in flies, thereby promoting lipid transport from neurons to glial cells [55]. The evidence indicates that APOE4-carrying neurons are vulnerable to lipid metabolism disorders. Reduced binding affinity with lipids in APOE4-carrying neurons also leads to lipid accumulation and subsequent hippocampal atrophy and cognitive deficits due to apoptotic neuronal death [56]. Pathological events also can aggravate the process in reverse. For example, elevated ROS can induce the lipids production in the neurons, which are subsequently transferred to glial cells and generate lipid droplets [55].

Variations in lipid and neuronal homeostasis critically affect neurological development and synaptic formation. High *APOE3* expression stimulates synaptic elongation, while *APOE4* sharply hampers synaptic branching and extension and impairs the process of cytoskeleton [57, 58]. Cerebral organoids from AD patients carrying APOE ε4/ε4 depicted greater apoptosis and decreased synaptic integrity [59]. Although it is still unclear how *APOE4* inhibits synaptic branching and extension, Ca^{2+} overload may be part of its mechanism. Ca^{2+} overload triggered by APOE result in Ca^{2+}

concentration rising and CaMKII abnormal phosphorylation, and finally aggravate oxidative stress and damaged neurons apoptosis [60]. GABAergic neurons system mainly involves cognitive processes, especially learning and memory [61]. GABAergic neural network is also affected by *APOE* genotypes. Compared with *APOE3*, dysfunction in APOE4 carrying GABAergic interneurons result in hippocampal neurogenesis and deficits in learning and memory [62]. Clinical studies have found that GABA levels in the brain and cerebrospinal fluid (CSF) are diminished in patients with AD and are more serious in *APOE4* carriers [63, 64]. Meanwhile, *APOE4* genotype has been associated with increased brain activity at rest and responses to memory tasks, proving the impairment of GABAergic neurons [65, 66]. In addition, *APOE* genotype attaches great significance to mature hippocampal neurogenesis. GABAergic neurons are reduced in *APOE4*-carrying brains, resulting in decreased GABA input to newborn neurons and inhibiting neurogenesis and maturation of neural stem cells [67]. Moreover, compared with *APOE3*, *APOE4*-expressing GABAergic neurons displayed a reduction in their growth, number, and branching of dendrites [68]. However, the specificity of *APOE4* isoforms varies according to the susceptibility of neurons toward stress conditions and the effects of *APOE4* in different brain regions [68, 69]. In brief, these findings demonstrate that *APOE4* may cause age-dependent damage to GABAergic interneurons, resulting in reduced hippocampal neurogenesis, as well as learning and memory deficits.

Last but not least, myelination, differentiation of oligodendrocytes, in CNS neuronal axons is linked to CL disorder resulted by APOE4. Through differential expression and gene set enrichment analysis of the postmortem samples, it is evidenced that expression of cholesterol-related genes in oligodendrocytes is raised in a APOE4 dose dependent way [70]. Another study implies that myelination might be affected by altered levels of intracellular and extracellular cholesterol of oligodendrocyte [71]. The mechanism how APOE4 affect myelination can be explained in two approaches. First, APOE4 directly interferes oligodendrocytes by changing its lipid composition, increasing lipid droplet synthesis and impairing cholesterol trafficking and subcellular localization [70]. It is found that cholesterol is abnormally deposition in myelinating oligodendrocytes [72]. Secondly, studies suggested that APOE4 indirectly disrupts oligodendrocyte differentiation by means of influencing astrocyte-derived lipid transport [73]. However, the pathway is needed for further exploration.

3.4 | Blood-brain barrier (BBB)

Blood-brain barrier is mainly composed of brain capillary endothelial cells (BMEC), pericytes, astrocytes, perivascular foot and basement membrane. The integrity of BBB can limit the free diffusion of ions between blood and brain tissue, preventing harmful substances from entering brain tissue. Recent studies found that the permeability of BBB increased by 40% in the brain of AD patients, possibly related to the injury and even death of vascular endothelial cells and pericytes. Moreover, damage to vascular endothelial cells and pericytes is closely related to the occurrence of dementia. *APOE4* can lead to an increase in amyloid protein at the peripheral level, which is related to the destruction of the BBB to a certain extent. In *APOE* knock-in and glial fibrillary acidic protein promoter transgenic mice, it was found that *APOE4* activated the proinflammatory cytokines cyclophilin A in pericytes and NF-KB/matrix metalloproteinase-9 signaling pathways, thereby increasing susceptibility to BBB impairment [74].

3.5 | Neuroinflammation

Neuroinflammation is major pathogenesis of AD [75]. Multiple immune cells, including microglia, are involved in the process, and APOE could exacerbate the neuroinflammatory process [76, 77]. APOE deficiency in mice is associated with Aβ-related inflammatory responses [78], and APOE isoforms may modulate inflammatory responses differently [79]. For example, *APOE4* knock-in mice were more susceptible to inflammation caused by lipopolysaccharides or Aβ deposition than *APOE2* and *APOE3* knock-in mice [80–82]. *APOE4* mice are also more susceptible to brain injury with a strong inflammatory component, such as traumatic brain injury [83]. Similar results have also been obtained from *in vitro* trials: APOE affects the inflammatory process of microglia and astrocytes, while *APOE4* has the strongest pro-inflammatory effect [84, 85]. Besides, it was also found that APOE4 ε4 allele may enhance susceptibility to AD and promotes the expressions of inflammatory factors in AD patients [86], and ApoE4 coupled with chronic low-grade inflammation was associated with an increased risk of AD [87]. A previous study reported that AD patients with APOE4 allele exhibited increased activation of the eicosanoid lipidome during chronic inflammation, which was identified as a potential therapeutic target for resolving this chronic inflammatory state [88].

In summary, the differences in inflammatory cytokines are related to the different APOE phenotypes, not only in CNS but also in the peripheral blood. However, the specific mechanism by which APOE genotypes regulate inflammatory response remains unclear and should be investigated.

4 | CLINICAL FEATURES BASED ON APOE4 STATUS

4.1 | Gender difference

As a basic feature, gender is a significant factor in analyzing a disease. Statistically, in China, the prevalence and

mortality of AD are remarkably higher in females than males [89]. Many contributors to this sex difference have been studied, such as education, occupation, menopause and so forth [90]. It is reported that women carrying *APOE4* have a greater risk than men with the same APOE genotype [91]. Nevertheless, the nature and direction of *APOE4* related to gender discrepancies remain controversial. Comprehensive research suggested that women carrying *APOE4* may show greater levels of AD pathology [92], more serious brain network integrity [93] and faster cognitive decline [94]. Furthermore, functional brain connectivity in healthy elders found that female *APOE4* carriers demonstrated reduced functional connectivity compared with male *APOE4* carriers in a cuneus/precuneus cluster of the posterior default mode network [95]. However, some studies reported the opposite results. A recent study implied that carrying *APOE4* influences cognitive decline to the same degree in two genders, while the dose-dependent effects of *APOE4* on cognitive decline, and the worsening of these effects with age, are stronger in men than women [96]. Otherwise, no difference between sexes carrying *APOE4* is also suggested [95, 96]. Overall, the interaction between gender and the number of *APOE4* may be complicated and should consider other factors (age and vascular risk factors) while analyzing.

4.2 | EEG alterations (neural network)

Electroencephalography (EEG) metrics are a critical early biomarker of preclinical AD [97]. Specifically, patients suffering from AD have decreased α coherence in temporal, occipital regions and parietal and increased δ coherence in the frontal and parieto-occipital regions [98]. As displayed in Table 1, recent EEG studies have found that APOE genotype can affect the neural network. Lehtovirta et al. found that *APOE4* carriers had more pronounced EEG slowing than non-carriers in patients with early AD [99]. *APOE4* homozygotes demonstrated the lowest fast-wave amplitudes, and highest slow-wave value in relative amplitudes and the lowest mean and peak frequencies after three years of follow-up [100]. Similarly, Ponomareva et al. suggested that *APOE4* carriers significantly reduced α power more than non-carriers in patients with AD. In addition, in the case of hyperventilation, the presence of the ε4 allele in relatives of patients with AD is associated with synchronized high-amplitude δ and θ activity and sharp wave performance, with a decrease in α and an increase in δ and θ relative power [101, 104]. In other words, *APOE4* allele may increase the abnormal EEG rate in AD patients and their relatives without cognitive dysfunction.

There was also evidence of a significant difference between APOE4 carriers and non-carriers, where an increase in a θ-α band in the left temporal region could be seen in *APOE4* carriers [102]. Meanwhile, in patients with MCI and AD, the amplitude range of α1 and α2 in the occipital, temporal and limbic regions of *APOE4* carriers was lower than that in non-carriers [103]. Overall, the presence of *APOE4* allele will likely increase excitability and accelerate dysfunction. These changes occurred before the first clinical symptoms. Consequently, APOE genotype may be a neurophysiological endophenotype.

4.3 | MRI (brain structure)

AD progression is characterized by significant atrophy (or cortical thinning), mostly in AD-susceptible areas such as the medial temporal lobe [104]. Senile plaques and neuronal tangles can appear in the medial temporal lobe (including the hippocampus and entorhinal cortex) in the early stages of AD. An entorhinal cortex-hippocampus projection fiber may be involved in hippocampal atrophy [105]. According to an MRI study, *APOE4* allele was associated with greater hippocampal atrophy; the degree of atrophy was higher in *APOE4* carriers than in non-carriers, especially in the medial temporal structures [106]. Moreover, APOE2 carriers had larger cortical thickness than APOE3 carriers in the temporal cortex, as well as larger cortical thickness than APOE4 carriers in the dorsolateral prefrontal cortex [107, 108]. However, these findings are inconsistent with other studies. The Alzheimer's Disease Neuroimaging Initiative (ADNI) study of subjects with AD and MCI did not find any significant effect of *APOE4* on atrophy [109]. Another study with a small number of AD patients found that APOE4 significantly affected the dentate gyrus and CA3, but these areas were considered less affected by AD [110]. APOE4 may contribute to increased hippocampal atrophy; however, this association is unclear (Table 1).

4.4 | FDG-PET metabolic patterns

The ^{18}-fluorodeoxyglucose PET (FDG-PET) imaging method measures the cerebral metabolic rates of glucose (CMRglc), a critical index for neuronal activity that correlates with disease progression and predicts histopathological diagnosis [111]. Few studies are exploring the effect of *APOE4* on FDG-PET. However, the overall conclusions are similar: *APOE4* carriers demonstrated a greater decrease in brain metabolism than non-carriers [112]. In addition, a metabolic decline has been observed in regions sensitive to AD (mainly the posterior cingulate, parietal, and temporal lobes) but was also found in the prefrontal cortex [113]. Similar results were observed in young (20–39 years) *APOE4* carriers [114]. Most importantly, the *APOE4* allele was found to have a gene-dose effect on brain metabolism, in which *APOE4* homozygous individuals exhibited more decreased brain metabolism than heterozygous ones [115]. Although the

available data suggest that *APOE4* is associated with decreased metabolism in AD-sensitive brain regions compared to APOE2 and APOE3, this feature requires further investigation.

4.5 | Neuropsychiatric symptoms

Neuropsychiatric symptoms are an important clinical feature of AD and cognitive impairment. Patients can suffer from psychosis (i.e., delusions and hallucinations) as well as affective and behavioral changes (i.e., depressive mood, anxiety, irritability, apathy, euphoria, disinhibition, and agitation) [116]. Depression and anxiety are common, even in the early stages of AD or MCI [117]. From a cohort of 112 patients with Alzheimer's dementia evaluated by the Neuropsychiatric Inventory (Nursing Home Version, NPI-NH), 92.9% had at least one neuropsychiatric symptom [118]. However, the association between APOE genotype and NPS in AD, whether *APOE4* increases anxiety and depression in AD, remains controversial. The prevalence rate of depression in *APOE4* allele carriers is significantly higher than in non-carriers, especially in female *APOE4* allele carriers [119, 120]. Nevertheless, this is not always the case. *APOE4* allele has depicted a protective effect on depression [121]. Studies with large sample sizes may be needed to investigate the differences in neural networks and the relationship between APOE genotypes and neuropsychic behavior abnormalities.

4.6 | Gait

Gait is associated with cognitive function in the elderly, especially AD patients. Cognitive impairment related to frontal lobe cognition in AD may lead to disturbances in the gait and motor parameters [122–124]. Kinematic parameters of gait are associated with an increased risk of falls in patients with AD. Compared with normal elders, people with AD are three times more at risk of falling [125], fractures, reduced mobility, and loss of independence, leading to increased cardiovascular morbidity and mortality [126, 127].

There are few studies on the correlation between gait and *APOE4*. One study found that *APOE4* carriers had shorter step sizes and greater dual-task-related step size interference [128]. APOE genotypes may also affect men and women differently through their effects on early disease processes, such as hypercholesterolemia, and these diseases may subsequently have a potential impact on AD pathogenesis [128]. Other longitudinal studies have demonstrated that decreased motor function in older adults predicts subsequent cognitive decline, and these changes are related to a greater genetic risk for AD [128]. In conclusion, the *APOE4* allele is likely to affect the gait characteristics of AD. This relationship has not been clarified, which requires thorough exploration.

5 | PRECISION MEDICINE BASED ON APOE4 CARRIER STATUS

According to the Precision Medicine Initiative, precision medicine is "an emerging approach for disease treatment and prevention that considers individual variability in genes, environment, and lifestyle for each person." *APOE4* is a major risk factor for AD, and strategies based on *APOE4* might hold promise within the precision medicine framework.

5.1 | Diagnoses and prevention based on APOE genotype

Prospective biomarkers comprising Aβ42, t-tau, p-tau, tau/Aβ42 in CSF, as well as t-tau, Aβ42/Aβ40, and NFL in peripheral blood, are related to AD progression, as summarized by a systematic review and analysis [129]. Otherwise, whole, left, and right HV, EC volume, MTA, 18 F-FDG PET and 11 C-PIB PET are prospective neuroimaging strategies applied in AD diagnoses [129]. According to the analysis, *APOE4* carrier has a great predictive ability for the progression with a RR of 2.16 and 95% CI of 1.83–2.55 [129]. Whether APOE genotype affects the accuracy of CSF biomarkers are evaluated by some research. A study reported that CSF levels of Aβ42 but not total and phosphorylated tau were lower in *APOE4* carriers than with noncarriers in AD and MCI patients [130]. However, CSF Aβ42 was strongly associated with diagnosing AD and cortical Aβ accumulation independent of APOE genotype [130].

On the other hand, *APOE4* demonstrated great potential in assessing the risk of cognitive decline and AD. In cognitively healthy older adults, *APOE4* can accelerate their age-related memory decline with *APOE4* carriers earlier than ten years than non-carriers in Aβ-positive elderly [131] and progress earlier to MCI or AD [132]. Accordingly, *APOE4* might help evaluate the potential risk of age-related cognitive decline and AD, especially in Aβ-positive people. When Aβ tests positive, APOE gene tests are strongly suggested and take interventions based on the gene test result.

In summary, the sensitivity and specificity APOE gene test are relatively low in diagnosing AD, while APOE4 has moderate diagnostic value and promising applications in preventing AD [133].

5.2 | Responses to clinical treatment based on APOE4 status

The differences in the structure and function of APOE genotypes determine differences in the evolutionary processes and fates of the neural network, metabolism, and other aspects of the nervous system. This can also determine the different responses to multiple treatments

(Table 2). *APOE4* carriers respond differently to treatment than non-carriers. For example, nonsteroidal anti-inflammatory drugs can lower the risk of AD in *APOE4* carriers but not in non-carriers [134]. Two-phase III trials of Bapineuzumab in AD displayed the same result: although Bapineuzumab did not change the overall clinical outcome in patients with AD, improvements in markers related to hyperphosphorylated Tau and amyloid plaque deposition were observed in *APOE4* carriers [135]. Another study revealed the sensitivity of *APOE4* non-carriers to drug treatment. Amyloid Aβ was significantly reduced in *APOE4* non-carriers but not in carriers after treatment with the retinoid X receptor (RXR) agonist bexarotene [136]. Moreover, a lasted phase IIa clinical trial of benfotiamine reported a stronger efficiency in APOE4 non-carriers than carriers [137]. In addition, phase II clinical trials of intranasal insulin in AD and MCI also reported different treatment effects modulated by APOE genotype status [138, 139]. Although different drug treatment mechanisms do not remain the same, carriers and non-carriers exhibit different drug treatment responses. Regarding non-drug therapy, Naili Wei et al. discovered that non-carriers of the *APOE4* allele were more sensitive to transcranial magnetic stimulation treatment in an AD RCT project, which can probably be explained as the difference in the neural network due to different genotypes [140]. Another study found that physical exercise was strongly associated with reduced Pittsburgh compound B (PiB) positivity rates in cognitively normal *APOE4* carriers, suggesting that a sedentary lifestyle in *APOE4* carriers may increase the risk of amyloid deposition [141]. However, it was also reported conversely results. A study using walking and lower limb strength training as an intervention suggested no significant difference between APOE4 alle carriers and non-carriers [142].

In conclusion, APOE4 carriers and non-carriers respond differently to medical interventions, indicating that APOE genotype can be a guide of precision medicine.

5.3 | Therapeutic strategies targeted on *APOE4* (and pathophysiology)

Currently, most studies on AD treatment methods target Aβ, but the results are unsatisfactory [123]. Therefore, new therapeutic targets and research directions are urgently required. APOE4 plays a vital role in AD pathogenesis, so APOE genotypes may be used as standards in clinical trials. A few studies have explored therapeutic targets based on APOE genotypes. A few studies have expored therapeutic approaches targets on APOE4, including immunotherapy, mimetic peptides therapy, structural correctors, gene therapies.

Immunotherapy is a promising way to decrease APOE4 and consequently alleviate Aβ plaque. HJ6.3 and HAE-4 are two antibodies that have been previously studied. HJ6.3 is a monoclonal antibody specific against APOE [143]. Amyloid model mice demonstrated decreased Aβ levels and amyloid plaques after being administrated HJ6.3 [143,144]. Anti-human APOE4 antibody (HAE-4) is an anti-human antibody that specifically recognizes human APOE4 and APOE3 and preferentially binds nonlipidated, aggregated APOE over the lipidated APOE found in circulation. Administration of HAE-4 in mice reduced Aβ plaques, Aβ-driven tau seeding/spreading, and neuritic dystrophy [145,146] while simultaneously protecting cerebrovascular integrity and function [147]. And mimetic peptide therapy is a strategy based on APOE structure and its biochemical interaction. Mimetic peptides are short peptide sequences that can compete for APOE binding, inhibiting APOE receptor binding and reducing its function [148]. Treatment with mimetic peptides significantly improved behavior while decreasing the inflammatory cytokine IL-6, neurofibrillary tangle-like and amyloid plaque-like structures in transgenic mice [149,150]. In addition, using small molecules as a structure corrector to disturb the interdomain interaction of APOE4 is also seen as a great therapeutic way. CB9032258 (a phthalazinone derivative) inhibits domain interaction in neuronal cells, which could restore functional activities of apoE4-expressing cells [151]. Another study also found that a small-molecule structure corrector could ameliorate the detrimental effects in APOE4-expressing neurons [152]. Importantly, it is well known that *APOE4* is a risk gene, whereas *APOE2* is a protective gene, and *APOE3* is relatively normal. Hence, converting *APOE4* to *APOE2* or *APOE3* is a possible method for AD therapy. Induced pluripotent stem cells (iPSCs) study found that utilizing CRISPR/Cas9 (a genome-editing system) to convert APOE4 to APOE3 was sufficient to attenuate multiple AD-related pathologies [153]. However, CRISPR/Cas9 system still immaturity and needs more exploration.

In conclusion, although APOE4-targeted therapeutic strategies still require further investigation, APOE4 targets could be considered promising therapeutic pathways for AD.

6 | APOE PHENOTYPIC CLASSIFICATION

Phenomics mainly studies how physical and chemical phenotypes of organisms change under mutations and environmental influences to systematically investigate all cell phenotypes of genotypes in different environments [154]. It can effectively trace the associations between genotypes, environmental factors, and phenotypes [154]. Phenome-wide association studies (PheWASs) are adopted to investigate one or more phenotypes associated with genetic variation [155]. Such phenomics research can help to discover risk and even pathogenic genes, determine different characteristics of diseases, facilitate drug application as well as achieve breakthroughs in precision medicine [155,156].

TABLE 2 Responses to therapeutics or interventions based upon APOE geneotype.

Authors (publish years)	Nubmers of patients included in studies	Treatment protocols	Main findings (p value)
Drug therapy			
S. Abushakra, et al. (2017)	2,025 AD patients (n = 112; 71.3%)	Randomized subjects received oral placebo, 100 mg BID, or 150 mg BID of tramiprosate.	The Mild subgroup of APOE4/4 AD patients showed larger benefits on the high dose of tramiprosate than the overall Mild and Moderate group ($p < 0.02$) [188].
S. H. Choi, et al. (2008)	51	5–10 mg of donepezil per day for 48 weeks	APOE ε4+ may respond more favorably to donepezil thanε4 noncarriers ($p \leq 0.05$) [189].
M. R. Farlow, et al. (1999)	959	once-daily placebo (n = 374) or metrifonate (30–60 mg based on weight or a 50-mg fixed dose, n = 585)	APOE genotype did not influence disease progression as evaluated by either cognitive performance ($p = 0.93$) or global function ($p = 0.64$) [190].
M. R. Farlow, et al. (1996)	460 (APOEε4-carriers:291; noncarriers:169)	Placebo or tacrine at dosages of 80, 120, or 160 mg/day	APOEε4 associated with a lower probability of cognitive improvement ($p \leq 0.05$) [191].
M. R. Farlow, et al. (1998)	528	Placebo or tacrine with daily dosages of 80, 120, or 160 mg/day	The treatment effect only found larger in the ε2-3 compared with ε4 women (ITT, 4.24 points, $p = 0.03$; evaluable, 7.20 points, $p = 0.01$) [192].
M. Gold, et al. (2010)	693	Once-daily placebo, 2 mg rosiglitazone extended release (RSG XR), 8 mg RSG XR or 10 mg donepezil (control)	No evidence of efficacy of 2 or 8 mg RSG XR monotherapy in cognition or global function was detected in the APOEε4− or other analysis populations [193].
S. T. Henderson, et al. (2009)	152	An oral ketogenic compound, AC-1202	Effects were most notable in APOEε4− who were dosage compliant ($p < 0.05$) [194].
M. A. Raskind, et al. (2000)	636	Placebo or galantamine 24 or 32 mg/day	Therapeutic response to galantamine was not affected by APOE genotype [195].
M. A. Reger, et al. (2006)	13 AD, 13 with amnestic mild cognitive impairment, 35 normal controls	Saline (placebo) or insulin (20 or 40 IU)	For memory-impaired subjects: APOEε4− > APOEε4+ ($p < 0.05$) [196].
A. S. Rigaud, et al. (2000)	76 (33ε4+; 43ε4−)	Tacrine dosages ranging from 40 mg/day up to the highest dosage (160 mg)	There was no tendency for the ε4− carriers to respond better than the ε4+ carriers [197].
M. E. Risner, et al. (2006)	511	Placebo or rosiglitazone (RSG) 2, 4, or 8 mg	Improvement in response to RSG: APOE ε4− >APOE ε4+ (only in exploratory analyses) [198].
G. H. Suh, et al. (2006)	202	Galantamine	ApoE epsilon4 genotype does not affect galantamine-related improvements in cognition, global rating, function and behavior [199].
Q. Xu, et al. (2020)	53	Medium-chain triglycerides (MCT) jelly or placebo jelly (canola oil) by mouth three times daily	MCT had positive effects on cognitive ability in mild to moderate AD patients with APOE4(−/−) ($p < 0.05$) [200].

(Continues)

TABLE 2 (Continued)

Authors (publish years)	Nubmers of patients included in studies	Treatment protocols	Main findings (p value)
O. Almkvist, et al. (2001)	24	Tacrine, a cholinesterase (ChE) inhibitors and placebo	The frequency of APOEε4 alleles was higher in responders ($p < 0.05$) [201].
X. A. Alvarez, et al. (1999)	30 patients with mild to moderate senile dementia	Citicoline or placebo	The efficacy of citicoline is greater in patients with mild mental deterioration and/or bearing the APOEε4 ($p < 0.05$) [202].
T. Babić, et al. (2004)	84	Galanthamine, a new cholinesterase inhibitor	APOE4 homozygous patients with AD in its mild to moderate stage may be considered as responders to galanthamine ($p = 0.032$) [203].
R. Blesa, et al. (2006)	214	Rivastigmine 1.5–6 mg twice daily for 26 weeks	APOE ε4 allele does not determine a difference in the response to treatment with rivastigmine [204].
L. De Beaumont, et al. (2016)	Tissues from temporal cortex ($n = 37$) and hippocampus ($n = 22$) from AD-confirmed cases	Donepezil or placebo	APOE-ϵ4 ($p = 0.07$) and butyrylcholinesterase K (KBCHE-K) ($p = 0.036$) positive subjects show a greater benefits to donepezil therapy [205].
S. I. Gavrilova, et al. (2005)		Neurotrophic (cerebrolysin) and cholinergic (exelon)	APOEε4+ did not differ in response to either drug from APOEε4− [206].
H. J. Han, et al. (2012)	206	Rivastigmine patch monotherapy or memantine plus rivastigmine patch for 24 weeks	Moderately severe AD patients with the APOE ε4 allele may respond more favorably to memantine plus rivastigmine patch than ε4 noncarriers ($p < 0.001$) [207].
C. Harrington, et al. (2011)	2981	Once daily placebo, 2 mg rosiglitazone extended release (RSG XR), or 8 mg RSG XR for 48 weeks	There was no evidence of an interaction between treatment and APOE status [208].
A. S. Rigaud, et al. (2002)	117	Donepezil	No evidence show that APOE phenotype and gender are predictors of the response to donepezil in Alzheimer's disease patients [209].
C. R. Jack, et al. (2008)	131	Vitamin E and donepezil	APOEε4+ show greater annual percent change (APC) than APOEε4− ($p < 0.000$) [210].
Y. Zhong, et al. (2013)	110	5–10 mg of donepezil daily for 6 months	No association was found between the APOE genotype and efficacy of donepezil [211].
J. Jia, et al. (2020)	241	Donepezil 5 mg/day for at least 4 weeks	Patients' MMSE scores improved significantly after treatment ($p = 0.0038$), especially for APOEε4− and patients ≤75 years [212].
L. S. Schneider and M. Farlow (1997)	318 (all female)	Placebo or tacrine	Among women on estrogen replacement therapy (ERT) receiving tacrine, there tended to be greater improvement relative to placebo among those without an APOEε4 allele [213].

TABLE 2 (Continued)

Authors (publish years)	Nubmers of patients included in studies	Treatment protocols	Main findings (p value)
S. H. MacGowan, et al. (1998)	107	Tacrine or galanthamine	APOE genotype did not modify response to therapy in the short term, there are indications that it may affect response over the longer term (up to 12 months) ($p < 0.05$) [214].
M. Sjögren, et al. (2001)	145	Tacrine	It showed a faster rate of decline in the ApoE4 AD compared to the ApoE2-3 ($p < 0.05$) [215].
E. Stefanova, et al. (2003)	27	Rivastigmine or tacrine	The CSF-tau changes were mainly seen in APOEε4 carriers ($p = 0.005$) [216].
N. Pomara, L. M. Willoughby, K. Wesnes and J. J. Sidtis (2004)	24	Trihexyphenidyl or placebo	APOEε4 allele plays a significant role in increasing cognitive sensitivity to trihexyphenidyl ($p = 0.01$) [217].
P. Riekkinen, et al. (1997)	19	Tetrahydroaminoacridine (THA)	APOE genotype may affect the response of cortical electrical arousal to cholinergic therapy that enhances the efficacy of presynaptic NB axons (APOEε4− > APOEε4+, $p < 0.05$) [218].
S. Y. Tai, et al. (2017)	60	Cilostazol	APOE ε4 status, were significantly associated with poor therapeutic outcomes [219].
G. S. Watson, et al. (2009)	16	Insulin (1 mU.kg(−1).min(−1)) and dextrose to maintain euglycemia; octreotide (150 μg/h); insulin, dextrose, and octreotide; saline.	APOEε4 genotype modulates responses to insulin and octreotide ($p < 0.05$) [220].
G. E. Gibson, et al. (2020)	70	Benfotiamine or placebo	The efficiency of benfotiamine was stronger in the APOEε4 non-carriers ($p < 0.0001$) [137].
I. C. Arellanes, et al. (2020)	33	Vitamin B complex (1 mg vitamin B12, 100 mg of vitamin B6 and 800 mcg of folic acid per day) and randomized to 2152 mg of docosahexaenoic acid (DHA) per day or placebo over 6 months	The increase in CSF eicosapentaenoic acid (EPA) in non-APOE4 carriers after the DHA supplementation was three times greater than APOE4 carriers ($p < 0.05$) [221].
A. S. Fleisher, et al. (2011)	313	Divalproex or placebo	No baseline differences were found between active treatment and placebo groups in APOE ε4 carrier status [222].
A. Valen-Sendstad, et al. (2010)	55	1-mg estradiol and 0.5-mg norethisterone or placebo once daily	Women without an APOEε4 allele may get better mood and cognition with hormone therapy (HT) ($p < 0.05$) [223].
R. Cacabelos, et al. (2000)	479	CDP-choline (1000 mg/day) + piracetam (2,400 mg/day) + anapsos (360 mg/day)	APOE-3/4 carriers showed the best efficiency, while APOE homozygote the reacted the worst ($p < 0.05$) [224].

(Continues)

TABLE 2 (Continued)

Authors (publish years)	Nubmers of patients included in studies	Treatment protocols	Main findings (p value)
S. Craft, S. Asthana, et al. (2003)	37	Insulin	AD patients who are not epsilon 4 homozygotes have reduced sensitivity to insulin that may interfere with such modulation ($p < 0.05$) [225].
A. Claxton, et al. (2015)	60	Placebo or 20 IU of insulin detemir or 40 IU of insulin detemir	This effect was moderated by APOE status ($p < 0.05$), reflecting improvement for APOE-ε4 carriers ($p < 0.02$), and worsening for non-carriers ($p < 0.02$) [226].
N. Torosyan, et al. (2018)	16	Caprylidene or placebo	APOEε4 non-carriers showed greater improvement with caprylidene ($p = 0.04$) [227].
Neuromodulation			
A. Jannati, et al. (2017)	18 healthy adults	Continuous theta-burst stimulation (cTBS)	No significant effect of APOE genotype. (FDR-adjusted $p > 0.32$) [228].
M. Huuhka, et al. (2005)	119	Electroconvulsive therapy (ECT)	APOEε4+ and APOEε4− had no difference in response to ECT [229].
C. A. Bousman, et al. (2015)	117	Electroconvulsive therapy (ECT)	No association was found between APOE genotype and ECT efficiency [230].
Other interventions			
A. Solomon, et al. (2018)	1175	Diet, exercise, cognitive training, and vascular risk management	The APOE ε4 carriers and noncarriers were not significantly different at baseline (except for serum cholesterol level) [231].
L. M. J. Sanders, et al. (2020)	91 patients with dementia	Walking and lower limb strength training	No significant difference between APOEε4+ and APOEε4− .[142].
I. L. Uijen, et al. (2020)	67	Cycling training or stretching and toning exercises	There was no significant associations between APOE ε4 status and global cognitive change [232].

AD treatment has long been unsatisfactory, and the failures make us constantly reconsider whether the original directions are correct. For instance, the failure of Aβ-targeted therapies has encouraged people to view Aβ as a pathological condition rather than a mechanism. Meanwhile, there have been no significant breakthroughs in developing drugs treating Tau's hyperphosphorylation. Currently, treatments or various drugs for AD are based on a certain phenomenon or evidence without comprehensive and sufficient consideration [157]. Drug development has included a variety of complex and unclear mechanisms. However, we reflected on the results of clinical drug treatment and found that APOE genotype greatly influenced treatment responses (Table 2). For example, *APOE4* carriers have different sensitivity to various drugs [158]. The difference in APOE genotype on treatment led us to consider whether *APOE4* carriers and non-carriers of *APOE4* should be classified into different phenotypic groups in clinical studies.

The phenotype group concept was proposed based on the different phenotypic characteristics of certain genes under the joint action of various epigenetic factors. The mechanism is the different regulation and modification of DNA expression by various epigenetic factors, including DNA and RNA methylation. According to the characteristics mentioned above, APOE genotypes appear to satisfy this characteristic. Specifically, APOE gene polymorphism leads to protein binding efficiency. In addition, different APOE phenotypes influence the epigenetic modification status, such as DNA methylation [159,160]. As APOE is involved in synapses, ribosomes, mitochondria, spliceosomes, endocytosis, oxidative phosphorylation, and proteasome functions, the status/change of the two sites could greatly impact individuals [160]. Therefore, it is different in CNS and cardiac circulation system disease states among APOE carriers [161,162], which is based on the environment or different stimulus conditions. Considering the above evidence, phenomics based on APOE genotypes is promising.

7 | CONCLUSION

APOE genotypes encode the metabolic efficacy lipoprotein in astrocytes, neurons, and microglia. *APOE4* has a high binding affinity with triglycerides and CL, which differ from the ability of APOE3. Such variations produce extensive differences between *APOE4* carriers and non-carriers in the neural network, pathological state, clinical features, imaging, electrophysiology, and treatment responses. All of these contribute to the two kinds of phenotypic features. Therefore, differentiating phenotypes based on *APOE4* carrier status should be considered. In future clinical studies, phenotypic classification should be applied to research and clinical treatments. These phenotypes will steer the direction of AD research to be more targeted and precise. Most importantly, this may pave the way for developing effective drugs.

AUTHOR CONTRIBUTIONS

Xiao-Yu Ji, Xin-Yuan Peng and Hai-Liang Tang: Writing and editing the manuscript. **Jie Wu and Jian Chen:** Language editing and major supervision. **Nai-Li-Wei:** Conception, supervision, and design of this article. All authors approved the submitted version.

ACKNOWLEDGMENTS

This work was supported by Grants from the National Natural Science Foundation of China (82001447; 82201629), the Natural Science Foundation of Guangdong Province (2022A1515010687), special funds for Guangdong Special Funds for Science and Technology, (STKJ2021075 and STKJ2021077), Guangdong Basic and Applied Basic Research Foundation (22202104030000234); the Natural Science Foundation of Guangdong Province (2214050005144), Dengfeng Project for the construction of high-level hospitals in Guangdong Province, the First Affiliated Hospital of Shantou University Medical College Supporting Funding (202003-29); and 2020 Li Ka Shing Foundation Cross-Disciplinary Research Grant (2020LKSFG11C; 2020LKSFG01A).

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The article is a review. It do not include any data.

ORCID

Nai-Li Wei https://orcid.org/0000-0003-3573-199X

REFERENCES

1. Soria Lopez JA, González HM, Léger GC. Alzheimer's disease. Handb Clin Neurol. 2019;167:231–55.
2. Alzheimer's disease facts and figures. Alzheimers Dement. 2022;18(4):700–89.
3. Koutsodendris N, Nelson MR, Rao A, Huang Y. Apolipoprotein E and Alzheimer's disease: findings, hypotheses, and potential mechanisms. Annu Rev Pathol. 2022;17:73–99.
4. Mahley RW. Central nervous system lipoproteins: apoE and regulation of cholesterol metabolism. Arterioscler Thromb Vasc Biol. 2016;36(7):1305–15.
5. Chen Y, Strickland MR, Soranno A, Holtzman DM. Apolipoprotein E: structural insights and links to Alzheimer disease pathogenesis. Neuron. 2021;109(2):205–21.
6. Reiman EM, Arboleda-Velasquez JF, Quiroz YT, Huentelman MJ, Beach TG, Caselli RJ, et al. Exceptionally low likelihood of Alzheimer's dementia in APOE2 homozygotes from a 5,000-person neuropathological study. Nat Commun. 2020;11(1):667.
7. Michaelson DM. APOE ε4: The most prevalent yet understudied risk factor for Alzheimer's disease. Alzheimers Dement. 2014;10(6):861–8.
8. Yamazaki Y, Zhao N, Caulfield TR, Liu CC, Bu G. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nat Rev Neurol. 2019;15(9):501–18.
9. Elshourbagy NA, Liao WS, Mahley RW, Taylor JM. Apolipoprotein E mRNA is abundant in the brain and adrenals, as well as in the liver, and is present in other peripheral tissues of rats and marmosets. Proc Natl Acad Sci U S A. 1985;82(1):203–7.
10. Boyles JK, Pitas RE, Wilson E, Mahley RW, Taylor JM. Apolipoprotein E associated with astrocytic glia of the central nervous

system and with nonmyelinating glia of the peripheral nervous system. J Clin Invest. 1985;76(4):1501–13.
11. Xu Q, Bernardo A, Walker D, Kanegawa T, Mahley RW, Huang Y. Profile and regulation of apolipoprotein E (ApoE) expression in the CNS in mice with targeting of green fluorescent protein gene to the ApoE locus. J Neurosci. 2006;26(19):4985–94.
12. Hatters DM, Budamagunta MS, Voss JC, Weisgraber KH. Modulation of apolipoprotein E structure by domain interaction: differences in lipid-bound and lipid-free forms. J Biol Chem. 2005;280 (40):34288–95.
13. Acharya P, Segall ML, Zaiou M, Morrow J, Weisgraber KH, Phillips MC, et al. Comparison of the stabilities and unfolding pathways of human apolipoprotein E isoforms by differential scanning calorimetry and circular dichroism. Biochim Biophys Acta. 2002;1584(1):9–19.
14. Munoz SS, Garner B, Ooi L. Understanding the role of ApoE fragments in Alzheimer's disease. Neurochem Res. 2019;44(6): 1297–305.
15. Elliott DA, Tsoi K, Holinkova S, Chan SL, Kim WS, Halliday GM, et al. Isoform-specific proteolysis of apolipoprotein-E in the brain. Neurobiol Aging. 2011;32(2):257–71.
16. Brecht WJ, Harris FM, Chang S, Tesseur I, Yu GQ, Xu Q, et al. Neuron-specific apolipoprotein e4 proteolysis is associated with increased tau phosphorylation in brains of transgenic mice. J Neurosci. 2004;24(10):2527–34.
17. Harris FM, Brecht WJ, Xu Q, Tesseur I, Kekonius L, Wyss-Coray T, et al. Carboxyl-terminal-truncated apolipoprotein E4 causes Alzheimer's disease-like neurodegeneration and behavioral deficits in transgenic mice. Proc Natl Acad Sci U S A. 2003;100(19): 10966–71.
18. Marques MA, Tolar M, Harmony JA, Crutcher KA. A thrombin cleavage fragment of apolipoprotein E exhibits isoform-specific neurotoxicity. Neuroreport. 1996;7(15-17):2529–32.
19. Tolar M, Keller JN, Chan S, Mattson MP, Marques MA, Crutcher KA. Truncated apolipoprotein E (ApoE) causes increased intracellular calcium and may mediate ApoE neurotoxicity. J Neurosci. 1999;19(16):7100–10.
20. Huang Y, Liu XQ, Wyss-Coray T, Brecht WJ, Sanan DA, Mahley RW. Apolipoprotein E fragments present in Alzheimer's disease brains induce neurofibrillary tangle-like intracellular inclusions in neurons. Proc Natl Acad Sci U S A. 2001;98(15): 8838–43.
21. Chang S, ran Ma T, Miranda RD, Balestra ME, Mahley RW, Huang Y. Lipid- and receptor-binding regions of apolipoprotein E4 fragments act in concert to cause mitochondrial dysfunction and neurotoxicity. Proc Natl Acad Sci U S A. 2005;102(51): 18694–9.
22. Dafnis I, Stratikos E, Tzinia A, Tsilibary EC, Zannis VI, Chroni A. An apolipoprotein E4 fragment can promote intracellular accumulation of amyloid peptide beta 42. J Neurochem. 2010;115(4): 873–84.
23. Dafnis I, Argyri L, Sagnou M, Tzinia A, Tsilibary EC, Stratikos E, et al. The ability of apolipoprotein E fragments to promote intraneuronal accumulation of amyloid beta peptide 42 is both isoform and size-specific. Sci Rep. 2016;6:30654.
24. Love JE, Day RJ, Gause JW, Brown RJ, Pu X, Theis DI, et al. Nuclear uptake of an amino-terminal fragment of apolipoprotein E4 promotes cell death and localizes within microglia of the Alzheimer's disease brain. Int J Physiol Pathophysiol Pharmacol. 2017;9(2):40–57.
25. Hussain G, Wang J, Rasul A, Anwar H, Imran A, Qasim M, et al. Role of cholesterol and sphingolipids in brain development and neurological diseases. Lipids Health Dis. 2019;18(1):26.
26. Zhang J, Liu Q. Cholesterol metabolism and homeostasis in the brain. Protein Cell. 2015;6(4):254–64.
27. Huebbe P, Rimbach G. Evolution of human apolipoprotein E (APOE) isoforms: gene structure, protein function and interaction with dietary factors. Ageing Res Rev. 2017;37:146–61.
28. Li X, Zhang J, Li D, He C, He K, Xue T, et al. Astrocytic ApoE reprograms neuronal cholesterol metabolism and histone-acetylation-mediated memory. Neuron. 2021;109(6):957–70.e8.
29. de Leeuw SM, Kirschner AWT, Lindner K, Rust R, Budny V, Wolski WE, et al. APOE2, E3, and E4 differentially modulate cellular homeostasis, cholesterol metabolism, and inflammatory response in isogenic iPSC-derived astrocytes. Stem Cell Reports. 2022;17(1):110–26.
30. Hirsch-Reinshagen V, Zhou S, Burgess BL, Bernier L, McIsaac SA, Chan JY, et al. Deficiency of ABCA1 impairs apolipoprotein E metabolism in brain. J Biol Chem. 2004;279(39):41197–207.
31. Dong LM, Weisgraber KH. Human apolipoprotein E4 domain interaction. Arginine 61 and glutamic acid 255 interact to direct the preference for very low density lipoproteins. J Biol Chem. 1996;271(32):19053–7.
32. Serrano-Pozo A, Qian J, Monsell SE, Betensky RA, Hyman BT. APOEepsilon2 is associated with milder clinical and pathological Alzheimer disease. Ann Neurol. 2015;77(6):917–29.
33. Pletnikova O, Kageyama Y, Rudow G, LaClair KD, Albert M, Crain BJ, et al. The spectrum of preclinical Alzheimer's disease pathology and its modulation by ApoE genotype. Neurobiol Aging. 2018;71:72–80.
34. Namba Y, Tomonaga M, Kawasaki H, Otomo E, Ikeda K. Apolipoprotein E immunoreactivity in cerebral amyloid deposits and neurofibrillary tangles in Alzheimer's disease and kuru plaque amyloid in Creutzfeldt-Jakob disease. Brain Res. 1991;541(1): 163–6.
35. Liu Y, Tan L, Wang HF, Liu Y, Hao XK, Tan CC, et al. Multiple effect of APOE genotype on clinical and neuroimaging biomarkers across Alzheimer's disease spectrum. Mol Neurobiol. 2016;53(7): 4539–47.
36. Keable A, O'Neill R, MacGregor Sharp M, Gatherer M, Yuen HM, Johnston DA, et al. ApoE4 astrocytes secrete basement membranes rich in fibronectin and poor in laminin compared to ApoE3 astrocytes. Int J Mol Sci. 2020;21(12):4371.
37. Huang YA, Zhou B, Wernig M, Sudhof TC. ApoE2, ApoE3, and ApoE4 differentially stimulate APP transcription and abeta secretion. Cell. 2017;168(3):427–41 e21.
38. Tedeschi A, Bradke F. The DLK signalling pathway-a double-edged sword in neural development and regeneration. EMBO Rep. 2013;14(7):605–14.
39. Hashimoto T, Serrano-Pozo A, Hori Y, Adams KW, Takeda S, Banerji AO, et al. Apolipoprotein E, especially apolipoprotein E4, increases the oligomerization of amyloid beta peptide. J Neurosci. 2012;32(43):15181–92.
40. Wood SJ, Chan W, Wetzel R. Seeding of A beta fibril formation is inhibited by all three isotypes of apolipoprotein E. Biochemistry. 1996;35(38):12623–8.
41. Deane R, Sagare A, Hamm K, Parisi M, Lane S, Finn MB, et al. apoE isoform-specific disruption of amyloid beta peptide clearance from mouse brain. J Clin Invest. 2008;118(12):4002–13.
42. Castellano JM, Kim J, Stewart FR, Jiang H, DeMattos RB, Patterson BW, et al. Human ApoE isoforms differentially regulate brain amyloid-β peptide clearance. Sci Transl Med. 2011;3(89): 89ra57.
43. Simonovitch S, Schmukler E, Bespalko A, Iram T, Frenkel D, Holtzman DM, et al. Impaired autophagy in APOE4 astrocytes. J Alzheimers Dis. 2016;51(3):915–27.
44. Strittmatter WJ, Weisgraber KH, Huang DY, Dong LM, Salvesen GS, Pericak-Vance M, et al. Binding of human apolipoprotein E to synthetic amyloid beta peptide: isoform-specific effects and implications for late-onset Alzheimer disease. Proc Natl Acad Sci U S A. 1993;90(17):8098–102.
45. Kara E, Marks JD, Roe AD, Commins C, Fan Z, Calvo-Rodriguez M, et al. A flow cytometry-based in vitro assay reveals that formation of apolipoprotein E (ApoE)-amyloid beta complexes depends on ApoE isoform and cell type. J Biol Chem. 2018; 293(34):13247–56.

46. Avila J, Lucas JJ, Perez M, Hernandez F. Role of tau protein in both physiological and pathological conditions. Physiol Rev. 2004; 84(2):361–84.
47. Lewis J, McGowan E, Rockwood J, Melrose H, Nacharaju P, Van Slegtenhorst M, et al. Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. Nat Genet. 2000;25(4):402–5.
48. Kobayashi M, Ishiguro K, Katoh-Fukui Y, Yokoyama M, Fujita SC. Phosphorylation state of tau in the hippocampus of apolipoprotein E4 and E3 knock-in mice. Neuroreport. 2003;14(5): 699–702.
49. Tesseur I, Van Dorpe J, Spittaels K, Van den Haute C, Moechars D, Van Leuven F. Expression of human apolipoprotein E4 in neurons causes hyperphosphorylation of protein tau in the brains of transgenic mice. The American Journal of Pathology. 2000;156(3): 951–64.
50. Mandecka M, Budziszewska M, Barczak A, Pepłoñska B, Chodakowska-Żebrowska M, Filipek-Gliszczyñska A, et al. Association between cerebrospinal fluid biomarkers for Alzheimer's disease, APOE genotypes and auditory verbal learning task in subjective cognitive decline, mild cognitive impairment, and Alzheimer's disease. J Alzheimers Dis. 2016;54(1):157–68.
51. Armstrong RA. Risk factors for Alzheimer's disease. Folia Neuropathol. 2019;57(2):87–105.
52. Kao YC, Ho PC, Tu YK, Jou IM, Tsai KJ. Lipids and Alzheimer's disease. Int J Mol Sci. 2020;21(4):1505.
53. Chung WS, Verghese PB, Chakraborty C, Joung J, Hyman BT, Ulrich JD, et al. Novel allele-dependent role for APOE in controlling the rate of synapse pruning by astrocytes. Proc Natl Acad Sci U S A. 2016;113(36):10186–91.
54. van Deijk AF, Camargo N, Timmerman J, Heistek T, Brouwers JF, Mogavero F, et al. Astrocyte lipid metabolism is critical for synapse development and function in vivo. Glia. 2017;65(4): 670–82.
55. Liu L, MacKenzie KR, Putluri N, Maletic-Savatic M, Bellen HJ. The glia-neuron lactate shuttle and elevated ROS promote lipid synthesis in neurons and lipid droplet accumulation in glia via APOE/D. Cell Metab. 2017;26(5):719–37 e6.
56. Djelti F, Braudeau J, Hudry E, Dhenain M, Varin J, Bièche I, et al. CYP46A1 inhibition, brain cholesterol accumulation and neurodegeneration pave the way for Alzheimer's disease. Brain. 2015; 138(Pt 8):2383–98.
57. Nathan BP, Jiang Y, Wong GK, Shen F, Brewer GJ, Struble RG. Apolipoprotein E4 inhibits, and apolipoprotein E3 promotes neurite outgrowth in cultured adult mouse cortical neurons through the low-density lipoprotein receptor-related protein. Brain Res. 2002; 928(1-2):96–105.
58. Taxier LR, Philippi SM, York JM, LaDu MJ, Frick KM. The detrimental effects of APOE4 on risk for Alzheimer's disease may result from altered dendritic spine density, synaptic proteins, and estrogen receptor alpha. Neurobiol Aging. 2022;112:74–86.
59. Zhao J, Fu Y, Yamazaki Y, Ren Y, Davis MD, Liu CC, et al. APOE4 exacerbates synapse loss and neurodegeneration in Alzheimer's disease patient iPSC-derived cerebral organoids. Nat Commun. 2020;11(1):5540.
60. Xu D, Peng Y. Apolipoprotein E 4 triggers multiple pathway-mediated Ca2+overload, causes CaMK II phosphorylation abnormity and aggravates oxidative stress caused cerebral cortical neuron damage. Eur Rev Med Pharmacol Sci. 2017;21(24):5717–28.
61. Andrews-Zwilling Y, Gillespie AK, Kravitz AV, Nelson AB, Devidze N, Lo I, et al. Hilar GABAergic interneuron activity controls spatial learning and memory retrieval. PLoS One. 2012;7(7): e40555.
62. Andrews-Zwilling Y, Bien-Ly N, Xu Q, Li G, Bernardo A, Yoon SY, et al. Apolipoprotein E4 causes age- and Tau-dependent impairment of GABAergic interneurons, leading to learning and memory deficits in mice. J Neurosci. 2010;30(41):13707–17.
63. Grouselle D, Winsky-Sommerer R, David JP, Delacourte A, Dournaud P, Epelbaum J. Loss of somatostatin-like immunoreactivity in the frontal cortex of Alzheimer patients carrying the apolipoprotein epsilon 4 allele. Neurosci Lett. 1998;255(1): 21–4.
64. Seidl R, Cairns N, Singewald N, Kaehler ST, Lubec G. Differences between GABA levels in Alzheimer's disease and down syndrome with Alzheimer-like neuropathology. Naunyn Schmiedebergs Arch Pharmacol. 2001;363(2):139–45.
65. Dennis NA, Browndyke JN, Stokes J, Need A, Burke JR, Welsh-Bohmer KA, et al. Temporal lobe functional activity and connectivity in young adult APOE varepsilon4 carriers. Alzheimers Dement. 2010;6(4):303–11.
66. Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, et al. Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. Proc Natl Acad Sci U S A. 2009;106(17):7209–14.
67. Li G, Bien-Ly N, Andrews-Zwilling Y, Xu Q, Bernardo A, Ring K, et al. GABAergic interneuron dysfunction impairs hippocampal neurogenesis in adult apolipoprotein E4 knockin mice. Cell Stem Cell. 2009;5(6):634–45.
68. Schonheit B, Glockner F, Ohm TG. Apolipoprotein E polymorphism and dendritic shape in hippocampal interneurons. Neurobiol Aging. 2007;28(5):677–86.
69. Panza F, Frisardi V, Seripa D, D'Onofrio G, Santamato A, Masullo C, et al. Apolipoprotein E genotypes and neuropsychiatric symptoms and syndromes in late-onset Alzheimer's disease. Ageing Res Rev. 2012;11(1):87–103.
70. Kingwell K. Oligodendrocytes take centre stage in APOE4-linked Alzheimer disease. Nat Rev Drug Discov. 2023;22(1):15.
71. Camargo N, Goudriaan A, van Deijk AF, Otte WM, Brouwers JF, Lodder H, et al. Oligodendroglial myelination requires astrocyte-derived lipids. PLoS Biol. 2017;15(5):e1002605.
72. Blanchard JW, Akay LA, Davila-Velderrain J, von Maydell D, Mathys H, Davidson SM, et al. APOE4 impairs myelination via cholesterol dysregulation in oligodendrocytes. Nature. 2022;611 (7937):769–79.
73. Mok KK, Yeung SH, Cheng GW, Ma IW, Lee RH, Herrup K, et al. Apolipoprotein E epsilon4 disrupts oligodendrocyte differentiation by interfering with astrocyte-derived lipid transport. J Neurochem. 2023;165(1):55–75.
74. Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, et al. Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. Nature. 2012;485(7399):512–6.
75. Bales KR, Du Y, Holtzman D, Cordell B, Paul SM. Neuroinflammation and Alzheimer's disease: critical roles for cytokine/Aß-induced glial activation, NF-ßB, and apolipoprotein E. Neurobiol Aging. 2000;21(3):427–32.
76. Lynch JR, Morgan D, Mance J, Matthew WD, Laskowitz DT. Apolipoprotein E modulates glial activation and the endogenous central nervous system inflammatory response. J Neuroimmunol. 2001;114(1-2):107–13.
77. Iannucci J, Sen A, Grammas P. Isoform-specific effects of apolipoprotein E on markers of inflammation and toxicity in brain glia and neuronal cells in vitro. Curr Issues Mol Biol. 2021;43(1): 215–25.
78. LaDu MJ, Shah JA, Reardon CA, Getz GS, Bu G, Hu J, et al. Apolipoprotein E and apolipoprotein E receptors modulate A beta-induced glial neuroinflammatory responses. Neurochem Int. 2001; 39(5-6):427–34.
79. Keene CD, Cudaback E, Li X, Montine KS, Montine TJ. Apolipoprotein E isoforms and regulation of the innate immune response in brain of patients with Alzheimer's disease. Curr Opin Neurobiol. 2011;21(6):920–8.
80. Zhu Y, Nwabuisi-Heath E, Dumanis SB, Tai LM, Yu C, Rebeck GW, et al. APOE genotype alters glial activation and loss of synaptic markers in mice. Glia. 2012;60(4):559–69.

81. Rodriguez GA, Tai LM, LaDu MJ, Rebeck GW. Human APOE4 increases microglia reactivity at A plaques in a mouse model of A deposition. J Neuroinflammation. 2014;11:111.
82. Ringman JM, Elashoff D, Geschwind DH, Welsh BT, Gylys KH, Lee C, et al. Plasma signaling proteins in persons at genetic risk for Alzheimer disease: influence of APOE genotype. Arch Neurol. 2012;69(6):757–64.
83. Mannix RC, Zhang J, Park J, Zhang X, Bilal K, Walker K, et al. Age-dependent effect of apolipoprotein E4 on functional outcome after controlled cortical impact in mice. J Cereb Blood Flow Metab. 2011;31(1):351–61.
84. Lynch JR, Tang W, Wang H, Vitek MP, Bennett ER, Sullivan PM, et al. APOE genotype and an ApoE-mimetic peptide modify the systemic and central nervous system inflammatory response. J Biol Chem. 2003;278(49):48529–33.
85. Arnaud L, Benech P, Greetham L, Stephan D, Jimenez A, Jullien N, et al. APOE4 drives inflammation in human astrocytes via TAGLN3 repression and NF-B activation. Cell Rep. 2022;40(7): 111200.
86. Fan YY, Cai QL, Gao ZY, Lin X, Huang Q, Tang W, et al. APOE epsilon4 allele elevates the expressions of inflammatory factors and promotes Alzheimer's disease progression: a comparative study based on Han and She populations in the Wenzhou area. Brain Res Bull. 2017;132:39–43.
87. Tao Q, Ang TFA, DeCarli C, Auerbach SH, Devine S, Stein TD, et al. Association of chronic low-grade inflammation with risk of Alzheimer disease in ApoE4 carriers. JAMA Netw Open. 2018;1 (6):e183597.
88. Ebright B, Assante I, Poblete RA, Wang S, Duro MV, Bennett DA, et al. Eicosanoid lipidome activation in post-mortem brain tissues of individuals with APOE4 and Alzheimer's dementia. Alzheimers Res Ther. 2022;14(1):152.
89. Ren RJ, Yin P, Wang ZH, Qi JL, Tang R, Wang JT, et al. China Alzheimer's disease report 2021. Theory Pract Diagn. 2021;20(4): 317–37.
90. Dubal DB. Sex difference in Alzheimer's disease: An updated, balanced and emerging perspective on differing vulnerabilities. Handb Clin Neurol. 2020;175:261–73.
91. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. a meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. Jama. 1997;278(16):1349–56.
92. Altmann A, Tian L, Henderson VW, Greicius MD. Alzheimer's disease neuroimaging initiative I. Sex modifies the APOE-related risk of developing Alzheimer disease. Ann Neurol. 2014;75(4): 563–73.
93. Heise V, Filippini N, Trachtenberg AJ, Suri S, Ebmeier KP, Mackay CE. Apolipoprotein E genotype, gender and age modulate connectivity of the hippocampus in healthy adults. Neuroimage. 2014;98:23–30.
94. Lin KA, Choudhury KR, Rathakrishnan BG, Marks DM, Petrella JR, Doraiswamy PM, et al. Marked gender differences in progression of mild cognitive impairment over 8 years. Alzheimers Dement (N Y). 2015;1(2):103–10.
95. Damoiseaux JS, Seeley WW, Zhou J, Shirer WR, Coppola G, Karydas A, et al. Gender modulates the APOE epsilon4 effect in healthy older adults: convergent evidence from functional brain connectivity and spinal fluid tau levels. J Neurosci. 2012;32(24): 8254–62.
96. Makkar SR, Lipnicki DM, Crawford JD, Kochan NA, Castro-Costa E, Lima-Costa MF, et al. APOE epsilon4 and the influence of sex, age, vascular risk factors, and ethnicity on cognitive decline. J Gerontol A Biol Sci Med Sci. 2020;75(10):1863–73.
97. Gaubert S, Raimondo F, Houot M, Corsi MC, Naccache L, Diego Sitt J, et al. EEG evidence of compensatory mechanisms in preclinical Alzheimer's disease. Brain. 2019;142(7):2096–112.
98. Locatelli T, Cursi M, Liberati D, Franceschi M, Comi G. EEG coherence in Alzheimer's disease. Electroencephalogr Clin Neurophysiol. 1998;106(3):229–37.
99. Lehtovirta M, Partanen J, Könönen M, Soininen H, Helisalmi S, Mannermaa A, et al. Spectral analysis of EEG in Alzheimer's disease: relation to apolipoprotein E polymorphism. Neurobiol Aging. 1996;17(4):523–6.
100. Lehtovirta M, Partanen J, Könönen M, Hiltunen J, Helisalmi S, Hartikainen P, et al. A longitudinal quantitative EEG study of Alzheimer's disease: relation to apolipoprotein E polymorphism. Dement Geriatr Cogn Disord. 2000;11(1):29–35.
101. Gutiérrez-de Pablo V, Gómez C, Poza J, Maturana-Candelas A, Martins S, Gomes I, et al. Relationship between the presence of the ApoE 4 allele and EEG complexity along the Alzheimer's disease continuum. Sensors (Basel). 2020;20(14):3849.
102. Ponomareva NV, Korovaitseva GI, Rogaev EI. EEG alterations in non-demented individuals related to apolipoprotein E genotype and to risk of Alzheimer disease. Neurobiol Aging. 2008;29(6): 819–27.
103. Babiloni C, Benussi L, Binetti G, Cassetta E, Dal Forno G, Del Percio C, et al. Apolipoprotein E and alpha brain rhythms in mild cognitive impairment: a multicentric electroencephalogram study. Ann Neurol. 2006;59(2):323–34.
104. O'Dwyer L, Lamberton F, Matura S, Tanner C, Scheibe M, Miller J, et al. Reduced hippocampal volume in healthy young ApoE4 carriers: an MRI study. PLoS One. 2012;7(11):e48895.
105. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. The Lancet. 2006;368(9533):387–403.
106. Chetelat G, Fouquet M. Neuroimaging biomarkers for Alzheimer's disease in asymptomatic APOE4 carriers. Rev Neurol (Paris). 2013;169(10):729–36.
107. Fan M, Liu B, Zhou Y, Zhen X, Xu C, Jiang T. Cortical thickness is associated with different apolipoprotein E genotypes in healthy elderly adults. Neurosci Lett. 2010;479(3):332–6.
108. Fennema-Notestine C, Panizzon MS, Thompson WR, Chen CH, Eyler LT, Fischl B, et al. Presence of ApoE 4 allele associated with thinner frontal cortex in middle age. J Alzheimers Dis. 2011; 26(Suppl 3):49–60.
109. Morra JH, Tu Z, Apostolova LG, Green AE, Avedissian C, Madsen SK, et al. Automated 3D mapping of hippocampal atrophy and its clinical correlates in 400 subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls. Hum Brain Mapp. 2009;30(9):2766–88.
110. Mueller SG, Weiner MW. Selective effect of age, Apo e4, and Alzheimer's disease on hippocampal subfields. Hippocampus. 2009;19(6): 558–64.
111. Mosconi L, Berti V, Glodzik L, Pupi A, De Santi S, de Leon MJ. Pre-clinical detection of Alzheimer's disease using FDG-PET, with or without amyloid imaging. J Alzheimers Dis. 2010;20(3):843–54.
112. Small GW, Mazziotta JC, Collins MT, Baxter LR, Phelps ME, Mandelkern MA, et al. Apolipoprotein E type 4 allele and cerebral glucose metabolism in relatives at risk for familial Alzheimer disease. Jama. 1995;273(12):942–7.
113. Reiman EM, Caselli RJ, Yun LS, Chen K, Bandy D, Minoshima S, et al. Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. N Engl J Med. 1996;334(12):752–8.
114. Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, et al. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. Proc Natl Acad Sci U S A. 2004;101(1):284–9.
115. Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, et al. Correlations between apolipoprotein E epsilon4 gene dose and brain-imaging measurements of regional hypometabolism. Proc Natl Acad Sci U S A. 2005;102(23):8299–302.
116. Finkel SI, Costa e Silva J, Cohen G, Miller S, Sartorius N. Behavioral and psychological signs and symptoms of dementia: a

consensus statement on current knowledge and implications for research and treatment. Int Psychogeriatr. 1996;8(Suppl 3): 497–500.
117. Beaudreau SA, O'Hara R. Late-life anxiety and cognitive impairment: a review. Am J Geriatr Psychiatry. 2008;16(10):790–803.
118. Chen S, Lin K, Wang H, Yamakawa M, Makimoto K, Liao X. Reliability and structural validity of the Chinese version of the Neuropsychiatric Inventory. Nursing Home version. Psychogeriatrics. 2018;18(2):113–22.
119. Delano-Wood L, Houston WS, Emond JA, Marchant NL, Salmon DP, Jeste DV, et al. APOE genotype predicts depression in women with Alzheimer's disease: a retrospective study. Int J Geriatr Psychiatry. 2008;23(6):632–6.
120. Ramachandran G, Marder K, Tang M, Schofield PW, Chun MR, Devanand DP, et al. A preliminary study of apolipoprotein E genotype and psychiatric manifestations of Alzheimer's disease. Neurology. 1996;47(1):256–9.
121. Ballard C, Massey H, Lamb H, Morris C. Apolipoprotein E: non-cognitive symptoms and cognitive decline in late onset Alzheimer's disease. J Neurol Neurosurg Psychiatry. 1997;63(2):273–4.
122. Sheridan PL, Hausdorff JM. The role of higher-level cognitive function in gait: executive dysfunction contributes to fall risk in Alzheimer's disease. Dement Geriatr Cogn Disord. 2007;24(2): 125–37.
123. Rossor MN, Tyrrell PJ, Warrington EK, Thompson PD, Marsden CD, Lantos P. Progressive frontal gait disturbance with atypical Alzheimer's disease and corticobasal degeneration. J Neurol Neurosurg Psychiatry. 1999;67(3):345–52.
124. Kluger A, Gianutsos JG, Golomb J, Ferris SH, George AE, Franssen E, et al. Patterns of motor impairement in normal aging, mild cognitive decline, and early Alzheimer's disease. J Gerontol B Psychol Sci Soc Sci. 1997;52b(1):P28–39.
125. Imamura T, Hirono N, Hashimoto M, Kazui H, Tanimukai S, Hanihara T, et al. Fall-related injuries in dementia with Lewy bodies (DLB) and Alzheimer's disease. Eur J Neurol. 2000;7(1):77–9.
126. Wilson RS, Schneider JA, Beckett LA, Evans DA, Bennett DA. Progression of gait disorder and rigidity and risk of death in older persons. Neurology. 2002;58(12):1815–9.
127. Bloem BR, Gussekloo J, Lagaay AM, Remarque EJ, Haan J, Westendorp RG. Idiopathic senile gait disorders are signs of subclinical disease. J Am Geriatr Soc. 2000;48(9):1098–101.
128. MacAulay RK, Allaire T, Brouillette R, Foil H, Bruce-Keller AJ, Keller JN. Apolipoprotein E genotype linked to spatial gait characteristics: predictors of cognitive dual task gait change. PLoS One. 2016;11(8):e0156732.
129. Li RX, Ma YH, Tan L, Yu JT. Prospective biomarkers of Alzheimer's disease: a systematic review and meta-analysis. Ageing Res Rev. 2022;81:101699.
130. Lautner R, Palmqvist S, Mattsson N, Andreasson U, Wallin A, Palsson E, et al. Apolipoprotein E genotype and the diagnostic accuracy of cerebrospinal fluid biomarkers for Alzheimer disease. JAMA Psychiatry. 2014;71(10):1183–91.
131. Lim YY, Kalinowski P, Pietrzak RH, Laws SM, Burnham SC, Ames D, et al. Association of beta-amyloid and apolipoprotein E epsilon4 with memory decline in preclinical Alzheimer disease. JAMA Neurol. 2018;75(4):488–94.
132. Bonham LW, Geier EG, Fan CC, Leong JK, Besser L, Kukull WA, et al. Age-dependent effects of APOE epsilon4 in preclinical Alzheimer's disease. Ann Clin Transl Neurol. 2016;3(9): 668–77.
133. Xiong X, Xiao H, Zhang Y, Yu D, Chuan J, Zhong L, et al. Diagnosis test meta-analysis for apolipoprotein E in Alzheimer's disease. Dis Markers. 2020;2020:6486031.
134. Szekely CA, Breitner JC, Fitzpatrick AL, Rea TD, Psaty BM, Kuller LH, et al. NSAID use and dementia risk in the cardiovascular health study: role of APOE and NSAID type. Neurology. 2008;70(1):17–24.
135. Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med. 2014;370(4):322–33.
136. Cramer PE, Cirrito JR, Wesson DW, Lee CY, Karlo JC, Zinn AE, et al. ApoE-directed therapeutics rapidly clear β-amyloid and reverse deficits in AD mouse models. Science. 2012;335(6075): 1503–6.
137. Gibson GE, Luchsinger JA, Cirio R, Chen H, Franchino-Elder J, Hirsch JA, et al. Benfotiamine and cognitive decline in Alzheimer's disease: results of a randomized placebo-controlled phase IIa clinical trial. J Alzheimers Dis. 2020;78(3):989–1010.
138. Rosenbloom MH, Barclay TR, Pyle M, Owens BL, Cagan AB, Anderson CP, et al. A single-dose pilot trial of intranasal rapid-acting insulin in apolipoprotein E4 carriers with mild-moderate Alzheimer's disease. CNS Drugs. 2014;28(12):1185–9.
139. Boz HE, Kocoglu K, Akkoyun M, Tuefekci IY, Ekin M, Oezcelik P, et al. The influence of stimulus eccentricity on prosaccade outcomes in patients with Alzheimer's disease dementia at an early stage and amnestic mild cognitive impairment. J Clin Exp Neuropsyc. 2022;44(10):713–29.
140. Wei N, Chen J. Repetitive transcranial magnetic stimulation for Alzheimer's disease based on apolipoprotein E genotyping: protocol for a randomized controlled study. Front Aging Neurosci. 2021;13:758765.
141. Head D, Bugg JM, Goate AM, Fagan AM, Mintun MA, Benzinger T, et al. Exercise engagement as a moderator of the effects of APOE genotype on amyloid deposition. Arch Neurol. 2012;69(5):636–43.
142. Sanders LMJ, Hortobagyi T, Karssemeijer EGA, Van der Zee EA, Scherder EJA, van Heuvelen MJG. Effects of low- and high-intensity physical exercise on physical and cognitive function in older persons with dementia: a randomized controlled trial. Alzheimers Res Ther. 2020;12(1):28.
143. Liao F, Hori Y, Hudry E, Bauer AQ, Jiang H, Mahan TE, et al. Anti-ApoE antibody given after plaque onset decreases Aβ accumulation and improves brain function in a mouse model of Aβ amyloidosis. J Neurosci. 2014;34(21):7281–92.
144. Kim J, Eltorai AE, Jiang H, Liao F, Verghese PB, Kim J, et al. Anti-apoE immunotherapy inhibits amyloid accumulation in a transgenic mouse model of Aβ amyloidosis. J Exp Med. 2012;209 (12):2149–56.
145. Liao F, Li A, Xiong M, Bien-Ly N, Jiang H, Zhang Y, et al. Targeting of nonlipidated, aggregated ApoE with antibodies inhibits amyloid accumulation. J Clin Invest. 2018;128(5):2144–55.
146. Gratuze M, Jiang H, Wang C, Xiong M, Bao X, Holtzman DM. APOE antibody inhibits Aβ -associated tau seeding and spreading in a mouse model. Ann Neurol. 2022;91(6):847–52.
147. Xiong M, Jiang H, Serrano JR, Gonzales ER, Wang C, Gratuze M, et al. APOE immunotherapy reduces cerebral amyloid angiopathy and amyloid plaques while improving cerebrovascular function. Sci Transl Med. 2021;13(581):eabd7522.
148. Wolska A, Reimund M, Sviridov DO, Amar MJ, Remaley AT. Apolipoprotein mimetic peptides: potential new therapies for cardiovascular diseases. Cells. 2021;10(3):597.
149. Vitek MP, Christensen DJ, Wilcock D, Davis J, Van Nostrand WE, Li FQ, et al. APOE-mimetic peptides reduce behavioral deficits, plaques and tangles in Alzheimer's disease transgenics. Neurodegener Dis. 2012;10(1-4):122–6.
150. Ghosal K, Stathopoulos A, Thomas D, Phenis D, Vitek MP, Pimplikar SW. The apolipoprotein-E-mimetic COG112 protects amyloid precursor protein intracellular domain-overexpressing animals from Alzheimer's disease-like pathological features. Neurodegener Dis. 2013;12(1):51–8.
151. Chen HK, Liu Z, Meyer-Franke A, Brodbeck J, Miranda RD, McGuire JG, et al. Small molecule structure correctors abolish detrimental effects of apolipoprotein E4 in cultured neurons. J Biol Chem. 2012;287(8):5253–66.

152. Wang C, Najm R, Xu Q, Jeong DE, Walker D, Balestra ME, et al. Gain of toxic apolipoprotein E4 effects in human iPSC-derived neurons is ameliorated by a small-molecule structure corrector. Nat Med. 2018;24(5):647–57.
153. Lin YT, Seo J, Gao F, Feldman HM, Wen HL, Penney J, 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(6):1141–54 e7.
154. Li H, Wei XL. Phenomics: a science of unravelling the genotype-phenotype relationship. Biotechnology Bulletin. 2013;07:47–53.
155. Denny JC, Bastarache L, Roden DM. Phenome-wide association studies as a tool to advance precision medicine. Annu Rev Genomics Hum Genet. 2016;17:353–73.
156. Bush WS, Oetjens MT, Crawford DC. Unravelling the human genome-phenome relationship using phenome-wide association studies. Nat Rev Genet. 2016;17(3):129–45.
157. Lyketsos CG. Treatment development for Alzheimer's disease: how are we doing? Adv Exp Med Biol. 2020;1195:19.
158. Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol. 2013;9(2):106–18.
159. Schenning KJ, Holden S, Davis BA, Mulford A, Nevonen KA, Quinn JF, et al. Gene-specific DNA methylation linked to postoperative cognitive dysfunction in apolipoprotein E3 and E4 mice. J Alzheimers Dis. 2021;83(3):1251–68.
160. Morris G, Berk M, Maes M, Puri BK. Could Alzheimer's disease originate in the periphery and if so how so? Mol Neurobiol. 2019;56(1):406–34.
161. Yin Y, Wang Z. ApoE and neurodegenerative diseases in aging. Adv Exp Med Biol. 2018;1086:77–92.
162. Marais AD. Apolipoprotein E in lipoprotein metabolism, health and cardiovascular disease. Pathology. 2019;51(2):165–76.
163. Rasmusson DX, Dal Forno G, Brandt J, Warren AC, Troncoso J, Lyketsos C. Apo-E genotype and verbal deficits in Alzheimer's disease. J Neuropsychiatry Clin Neurosci. 1996;8(3):335–7.
164. Lehtovirta M, Soininen H, Helisalmi S, Mannermaa A, Helkala EL, Hartikainen P, et al. Clinical and neuropsychological characteristics in familial and sporadic Alzheimer's disease: relation to apolipoprotein E polymorphism. Neurology. 1996;46(2):413–9.
165. Finton MJ, Lucas JA, Rippeth JD, Bohac DL, Smith GE, Ivnik RJ, et al. Cognitive asymmetries associated with apolipoprotein E genotype in patients with Alzheimer's disease. J Int Neuropsychol Soc. 2003;9(5):751–9.
166. Houston WS, Delis DC, Lansing A, Jacobson MW, Cobell KR, Salmon DP, et al. Executive function asymmetry in older adults genetically at-risk for Alzheimer's disease: verbal versus design fluency. J Int Neuropsychol Soc. 2005;11(7):863–70.
167. Hoyt BD, Massman PJ, Schatschneider C, Cooke N, Doody RS. Individual growth curve analysis of APOE epsilon 4-associated cognitive decline in Alzheimer disease. Arch Neurol. 2005;62(3):454–9.
168. Wang X, Wang J, He Y, Li H, Yuan H, Evans A, et al. Apolipoprotein E epsilon4 modulates cognitive profiles, hippocampal volume, and resting-state functional connectivity in Alzheimer's disease. J Alzheimers Dis. 2015;45(3):781–95.
169. Saeed U, Mirza SS, MacIntosh BJ, Herrmann N, Keith J, Ramirez J, et al. APOE-epsilon4 associates with hippocampal volume, learning, and memory across the spectrum of Alzheimer's disease and dementia with Lewy bodies. Alzheimers Dement. 2018;14(9):1137–47.
170. Lyketsos CG, Baker L, Warren A, Steele C, Brandt J, Steinberg M, et al. Depression, delusions, and hallucinations in Alzheimer's disease: no relationship to apolipoprotein E genotype. J Neuropsychiatry Clin Neurosci. 1997;9(1):64–7.
171. Holmes C, Russ C, Kirov G, Aitchison KJ, Powell JF, Collier DA, et al. Apolipoprotein E: depressive illness, depressive symptoms, and Alzheimer's disease. Biol Psychiatry. 1998;43(3):159–64.
172. Scarmeas N, Brandt J, Albert M, Devanand DP, Marder K, Bell K, et al. Association between the APOE genotype and psychopathologic symptoms in Alzheimer's disease. Neurology. 2002;58(8):1182–8.
173. Bondi MW, Houston WS, Salmon DP, Corey-Bloom J, Katzman R, Thal LJ, et al. Neuropsychological deficits associated with Alzheimer's disease in the very-old: discrepancies in raw vs. standardized scores. J Int Neuropsychol Soc. 2003;9(5):783–95.
174. Chang JB, Wang PN, Chen WT, Liu CY, Hong CJ, Lin KN, et al. ApoE epsilon4 allele is associated with incidental hallucinations and delusions in patients with AD. Neurology. 2004;63(6):1105–7.
175. Lehtovirta M, Soininen H, Laakso MP, Partanen K, Helisalmi S, Mannermaa A, et al. SPECT and MRI analysis in Alzheimer's disease: relation to apolipoprotein E epsilon 4 allele. J Neurol Neurosurg Psychiatry. 1996;60(6):644–9.
176. Yasuda M, Mori E, Kitagaki H, Yamashita H, Hirono N, Shimada K, et al. Apolipoprotein E epsilon 4 allele and whole brain atrophy in late-onset Alzheimer's disease. Am J Psychiatry. 1998;155(6):779–84.
177. Fleisher A, Grundman M, Jack CR Jr, Petersen RC, Taylor C, Kim HT, et al. Sex, apolipoprotein E epsilon 4 status, and hippocampal volume in mild cognitive impairment. Arch Neurol. 2005;62(6):953–7.
178. van de Pol LA, van der Flier WM, Korf ES, Fox NC, Barkhof F, Scheltens P. Baseline predictors of rates of hippocampal atrophy in mild cognitive impairment. Neurology. 2007;69(15):1491–7.
179. Pievani M, Galluzzi S, Thompson PM, Rasser PE, Bonetti M, Frisoni GB. APOE4 is associated with greater atrophy of the hippocampal formation in Alzheimer's disease. Neuroimage. 2011;55(3):909–19.
180. Mirza SS, Saeed U, Knight J, Ramirez J, Stuss DT, Keith J, et al. APOE epsilon4, white matter hyperintensities, and cognition in Alzheimer and Lewy body dementia. Neurology. 2019;93(19):e1807–19.
181. Dunk MM, Driscoll I. Total cholesterol and APOE-related risk for Alzheimer's disease in the Alzheimer's disease neuroimaging initiative. J Alzheimers Dis. 2022;85(4):1519–28.
182. Barthel H, Gertz HJ, Dresel S, Peters O, Bartenstein P, Buerger K, et al. Cerebral amyloid-⊠ PET with florbetaben (18F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study. Lancet Neurol. 2011;10(5):424–35.
183. Jelic V, Julin P, Shigeta M, Nordberg A, Lannfelt L, Winblad B, et al. Apolipoprotein E epsilon4 allele decreases functional connectivity in Alzheimer's disease as measured by EEG coherence. J Neurol Neurosurg Psychiatry. 1997;63(1):59–65.
184. Canuet L, Tellado I, Couceiro V, Fraile C, Fernandez-Novoa L, Ishii R, et al. Resting-state network disruption and APOE genotype in Alzheimer's disease: a lagged functional connectivity study. PLoS One. 2012;7(9):e46289.
185. Whitson HE, Potter GG, Feld JA, Plassman BL, Reynolds K, Sloane R, et al. Dual-task gait and Alzheimer's disease genetic risk in cognitively normal adults: a pilot study. J Alzheimers Dis. 2018;64(4):1137–48.
186. Lehtimäki T, Pirttilä T, Mehta PD, Wisniewski HM, Frey H, Nikkari T. Apolipoprotein E (apoE) polymorphism and its influence on ApoE concentrations in the cerebrospinal fluid in Finnish patients with Alzheimer's disease. Hum Genet. 1995;95(1):39–42.
187. Morris JK, Uy RAZ, Vidoni ED, Wilkins HM, Archer AE, Thyfault JP, et al. Effect of APOE epsilon4 genotype on metabolic biomarkers in aging and Alzheimer's disease. J Alzheimers Dis. 2017;58(4):1129–35.
188. Abushakra S, Porsteinsson A, Scheltens P, Sadowsky C, Vellas B, Cummings J, et al. Clinical effects of tramiprosate in APOE4/4 homozygous patients with mild Alzheimer's disease suggest disease modification potential. J Prev Alzheimers Dis. 2017;4(3):149–56.
189. Choi SH, Kim SY, Na HR, Kim BK, Yang DW, Kwon JC, et al. Effect of ApoE genotype on response to donepezil in patients with

Alzheimer's disease. Dement Geriatr Cogn Disord. 2008;25(5): 445–50.
190. Farlow MR, Cyrus PA, Nadel A, Lahiri DK, Brashear A, Gulanski B. Metrifonate treatment of AD: influence of APOE genotype. Neurology. 1999;53(9):2010–6.
191. Farlow MR, Lahiri DK, Poirier J, Davignon J, Hui S. Apolipoprotein E genotype and gender influence response to tacrine therapy. Ann N Y Acad Sci. 1996;802:101–10.
192. Farlow MR, Lahiri DK, Poirier J, Davignon J, Schneider L, Hui SL. Treatment outcome of tacrine therapy depends on apolipoprotein genotype and gender of the subjects with Alzheimer's disease. Neurology. 1998;50(3):669–77.
193. Gold M, Alderton C, Zvartau-Hind M, Egginton S, Saunders AM, Irizarry M, et al. Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. Dement Geriatr Cogn Disord. 2010;30(2):131–46.
194. Henderson ST, Vogel JL, Barr LJ, Garvin F, Jones JJ, Costantini LC. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. Nutr Metab (Lond). 2009;6:31.
195. Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 study group. Neurology. 2000;54(12):2261–8.
196. Reger MA, Watson GS, Frey WH 2nd, Baker LD, Cholerton B, Keeling ML, et al. Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. Neurobiol Aging. 2006;27(3):451–8.
197. Rigaud AS, Traykov L, Caputo L, Guelfi MC, Latour F, Couderc R, et al. The apolipoprotein E epsilon4 allele and the response to tacrine therapy in Alzheimer's disease. Eur J Neurol. 2000;7(3): 255–8.
198. Risner ME, Saunders AM, Altman JF, Ormandy GC, Craft S, Foley IM, et al. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. Pharmacogenomics J. 2006;6(4):246–54.
199. Suh GH, Jung HY, Lee CU, Oh BH, Lee SK, Lee N, et al. Effect of the apolipoprotein E epsilon4 allele on the efficacy and tolerability of galantamine in the treatment of Alzheimer's disease. Dement Geriatr Cogn Disord. 2006;21(1):33–9.
200. Xu Q, Zhang Y, Zhang X, Liu L, Zhou B, Mo R, et al. Medium-chain triglycerides improved cognition and lipid metabolomics in mild to moderate Alzheimer's disease patients with APOE4(-/-): A double-blind, randomized, placebo-controlled crossover trial. Clin Nutr. 2020;39(7):2092–105.
201. Almkvist O, Jelic V, Amberla K, Hellstrom-Lindahl E, Meurling L, Nordberg A. Responder characteristics to a single oral dose of cholinesterase inhibitor: a double-blind placebo-controlled study with tacrine in Alzheimer patients. Dement Geriatr Cogn Disord. 2001;12(1):22–32.
202. Alvarez XA, Mouzo R, Pichel V, Perez P, Laredo M, Fernandez-Novoa L, et al. Double-blind placebo-controlled study with citicoline in APOE genotyped Alzheimer's disease patients. Effects on cognitive performance, brain bioelectrical activity and cerebral perfusion. Methods Find Exp Clin Pharmacol. 1999;21(9):633–44.
203. Babi T, Mahovi Lakusi D, Serti J, Petrovecki M, Stavljeni -Rukavina A. ApoE genotyping and response to galanthamine in Alzheimer's disease--a real life retrospective study. Coll Antropol. 2004;28(1):199–204.
204. Blesa R, Aguilar M, Casanova JP, Boada M, Martínez S, Alom J, et al. Relationship between the efficacy of rivastigmine and apolipoprotein E (epsilon4) in patients with mild to moderately severe Alzheimer disease. Alzheimer Dis Assoc Disord. 2006;20(4): 248–54.
205. De Beaumont L, Pelleieux S, Lamarre-Theroux L, Dea D, Poirier J. Butyrylcholinesterase K and apolipoprotein E-varepsilon4 reduce the age of onset of Alzheimer's disease, accelerate cognitive decline, and modulate donepezil response in mild cognitively impaired subjects. J Alzheimers Dis. 2016;54(3):913–22.
206. Gavrilova SI, Kolykhalov IV, Korova tseva GI, Zharikov GA, Kalyn Ia B, Selezneva ND. ApoE genotype and efficacy of neurotrophic and cholinergic therapy in Alzheimer's disease. Zh Nevrol Psikhiatr Im S S Korsakova. 2005;105(4):27–34.
207. Han HJ, Kim BC, Lee JY, Ryu SH, Na HR, Yoon SJ, et al. Response to rivastigmine transdermal patch or memantine plus rivastigmine patch is affected by apolipoprotein E genotype in Alzheimer patients. Dement Geriatr Cogn Disord. 2012;34(3-4): 167–73.
208. Harrington C, Sawchak S, Chiang C, Davies J, Donovan C, Saunders AM, et al. Rosiglitazone does not improve cognition or global function when used as adjunctive therapy to AChE inhibitors in mild-to-moderate Alzheimer's disease: two phase 3 studies. Curr Alzheimer Res. 2011;8(5):592–606.
209. Rigaud AS, Traykov L, Latour F, Couderc R, Moulin F, Forette F. Presence or absence of at least one epsilon 4 allele and gender are not predictive for the response to donepezil treatment in Alzheimer's disease. Pharmacogenetics. 2002;12(5):415–20.
210. Jack CR Jr, Petersen RC, Grundman M, Jin S, Gamst A, Ward CP, et al. Longitudinal MRI findings from the vitamin E and donepezil treatment study for MCI. Neurobiol Aging. 2008;29(9): 1285–95.
211. Zhong Y, Zheng X, Miao Y, Wan L, Yan H, Wang B. Effect of CYP2D6*10 and APOE polymorphisms on the efficacy of donepezil in patients with Alzheimer's disease. Am J Med Sci. 2013;345 (3):222–6.
212. Jia J, Wei C, Chen W, Jia L, Zhou A, Wang F, et al. Safety and efficacy of donepezil 10 mg/day in patients with mild to moderate Alzheimer's disease. J Alzheimers Dis. 2020;74(1):199–211.
213. Schneider LS, Farlow M. Combined tacrine and estrogen replacement therapy in patients with Alzheimer's disease. Ann N Y Acad Sci. 1997;826:317–22.
214. MacGowan SH, Wilcock GK, Scott M. Effect of gender and apolipoprotein E genotype on response to anticholinesterase therapy in Alzheimer's disease. Int J Geriatr Psychiatry. 1998;13(9):625–30.
215. Sjogren M, Hesse C, Basun H, Kol G, Thostrup H, Kilander L, et al. Tacrine and rate of progression in Alzheimer's disease--relation to ApoE allele genotype. J Neural Transm (Vienna). 2001;108(4): 451–8.
216. Stefanova E, Blennow K, Almkvist O, Hellstrom-Lindahl E, Nordberg A. Cerebral glucose metabolism, cerebrospinal fluid-beta-amyloid1-42 (CSF-Abeta42), tau and apolipoprotein E genotype in long-term rivastigmine and tacrine treated Alzheimer disease (AD) patients. Neurosci Lett. 2003;338(2):159–63.
217. Pomara N, Willoughby LM, Wesnes K, Sidtis JJ. Increased anticholinergic challenge-induced memory impairment associated with the APOE-epsilon4 allele in the elderly: a controlled pilot study. Neuropsychopharmacology. 2004;29(2):403–9.
218. Riekkinen P Jr, Soininen H, Partanen J, Pääkkönen A, Helisalmi S, Riekkinen P Sr. The ability of THA treatment to increase cortical alpha waves is related to apolipoprotein E genotype of Alzheimer disease patients. Psychopharmacology (Berl). 1997;129(3): 285–8.
219. Tai SY, Chen CH, Chien CY, Yang YH. Cilostazol as an add-on therapy for patients with Alzheimer's disease in Taiwan: a case control study. BMC Neurol. 2017;17(1):40.
220. Watson GS, Baker LD, Cholerton BA, Rhoads KW, Merriam GR, Schellenberg GD, et al. Effects of insulin and octreotide on memory and growth hormone in Alzheimer's disease. J Alzheimers Dis. 2009;18(3):595–602.
221. Arellanes IC, Choe N, Solomon V, He X, Kavin B, Martinez AE, et al. Brain delivery of supplemental docosahexaenoic acid (DHA): A randomized placebo-controlled clinical trial. EBioMedicine. 2020;59:102883.

222. Fleisher AS, Truran D, Mai JT, Langbaum JB, Aisen PS, Cummings JL, et al. Chronic divalproex sodium use and brain atrophy in Alzheimer disease. Neurology. 2011;77(13):1263–71.
223. Valen-Sendstad A, Engedal K, Stray-Pedersen B, Group AS, Strobel C, Barnett L, et al. Effects of hormone therapy on depressive symptoms and cognitive functions in women with Alzheimer disease: a 12 month randomized, double-blind, placebo-controlled study of low-dose estradiol and norethisterone. Am J Geriatr Psychiatry. 2010;18(1):11–20.
224. Cacabelos R, Alvarez A, Fenandez-Novoa L, Lombardi VR. A pharmacogenomic approach to Alzheimer's disease. Acta Neurol Scand Suppl. 2000;176:12–9.
225. Craft S, Asthana S, Cook DG, Baker LD, Cherrier M, Purganan K, et al. Insulin dose-response effects on memory and plasma amyloid precursor protein in Alzheimer's disease: interactions with apolipoprotein E genotype. Psychoneuroendocrinology. 2003;28 (6):809–22.
226. Claxton A, Baker LD, Hanson A, Trittschuh EH, Cholerton B, Morgan A, et al. Long acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease dementia. J Alzheimers Dis. 2015;45(4): 1269–70.
227. Torosyan N, Sethanandha C, Grill JD, Dilley ML, Lee J, Cummings JL, et al. Changes in regional cerebral blood flow associated with a 45 day course of the ketogenic agent, caprylidene, in patients with mild to moderate Alzheimer's disease: results of a randomized, double-blinded, pilot study. Exp Gerontol. 2018;111: 118–21.
228. Jannati A, Block G, Oberman LM, Rotenberg A, Pascual-Leone A. Interindividual variability in response to continuous theta-burst stimulation in healthy adults. Clin Neurophysiol. 2017;128(11): 2268–78.
229. Huuhka M, Anttila S, Leinonen E, Huuhka K, Rontu R, Mattila KM, et al. The apolipoprotein E polymorphism is not associated with response to electroconvulsive therapy in major depressive disorder. J ECT. 2005;21(1):7–11.
230. Bousman CA, Katalinic N, Martin DM, Smith DJ, Ingram A, Dowling N, et al. Effects of COMT, DRD2, BDNF, and APOE genotypic variation on treatment efficacy and cognitive side effects of electroconvulsive therapy. J ECT. 2015;31(2):129–35.
231. Solomon A, Turunen H, Ngandu T, Peltonen M, Levalahti E, Helisalmi S, et al. Effect of the apolipoprotein E genotype on cognitive change during a multidomain lifestyle intervention: A subgroup analysis of a randomized clinical trial. JAMA Neurol. 2018; 75(4):462–70.
232. Uijen IL, Aaronson JA, Karssemeijer EGA, Olde Rikkert MGM, Kessels RPC. Individual differences in the effects of physical activity on cognitive function in people with mild to moderate dementia. J Alzheimers Dis. 2020;74(2):435–9.

How to cite this article: Ji X-Y, Peng X-Y, Tang H-L, Pan H, Wang W-T, Wu J, et al. Alzheimer's disease phenotype based upon the carrier status of the apolipoprotein E ϵ4 allele. Brain Pathology. 2024;34(1):e13208. https://doi.org/10.1111/bpa.13208