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APOE Genotype and Alzheimer's Disease: The Influence of Lifestyle and Environmental Factors

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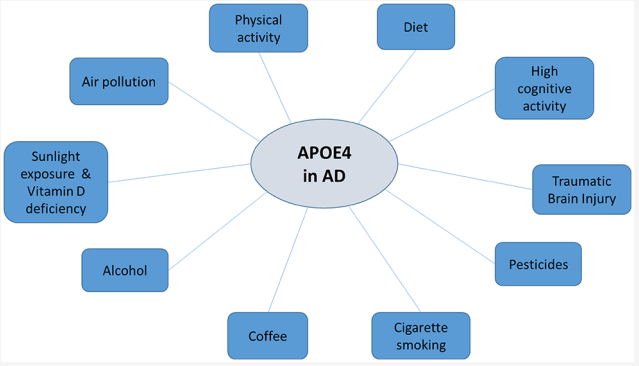
ABSTRACT: Alzheimer's disease (AD) is the most common neurodegenerative disorder with obscure pathogenesis and no disease-modifying therapy to date. AD is multifactorial disease that develops from the complex interplay of genetic factors and environmental exposures. The E4 allele of the gene encoding apolipoprotein E (*APOE*) is the most common genetic risk factor for AD, whereas the E2 allele acts in a protective manner. A growing amount of epidemiological evidence suggests that several lifestyle habits and environmental factors may interact with APOE alleles to synergistically affect the risk of AD development. Among them, physical exercise, dietary habits including fat intake and ketogenic diet, higher education, traumatic brain injury, cigarette smoking, coffee consumption, alcohol intake, and exposure to pesticides and sunlight have gained increasing attention. Although the current evidence is inconsistent, it seems that younger APOE4 carriers in preclinical stages may benefit mostly from preventive lifestyle interventions, whereas older APOE4 noncarriers with dementia may show the most pronounced effects. The large discrepancies between the epidemiological studies may be attributed to differences in the sample sizes, the demographic characteristics of the participants, including age and sex, the methodological design, and potential related exposures and comorbidities as possible cofounding factors. In this Review, we aim to discuss available evidence of the prominent APOE genotype−environment interactions in regard to cognitive decline with a focus on AD, providing an overview of the current landscape in this field and suggesting future directions.



KEYWORDS: *Dementia, cognitive impairment, APOE4, gene−environment interactions*

1. INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disorder and is the main cause of dementia, affecting ∼4.5% of the population above the age of 65.[1] It has been estimated that the prevalence of dementia will triple by 2050, resulting in an increasing economic and social burden worldwide.[2−4] The etiology of AD remains obscure. Experimental and clinical evidence suggest that AD is a multifactorial disease because an interplay of genetic, lifestyle, and environmental factors contributes to its onset.[1] The vast majority of AD cases are sporadic, whereas amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) gene mutations are responsible for some familial forms of AD.[5] The key neuropathological and pathophysiological features of the disease involve aberrant extracellular amyloid-beta plaque accumulation and intracellular neurofibrillary tangles consisting of abnormally hyperphosphorylated tau protein, disrupted glucose and lipid metabolism, neuroinflammation, defective response to oxidative stress, and mitochondrial impairment.[6] To date, there is no established disease-modifying therapy for AD, and the current symptomatic pharmacological treatments, including acetylcholinesterase inhibitors and memantine, fail to halt the progression of the disease.[7] Hence, the identification of potentially modifiable risk factors, their relationship with specific AD-related genes, and the exploration of lifestyle preventive strategies that could delay disease progression are of paramount importance. Whereas advances in novel genomic technologies have majorly contributed to the detection of genetic susceptibility factors, the analysis of exposome, the environmental exposures throughout the lifespan, has received increasing attention.[8]

Aging, female sex, family history of the disease, and genetic predisposition represent some of the nonmodifiable risk factors

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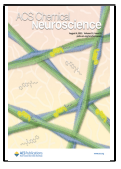

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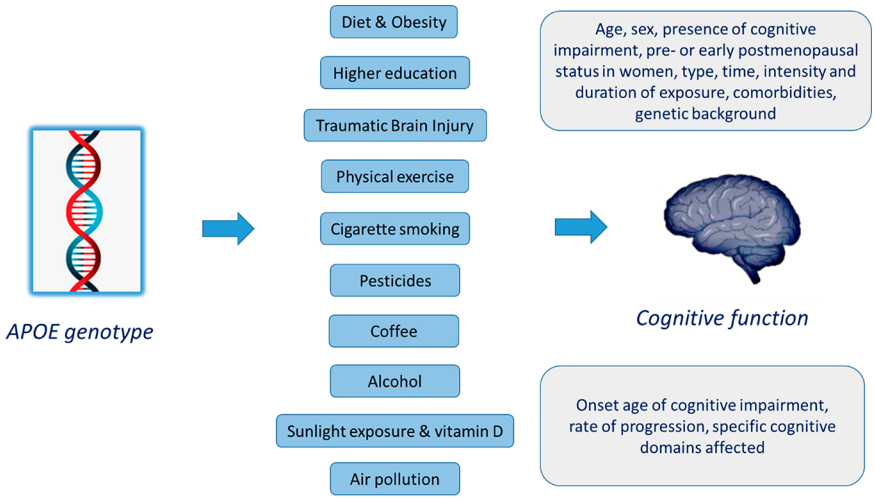

Figure 1. APOE4 genotype and potential interaction with environmental exposures that affect cognitive function.

for AD development.[9] On the contrary, cardiovascular risk factors, including diabetes mellitus, smoking, obesity, hypercholesterolemia and hypertension, traumatic brain injury (TBI), air pollution, education, physical activity, and coffee and alcohol consumption are potentially modifiable factors that affect AD risk.[10] Around 40% of dementia cases might be prevented by modifying lifestyle risk factors, such as dietary alterations, physical exercise, and the effective management of several comorbidities, including diabetes and dyslipidemia.[11,12] Hence, determining the most appropriate individuals for such lifestyle modifications is of paramount importance.

Apolipoprotein E (APOE) is the main brain apolipoprotein and is critically involved in lipid transport and homeostasis.[13] APOE is encoded by the *APOE* gene situated at the long arm of chromosome 19.[13] In humans, three *APOE* gene alleles are present, known as *ε2*, *ε3*, and *ε4*, which differ by the existence of either cysteine or arginine at specific residues.[9,14] APOE4 variant is the strongest AD genetic risk factor, present in ∼60% of AD cases.[15,16] Although APOE is the most well studied genetic contributor to AD,[9] the exact molecular mechanisms underlying its effects on disease onset have not been clarified. Several lifestyle factors, such as diet, smoking, and physical exercise, may interact with the APOE genotype to affect cognitive impairment.[9]

Herein, on the basis of the growing epidemiological evidence, we critically discuss the potential interaction between lifestyle−environmental factors and the APOE genotype in regard to their impact on the risk of cognitive impairment, contributing to AD. The elucidation of these genetic−environmental interactions through the integration of the genome and exposome cues will substantially enhance our deeper understanding of the complex pathophysiology of AD. Moreover, it will pave the way for the development of effective and more personalized precision-medicine-oriented preventive and therapeutic approaches.

2. APOLIPOPROTEIN E: STRUCTURE, ISOFORMS, NORMAL FUNCTION, AND DISEASE RISK

The different combinations of the three APOE alleles give rise to six different genotypes (*ε2*/*ε2*, *ε2*/*ε3*, *ε2*/*ε4*, *ε3*/*ε3*, *ε3*/*ε4*, and *ε4*/*ε4*).[14] In white populations, the frequencies of *ε2*, *ε3*, and *ε4* alleles are approximately 5, 75, and 15−20%, respectively.[17] APOE is a 34 kDa protein consisting of 299 amino acids. It comprises two structural helical domains, a N-terminal domain that contains a region responsible for receptor binding and a smaller C-terminal domain that determines its lipid-binding properties, which are connected via a nonhelical hinge region.[18] APOE is a lipid transport protein that majorly contributes to lipid metabolism and cholesterol homeostasis. It is implicated in the delivery of lipids from one tissue or cell to another via APOE receptors and other proteins as well as through additional cellular processes including neuronal signaling, glucose metabolism, insulin signaling, mitochondrial function, and inflammation.[19] Compared with APOE2 and APOE3, APOE4 is more unstable and compact[13] and displays different organizations in the C-terminal domain, resulting in lower lipid-binding affinity, which crucially affects the normal function of the protein.[14] APOE is mostly expressed in the liver followed by the brain, mainly in astrocytes.[9]

The APOE2 allele is associated with lower plasma cholesterol levels compared with the APOE3 allele, whereas individuals with the APOE4 allele display increased plasma total cholesterol levels. Apart from AD, the APOE4 allele is associated with a higher risk for cardiovascular diseases, mortality and morbidity in the elderly,[20] and poorer outcomes after stroke or TBI.[16] On the contrary, the APOE2 allele seems to act as a protective factor against AD and cardiovascular diseases, whereas it is related to type III hyperlipoproteinemia.[16] The APOE3 allele is generally considered as risk-neutral.[21]

In regard to the pathophysiological mechanisms underlying the impact of APOE alleles on AD, APOE isoforms demonstrate different lipid-binding capacities, which may be implicated in their ability to bind to and clear amyloid beta.[22] The APOE4 isoform is the least able to bind to and clear amyloid beta 40 and 42.[22] Proposed mechanisms of the APOE4-related neurodegeneration involve worse neuronal repair, enhanced amyloid plaque formation, greater susceptibility to oxidative stress, neuroinflammation, dysregulated lipid metabolism, impaired cerebral glucose metabolism, mitochondrial impairment, and abnormal synaptic plasticity.[13,23] APOE also modulates *APP* transcription and amyloid-beta production in neurons, and APOE4 enhances its expression.[24]

Importantly, the epigenetic regulation of gene expression mediated by histone deacetylases (HDACs), which act by removing acetyl groups from histones, resulting in gene

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silencing, has been demonstrated to play a substantial role in AD pathophysiology.[25,26] HDACs are critically involved in the regulation of the expression of genes involved in lipid metabolism and long-term potentiation, and HDAC inhibitors (HDACi's) represent a promising therapeutic approach against AD.[27] In this regard, pan class I HDACi's were recently indicated to increase astrocytic APOE expression and secretion.[28] Interestingly, physical exercise has been shown to inhibit HDAC activity in the hippocampus in some studies,[29,30] and TBI has been associated with dysregulated HDAC activity in the brain.[31] In addition, DNA methylation, another epigenetic mechanism, is also implicated in AD pathogenesis.[32] A post-mortem study showed that the *APOE* gene was differentially methylated in the brain of AD patients in an *APOE* genotype-specific manner,[33] and DNA methylation is a potential mechanism underlying the effects of physical exercise on cognition.[34] Collectively, although the existing evidence is still limited, it could be suggested that epigenetic mechanisms could play a crucial role in the relationship between lifestyle factors and APOE with respect to cognitive impairment, which definitely deserves further study.

3. APOE AND AD: POTENTIAL GENE−ENVIRONMENT INTERACTIONS

Compared with APOE3 homozygotes, the presence of one APOE4 allele increases the risk of AD development by approximately 4-fold, whereas two APOE4 alleles increase this risk to 14-fold.[16] Given the fact that not all individuals carrying the APOE4 allele develop AD, other genetic or environmental factors may affect this risk. Among them, lifestyle and environmental factors, including physical exercise, dietary habits, higher education, TBI, smoking, coffee consumption, alcohol intake, and exposure to pesticides and sunlight have received growing attention, given the possible lifestyle modifications that could be applied in individuals at risk, especially those carrying one or two APOE4 alleles (Figure 1). Furthermore, the APOE4 allele has been associated with earlier age at disease onset and faster disease progression, suggesting that specific environmental factors may also alter the onset age or the rate of progression of cognitive decline.[19]

3.1. Physical Activity. A higher physical exercise level has been associated with improved cognitive function in healthy individuals.[25] A systematic review indicated that physical exercise reduced the risk of AD by ∼50%.[35] The APOE genotype has been shown to modulate the expression of brain-derived neurotrophic factor (BDNF),[36] and physical exercise is also known to upregulate BDNF expression in AD patients.[37] Several studies have investigated the role of physical exercise and APOE4 interaction on cognitive function and dementia risk, although available evidence is inconsistent.[38]

It has been shown that compared with APOE4 noncarriers, APOE4 carriers are more susceptible to the beneficial impact of physical exercise on cognition.[25,39] Physically active APOE4 carriers displayed less cognitive decline and hippocampal atrophy compared with APOE4 carriers who were physically inactive, suggesting that greater physical activity may protect against AD-related neurodegeneration in APOE4 carriers.[40] Long-term physical activity that is initiated during middle life has been associated with reduced amyloid-beta burden, in particular, in APOE4 carriers.[41] A more sedentary lifestyle was also associated with higher amyloid burden on ^{11}C Pittsburgh compound-B (PiB) positron emission tomography (PET) in APOE4 carriers,[41] and higher levels of physical activity during middle life could mitigate the effects of APOE4 on AD-related cerebral glucose hypometabolism.[42] Another study demonstrated that physical exercise stabilized the levels of IFN-γ, a neuroinflammatory marker, in the cerebrospinal fluid (CSF) of APOE4 carriers, although the sample size of the APOE4 subgroup was particularly small.[43] Three studies based on the CAIDA data set among relatively young participants demonstrated that the beneficial effects of physical exercise were more evident among APOE4 carriers.[44−46] A clinical study among nondementia older adults using magneto-encephalography (MEG), which evaluates synaptic function, demonstrated that physical activity was associated with reduced hypersynchronization in the left temporal lobe, a characteristic of preclinical AD, in both APOE4 carriers and noncarriers.[47] However, this network profile was related to better episodic and working memory only in the subgroup of APOE4 noncarriers, whereas in APOE4 carriers, left temporal synaptic hypoconnectivity was related to the increased preservation of brain structure, especially in regions mostly involved in AD-related pathology (hippocampus, amygdala, and uncinate tract).[47] These findings highlight the diverse effects of the APOE genotype on abnormal hypersynchronization upon physical activity, although the underlying mechanisms remain to be elucidated.

On the contrary, a randomized clinical trial showed that the beneficial effects of aerobic exercise on executive function were less pronounced in APOE4 carriers compared with noncarriers in younger adults less than 67 years of age.[48] Another large population-based study among relatively old individuals indicated that physical activity significantly reduced the risk of dementia only in APOE noncarriers during a 5 year follow-up period.[49] The beneficial effects of physical exercise were also absent in APOE4 carriers in another large prospective study among relatively old participants,[50] and findings from three longitudinal cohort studies demonstrated no interaction effect between physical exercise and the APOE genotype in cognitive decline among older adults.[51] Furthermore, although aerobic exercise induced a significant increase in plasma BDNF levels in elderly African patients with MCI carrying no APOE4 allele, this intervention did not affect the BDNF concentration in APOE4 carriers.[52]

The large differences in age among studies, the different protocols used to define the degree of physical exercise, the subjective measures of physical activity via questionnaires, the recall bias among cross-sectional studies, and age differences may at least partially account for these contradictory findings. It has been suggested that there could be a possible age-related threshold above which the neurodegenerative process among APOE4 carriers might be too extensive for these individuals to benefit from the positive impact of physical activity.[49] Collectively, it seems that increased physical activity may protect against cognitive impairment in older APOE4 noncarriers, whereas in APOE4 carriers, earlier intervention at younger ages and preclinical stages could be beneficial.[53] Longitudinal studies with objective measures of physical exercise in younger and older individuals are needed to clarify its interaction with the APOE allele status and the effects on cognitive decline. In this regard, a phase II randomized clinical trial (PAAD-2) that aims to investigate the effect of physical activity on cognition in relation to the APOE genotype is also in the recruitment stage.[54]

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3.2. Diet. Epidemiological studies have shown that a high-fat diet, increased total cholesterol, reduced micronutrient intake (thiamine, folate, vitamin C, E, B6, choline, several antioxidants), increased consumption of trans- and saturated fats, as well as lower $n-3$ fatty acids may predispose individuals to AD.[55] Among them, it seems that lipid metabolism dysregulation may be the strongest risk factor for AD.[56] Given the crucial role of APOE in lipid metabolism, the effects of the APOE genotype−dietary interactions on cognitive impairment have been investigated with inconsistent results.

The effect of dietary patterns on cognitive impairment has been shown to be influenced by the APOE genotype in some but not all studies. Regular fish and omega-6 rich oil consumption was associated with a reduced risk of dementia and AD only in APOE4 noncarriers in a large study.[57] Compared with lean fish, fatty fish consumption, including tuna or other fish, has been shown to protect against AD only in APOE4 noncarriers.[58] These clinical findings agree with experimental evidence showing that dietary interventions such as omega-3 fatty acid consumption show more promising results for AD treatment among models not carrying APOE4 allele.[59]

On the contrary, there is also evidence that the APOE4 allele does not affect or even enhance the beneficial effects of healthier dietary interventions on cognitive impairment. The Mediterranean diet, including large amounts of vegetables, olive oil, and polyunsaturated fat, has been associated with a reduced risk of both AD and AD mortality, but the presence of the APOE4 allele did not change these relationship.[60,61] However, in another study, the Nordic diet, including abundant fruits, vegetables, and fish and resembling the Mediterranean diet, brain training, and exercise were associated with the prevention of cognitive impairment, and APOE4 carriers benefited the most in a subgroup analysis.[62] Higher seafood consumption has been correlated with slower global cognitive decline only among APOE4 carriers in another study.[63] The beneficial effects of omega-3 among APOE4 carriers have been observed, in particular, in younger individuals, in two studies,[64,65] highlighting the crucial factor of age in the APOE4−environment interaction with respect to cognitive impairment.

Interestingly, among cognitively normal individuals, APOE4 carriers demonstrated improved cognitive performance after a meal with increased levels of total fat, saturated fat, and glycemic index (HIGH meal) compared with a meal with lower levels of these parameters (LOW meal).[66] On the contrary, cognitively normal APOE4 noncarriers showed the opposite relationship in this study. Although cognitively impaired APOE4 noncarriers displayed enhanced memory after the HIGH meal, the memory performance of cognitively impaired APOE4 carriers was not affected by these meal changes, suggesting that these patients were unable to use energy sources from the HIGH meal to alter the metabolic pathways to improve memory function.[66] However, executive function was also improved in this subgroup of patients,[66] highlighting that diverse cognitive domains may be differentially affected by meal changes in APOE4 carriers. Therefore, the presence of cognitive impairment seems to be a crucial factor influencing the potential APOE4−dietary factor interaction, and it could at least partially explain the contradictory results of previous studies. The lipidation status of APOE affects its ability to bind and clear amyloid beta. In a randomized clinical trial, patients with MCI displayed higher levels of lipid-depleted amyloid beta in their CSF compared with healthy controls, and this relationship was more pronounced in the APOE4 carriers.[67] Moreover, a diet with a high glycemic index and a high saturated fat content was associated with increased lipid-depleted amyloid beta in the CSF of the participants. However, because of small sample sizes, a further subgroup analysis regarding APOE4 status was not performed. Nevertheless, these findings suggest that a diet with greater saturated fat and a higher glycemic index may affect the lipidation status of amyloid beta in the CSF, which could reflect an altered amyloid-beta metabolism in the brain. Further evidence is needed toward the diverse effects of this type of dietary intervention in regard to the APOE genotype.

During the preclinical stages of AD, abnormal brain energy metabolism is observed. Healthy individuals at risk for AD, including APOE4 carriers, display decreased glucose cerebral metabolism in the parietal, posterior cingulate, temporal, and prefrontal cortices.[68,69] For the brain, ketone bodies constitute a potential alternative energy substrate.[70]

In this context, a study among patients with AD or MCI demonstrated that the oral consumption of medium-chain triglycerides (MCTs) could elevate plasma ketone body levels and improve cognitive function only in APOE4 noncarriers.[70] In accordance, a randomized placebo-controlled trial demonstrated that the daily administration of the ketogenic agent AC-1202 to patients with mild to moderate AD was correlated with improved cognitive performance, especially in APOE4 noncarriers.[71] These findings are further supported by *in vivo* evidence, showing that APOE isoforms differentially regulate glucose and ketone body metabolism pathways in the brain[15] as well as the signaling of insulin/insulin-like growth factor (IGF) and amyloid-beta-related pathways.[72]

Obesity is another factor related to diet that has been also associated with increased AD risk. A randomized clinical trial among overweight or obese patients with type 2 diabetes demonstrated that compared with only support and education about diabetes, intensive lifestyle intervention was related to improved cognitive function only in younger and pre- or early postmenopausal women not carrying one or two APOE4 alleles.[73] Therefore, the beneficial effects of weight loss on cognitive function seem to depend on an interaction between the APOE genotype and menopause status. Weight loss in APOE4 carriers may deprive them of fat released from adipose tissue, which is a significant fuel source.[14] Hence although some studies indicate that APOE4 noncarriers may benefit the most from dietary alterations, there is also evidence that does not support this association. The type of dietary intervention, sex, age, menopause status for women, cognitive function, and time of intervention (in the preclinical or clinical stage) seem to affect the results of the previously mentioned studies. In this context, longitudinal studies with larger sample sizes and objective measures of dietary habits among both cognitively normal and impaired individuals are further needed. In addition, a Western diet also increases the risk of cardiovascular diseases, hypertension, obesity, and diabetes, which are also correlated with a higher risk for AD, raising concerns about a direct causal relationship between cognitive impairment and the APOE4 genotype−diet interaction.[56] These comorbidities should be also considered as covariates in future studies for a deeper understanding of this association.

3.3. Education and High Cognitive Activity. High education is one of the best studied environmental factors affecting AD risk. More educated individuals display better

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cognitive function compared with less educated individuals with similar AD-related pathology, suggesting that higher education may provide a cognitive reserve that could allow a greater tolerance to the pathological brain processes.[74] A meta-analysis indicated that lower education levels increase the AD risk.[75] In regard to the effects of higher education on APOE4-related cognitive decline, the results of the epidemiological studies are rather mixed. A large clinical study demonstrated that higher education might protect against dementia among APOE4 carriers.[76] Additive interactions between high education and frequent leisure activities with APOE4 allele status were shown to affect the risk of dementia.[77] APOE4 carriers demonstrate poorer cognitive performance only after adjustments for education level.[78] Old-age cognitive decline in APOE4 carriers who complete college was rescued in another study, and these effects were independent of higher socio-economic status or better access to healthcare.[79] In agreement with this evidence, higher cognitive activity during early and middle life was associated with reduced cortical amyloid deposition assessed via ^{11}C PiB PET, especially in APOE4 carriers.[80] The acceleration of executive function decline was especially pronounced in APOE4 carriers with lower education in another study, suggesting that lower education may also increase the progression rate of cognitive decline.[81] In accordance, higher education was correlated with greater frontotemporal fluorodeoxyglucose (FDG)−PET metabolism and higher performance on episodic memory tests only in APOE4 carriers, independent of amyloid burden, as evaluated by ^{11}C PiB PET.[82]

On the contrary, there is also evidence that APOE4 carriers with more than 8 years of education demonstrate greater cognitive decline over time, whereas for those having fewer than 8 years of education, time trends were not affected by the APOE genotype.[83] The findings of this study suggest that education may possibly accelerate the detrimental effects of the APOE4 allele on cognition. Another study found no significant associations between APOE4 status and education in regard to cognitive impairment.[84] These partially contradictory results may be explained by the different design and population of the previously mentioned studies. In addition, the functional neuroimaging biomarkers (FDG−PET metabolism, amyloid burden) utilized by previous studies strengthen the hypothesis that higher education may protect against cognitive impairment in individuals carrying the APOE4 allele.

Apart from limited education, lower literacy in old age has been also associated with an increased risk of dementia.[85] Interestingly, the APOE4 allele has been shown to be related to both lower total literacy and lower health literacy in old adults without dementia, after adjustments for age, sex, education, and global cognition. Literacy is considered to rely on the complex coordinated function of an extensive neuronal network, involving both general and domain-specific knowledge, as well as computational and goal-oriented abilities that depend to a great extent on frontal cortex activity.[86] In this context, APOE4 non-dementia individuals have shown ventromedial frontal cortex alterations in functional neuroimaging studies, further supporting this hypothesis.[86]

Overall, most studies suggest that greater cognitive engagement or higher education may reduce the risk or postpone the development of cognitive decline in APOE4 carriers, potentially via reducing amyloid-beta-associated AD pathology and enhancing metabolism in the frontotemporal regions in the brain, thereby promoting neural efficiency in both amyloid-beta- and non-amyloid-beta-related pathways; however, a reverse causality cannot be excluded because individuals with more efficient cognitive abilities may seek and obtain higher education.[82] Given the conflicting results of the studies, further evidence is needed to clarify the APOE genotype−cognitive engagement interaction in regards to cognitive decline.

3.4. TBI. Although epidemiological evidence remains controversial, TBI seems to constitute a potential risk factor for AD development, and there is some evidence that the APOE genotype may affect this relationship.[10] TBI has been demonstrated to reduce the age at onset of AD or be associated with more accelerated cognitive decline.[9] Repetitive mild TBI-related chronic traumatic encephalopathy and AD share some common pathophysiological mechanisms, including neuronal loss, abnormal accumulation of hyperphosphorylated tau protein, amyloid-beta accumulation, neuroinflammation and microglial activation, mitochondrial dysfunction, and oxidative stress.[87,88]

AD development has been shown to be 10 times more likely among APOE4 carriers after TBI compared with a two-fold increase in APOE4 carriers without a history of head injury.[89] On the contrary, TBI was not an AD risk factor in APOE4 noncarriers in this study. Memory performance was also worse after TBI among APOE4 carriers, whereas executive function was not altered.[90] Furthermore, a 4 year follow-up study indicated the impact of the APOE4 genotype on cognitive decline, as demonstrated on the Mini-Mental Status Examination (MMSE) and Symbol Digit Modalities Test, only after adjusting for head injury in another study, suggesting a potential interaction between TBI and APOE4 in regard to cognitive performance.[78] Furthermore, APOE4 allele has been recently associated with worse memory performance related to higher ball-heading exposure among amateur soccer players.[91] On the contrary, there are data that do not support the link between the APOE genotype, TBI, and AD development.[92]

Given the above controversies in the elucidation of the potential interaction between the APOE genotype and TBI, larger longitudinal studies are needed that also explore the severity and frequency of TBI as well as the incident of consciousness loss during the injury because these factors may significantly affect the outcomes.

3.5. Exposure to Pesticides. An increased prevalence of AD has been reported in rural regions compared with urban settings, and pesticide exposure is one of the proposed factors contributing to this relationship.[93] Occupational exposure to pesticides has been correlated with an increased risk of AD onset in epidemiological studies.[94,95] Proposed mechanisms involve the inhibition of acetylcholinesterase at the synapses in the brain, axonal transport impairment, lipid peroxidation, and oxidative damage.[95]

Higher circulating levels of dichlorodiphenyldichloroethylene (DDE), which is the metabolite of the pesticide dichlorodiphenyltrichloroethane (DDT), have been associated with an increased risk of AD development.[96] Notably, in the case of the highest serum levels of DDE (in the third tertile), the MMSE score in APOE4 carriers was significantly lower compared with that in noncarriers in this study.[96] These findings suggest that APOE4 carriers with increased serum DDE levels may exacerbate cognitive decline, reflecting an increased AD risk or AD progression rate. Hence, evaluating serum DDE levels together with APOE genotyping may constitute a useful tool for the identification of individuals at risk for AD.

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3.6. Cigarette Smoking. Most studies have demonstrated that smoking may increase the AD risk, although there is also controversial evidence showing the inverse relationship. A meta-analysis of 37 prospective studies indicated that current smoking increased the risk of AD only in the case of APOE4 noncarriers,[97] highlighting the significant interaction between the APOE genotype status and the smoking impact on AD risk.

More specifically, a clinical study has indicated that ever smoking was associated with late-onset AD in APOE2 or APOE3 carriers but not APOE4 carriers.[98] Similarly, smoking had no effect on individuals with the APOE4 allele, whereas it was a risk factor for AD in those without this allele.[99,100] In agreement with this evidence, smokers displayed the highest AD risk in the case in which they did not carry the APOE4 allele.[101] In early onset AD, a potential protective role of smoking has been shown to be restricted to APOE4 carriers with a family history of dementia.[102] However, the total smoking duration and the intensity did not differ between APOE4 carriers and noncarriers in both normal cognition and MCI groups,[103] whereas the APOE4 allele did not show any interaction with smoking in regard to cognitive decline during aging.[81]

A study among elderly individuals with normal cognition demonstrated that the APOE genotype interacted with smoking status because APOE4 carriers who ever smoked displayed reduced glucose metabolism, as evaluated by PET, and worse cognitive performance compared with never-smoker APOE4 carriers, never-smoker APOE4 noncarriers, and ever-smoker APOE4 noncarriers.[104] These findings suggest an additive effect of smoking and APOE4 on cognitive impairment, and the exact impact of the APOE genotype on the interaction between smoking and cognitive function has to be specifically explored.

Interestingly, a placebo-controlled clinical trial has indicated that transdermal nicotine may improve executive cognitive function in nonsmokers with MCI, an effect that was more profound among APOE4 carriers.[105] In agreement with this evidence, nicotine showed a greater cognitive enhancement in APOE4 carriers, especially at a younger age, suggesting that nicotine may upregulate the cholinergic system in this subgroup of patients.[106]

Potential interpretations of the interaction between smoking and APOE allele status on cognitive impairment may involve the effect of the APOE genotype on the risk of coronary heart disease among smokers, which could indirectly affect AD risk.[107] Because the APOE4 allele increases the risk of cardiovascular disease, mortality rates could be higher among APOE4 carriers who smoke.[99] Furthermore, AD patients with the APOE4 allele display a reduced number of nicotinic-receptor binding sites,[108] and nicotine may increase the density of these receptors or enhance acetylcholine release, thereby constituting a potential underlying molecular mechanism.[99,102]

Notably, it has been also suggested that the APOE allele status may affect the susceptibility to smoking cessation, thereby further affecting the impact of smoking on cognitive decline. In this regard, among smokers over the age of 60 years, APOE4 carriers were significantly less likely to stop smoking and relapsed more easily compared with noncarriers, whereas at a younger age, this relationship was not significant.[109]

3.7. Coffee Intake. Several studies have demonstrated that caffeine intake may reduce the risk of several forms of dementia, including AD, whereas others have found no such associations.[110] The main dietary source of caffeine is coffee, although it is also present in green tea, cocoa, and energy drinks. Caffeine acts by blocking adenosine A_1 and A_{2A} receptors in the central and peripheral nervous system, thereby enhancing alertness, wakefulness, and psychomotor vigilance. Experimental evidence has indicated that caffeine may inhibit cognitive impairment by regulating synaptic plasticity and inhibiting synaptotoxicity, reducing neuroinflammation and microglia activation, inhibiting glutamatergic excitotoxicity, and decreasing amyloid-beta levels in the hippocampus of transgenic mice via A_{2A} receptor antagonism.[111]

Recently, a meta-analysis based on 61 studies demonstrated that caffeine consumption through coffee or green tea may be associated with a reduced risk of cognitive impairment and dementia as well as the amelioration of cognitive decline in cognitively impaired patients.[112] However, the influence of APOE status on the impact of caffeine consumption on dementia risk was not particularly analyzed in this study. Higher lifetime coffee consumption has been associated with reduced abnormal cerebral amyloid-beta deposition, as assessed by ^{11}C PiB PET in nondementia individuals with normal cognitive function or mild cognitive impairment (MCI).[113] In this study, the APOE4 status did not affect the relationship of coffee intake with amyloid-beta positivity. In agreement with this evidence, an *in silico* analysis revealed no correlation between APOE polymorphisms related to coffee consumption and AD diagnosis, indicating that there is likely no strong impact of the APOE4 allele on the effect of coffee on AD risk.[114]

3.8. Alcohol Consumption. Clinical studies have shown that the elderly population exposed to moderate alcohol consumption may be protected against cognitive decline[115] and dementia risk.[116] Proposed molecular mechanisms underlying the potential neuroprotective effects of alcohol against cognitive impairment involve the inhibition of neuroinflammation and oxidative stress, whereas the moderate alcohol-consumption-mediated decreased risk of cardiovascular factors including stroke, diabetes mellitus, and coronary heart disease[117] may also contribute to this association.[118] However, heavy alcohol intake may increase the AD risk.[119]

During late life, higher alcohol consumption has been correlated with a reduced risk of cognitive impairment for APOE4 noncarriers, whereas carriers of one or two APOE4 alleles showed the opposite trend in this study.[120] Additionally, increased alcohol intake could increase the dementia risk only among APOE4 carriers and not APOE4 noncarriers.[121] Similarly, a trend toward a greater risk of dementia was associated with heavy alcohol intake in APOE4 carriers.[119] In agreement with these findings, an additive effect of heavy alcohol consumption and the APOE4 allele on the age of onset of AD was also observed.[122] Daily moderate wine consumption was associated with a reduced AD risk when restricted to the elderly individuals without any APOE4 allele.[123] In accordance, light and moderate consumption of alcohol during late life has been correlated with greater cognitive impairment among carriers of at least one APOE4 allele, whereas among individuals with no APOE4 alleles, light and moderate intake of alcohol was associated with improved cognitive function.[118] The APOE allele status did not seem to affect the impact of midlife alcohol consumption on learning and memory in late life in this study. The APOE4 status did not alter the correlation between moderate lifetime alcohol consumption and amyloid-beta deposition, as assessed by ^{11}C PiB PET.[124] In another study, nonalcohol drinking accelerated memory

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impairment only in APOE4 carriers, suggesting that alcohol consumption and APOE4 interaction may affect the rate of progression of cognitive decline.[81]

Notably, moderate alcohol consumption has been correlated with increased levels of low-density lipoprotein (LDL) in APOE4 carriers compared with noncarriers.[125] Because higher midlife LDL levels may increase AD risk,[126] the subsequent increased APOE4-mediated LDL levels may contribute to the detrimental effects of alcohol consumption on APOE4 carriers. It has been also suggested that the neurotoxic effects of alcohol could be more detrimental in APOE4 carriers, because these individuals have been shown to display dysfunctional neuronal repair mechanisms.[127]

Collectively, most studies show that moderate alcohol consumption during late life might potentially protect against AD only in APOE4 noncarriers. However, given the negative association found in the study using ^{11}C PiB PET and the multiple potential confounding factors (other comorbidities, hypercholesterolemia, liver failure), further larger prospective studies confirming these results with AD neuroimaging or CSF biomarkers would be useful to clarify this relationship.

3.9. Sunlight Exposure and Vitamin D Deficiency. Vitamin D deficiency has been associated with several medical conditions, including atherosclerosis, hypertension, coronary artery disease, and diabetes mellitus.[128,129] On the contrary, reduced exposure to sunlight, inadequate dietary intake, gastrointestinal malabsorption, smoking, pollution, kidney and liver disease, medications, and genetic factors have been shown to predispose an individual to vitamin D insufficiency.[129]

Preclinical evidence suggests that vitamin D can be locally synthesized in the central nervous system because its metabolites and nuclear receptors have been detected in the brain,[130] and enzymes responsible for the synthesis of its bioactive form -1,25-$(OH)_2D_3$- are expressed in several brain regions including the thalamus, basal ganglia, and hippocampus, suggesting its potential role in cognition.[131] *In vitro*, vitamin D enhances the clearance of amyloid plaques by macrophages,[132] inhibits amyloid-induced neurotoxicity and apoptosis,[133] displays antioxidant properties, affects the metabolism of several neurotransmitters including acetylcholine, and regulates the expression of neurotrophic factors,[134] highlighting its potential neuroprotective properties in AD development and progression.

A growing amount of epidemiological evidence shows that a lower serum vitamin D concentration may be correlated with poorer cognitive abilities and an increased risk of AD.[135] However, a recent meta-analysis of prospective cohort studies indicated that vitamin D deficiency or insufficiency was not significantly associated with increased AD risk after adjustment for serum cholesterol levels, alcohol, physical activity, cardiovascular disease, and cancer.[136] It is unclear whether vitamin D deficiency might be a causal factor or a consequence of the disease because decreased outdoor activities and possible dietary alterations after AD onset may reduce vitamin D levels.[137] In addition, it is still elusive which specific genetic or environmental factors may affect this intriguing relationship.

Furthermore, it has been demonstrated that countries with lower exposure to sunlight display higher AD mortality rates.[134] Although greater life expectancy in regions with lower sunlight exposure and ethnicity heterogeneity could constitute significant biasing factors, these data indicate that exposure to sunlight might potentially affect the disease progression rate and mortality of AD patients. However, larger cohort studies are required to confirm this association, and the underlying mechanisms remain largely unknown.

Interestingly, the frequency of APOE4 carriers tends to be higher in areas with lower levels of solar irradiation, with increasing geographical latitude, and among people with darker skin pigmentation.[18,138] Although the pathophysiological mechanisms remain obscure, it has been hypothesized that the APOE4 allele may protect against vitamin D deficiency under these conditions.[138] The APOE4 allele is correlated with higher serum vitamin D levels compared with the APOE2 and APOE3 alleles,[139] and healthy humans with the APOE4 allele display increased circulating vitamin D levels compared with noncarriers.[139] APOE4 allele carriers may better endure lower solar ultraviolet B irradiance, which could offer them an advantage in comparison with the evolutionary younger APOE3 allele.[18] Given the fact that APOE is crucially implicated in the transport and metabolism of lipid soluble vitamins, it has been proposed that vitamin D's potential role in AD might be affected by the presence of the APOE4 allele.

In this context, a large population-based British study demonstrated that the APOE genotype affected the association between vitamin D levels and memory function in mid-adulthood individuals.[140] Elevated vitamin D levels were correlated with better memory scores in participants with two APOE4 alleles, whereas memory function was slightly poorer with higher vitamin D concentration in individuals with one or no APOE4 allele.[140] These data were adjusted for education level, gender, and depressive symptoms, and the results were unaffected by smoking and body mass index,[140] suggesting that these covariates were not responsible for the observed vitamin D role in cognitive function in regard to the APOE4 genotype. Another study indicated that serum vitamin D levels were lower in APOE4 noncarriers compared with APOE4 carriers only in the subgroup of patients with late-onset AD (LOAD, >65 years of age at onset) and not with early onset AD (EOAD, <65 years of age at onset).[141] In addition, circulating vitamin D levels were lower in late-onset Parkinson's disease (LOPD) patients compared with those with MCI or healthy controls only in the subgroup of APOE4 noncarriers and not in that of APOE4 carriers.[141]

Therefore, it seems that APOE4 allele status may affect vitamin D levels in AD patients, and the age of disease onset could also influence this relationship. The first study involved individuals in their mid-adulthood, and there were no subgroup analyses among AD, MCI, or healthy conditions compared with the second study. Hence the partially contradictory results of the previously mentioned findings could be explained by the different populations and methodological designs. Additional prospective studies considering potential confounding factors, such as smoking, cardiovascular diseases, homocysteine levels, and chronic kidney disease, which might affect vitamin D levels, APOE4 allele status, and AD risk, are required to clarify the relationship between APOE4 and vitamin D levels in AD. Furthermore, subgroup analyses including moderate and severe deficiency would be useful given the observed diverse effects of these two conditions on cognitive function.[131] The elucidation of the influence of the APOE4 allele on the vitamin D levels in AD will further clarify the potential impact of diet or even sunlight exposure on the incidence and progression of AD in specific patient subgroups depending on their APOE status or age at onset.

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Table 1. Clinical Evidence of the Potential Impact of Lifestyle and Environmental Factors on the Effect of the APOE Genotype in AD

lifestyle/ environmental factor	study	main results	references
physical exercise	Colovati 2020 and Jensen 2019	APOE4 carriers are more susceptible to the beneficial impact of exercise on cognition compared with APOE4 noncarriers.	25 and 39
	Smith 2016	Physically active APOE4 carriers displayed less cognitive decline and hippocampal atrophy compared with physically inactive APOE4 carriers.	40
	Head 2012	Physical activity initiated during middle life was associated with reduced amyloid-beta burden on PiB PET, in particular, in APOE4 carriers.	41
	Jeon 2020	Physical activity during middle life could mitigate the effects of APOE4 on AD-related cerebral glucose hypometabolism.	42
	Jensen 2019	Physical exercise stabilized the levels of IFN-γ in the CSF of APOE4 carriers.	43
	Rovio 2005, Kivipelto 2008, and Tolppanen 2015	The beneficial effects of physical exercise were more evident among APOE4 carriers.	44−46
	de Frutos-Lucas 2020	Physical activity was associated with reduced hypersynchronization in the left temporal lobe (assessed by MEG) in nondementia APOE4 carriers and noncarriers.	47
		This network profile was related to better episodic and working memory only in the subgroup of APOE4 noncarriers.	
		In APOE4 carriers, left temporal synaptic hypoconnectivity was related to an increased preservation of brain structure, especially in AD-related regions.	
	Stern 2019	The beneficial effects of aerobic exercise on executive function were less pronounced in APOE4 carriers compared with noncarriers.	48
	Fenesi 2017	Physical activity reduced the risk of dementia only in APOE noncarriers.	49
	Podewils 2005	The beneficial effects of physical exercise were absent in APOE4 carriers.	50
	Stringa 2020	There is no interaction effect between physical exercise and the APOE genotype in cognitive decline.	51
	Allard 2017	Aerobic exercise increased plasma BDNF levels only in elderly African patients with MCI carrying no APOE4 allele.	52
diet	Barberger-Gateau 2007	Fish and omega-6 rich oil consumption were associated with a reduced risk of AD only in APOE4 noncarriers.	57
	Huang 2005	Compared with lean fish, fatty fish consumption could protect against AD only in APOE4 noncarriers.	58
	Scarmeas 2006 and Scarmeas 2007	APOE4 allele did not affect the relationship between Mediterranean diet and AD risk.	60 and 61
	Solomon 2018	Nordic diet, brain training, and exercise were associated with the prevention of cognitive impairment, and APOE4 carriers benefited the most.	62
	van de Rest 2016	Higher seafood consumption has been associated with slower global cognitive decline only among APOE4 carriers.	63
	Stonehouse 2013 and Laitinen 2006	The beneficial effects of omega-3 among APOE4 carriers were observed, in particular, in younger individuals.	64 and 65
	Hanson 2015	APOE4 cognitively normal carriers demonstrated improved cognitive performance after a meal with increased levels of total fat, saturated fat, and glycemic index compared with a meal with lower levels of these parameters.	66
		Cognitively normal APOE4 noncarriers showed the opposite relationship.	
		Cognitively impaired APOE4 noncarriers displayed enhanced memory after the HIGH meal. The memory performance of cognitively impaired APOE4 carriers was not affected by these meal changes, although executive function was also improved in this subgroup.	
	Hanson 2013	MCI patients displayed higher levels of lipid-depleted amyloid beta in their cerebrospinal fluid compared with healthy controls, and this relationship was more pronounced in the APOE4 carriers.	67
	Reger 2004	Among patients with AD or MCI, oral consumption of MCTs could elevate plasma ketone body levels and improve cognitive function only in APOE4 noncarriers.	70
	Henderson 2009	Daily administration of the ketogenic agent AC-1202 to AD patients was associated with improved cognitive performance, especially in APOE4 noncarriers.	71
	Yassine 2020	Among overweight or obese DM2 patients, it was demonstrated that intensive lifestyle intervention was related to improved cognitive function only in younger and pre- or early postmenopausal women not carrying one or two APOE4 alleles.	73
education	Wang 2012	Higher education might protect against dementia among APOE4 carriers.	76
	Ferrari 2012	Additive interactions between high education and frequent leisure activities with APOE4 allele status may affect the risk of dementia.	77
	Christensen 2008	APOE4 carriers show poorer cognitive performance only after adjustments for education level.	78
	Cook 2015	Old-age cognitive decline in APOE4 carriers who completed college was rescued, independent of higher socioeconomic status or better access to healthcare.	79
	Wirth 2014	Higher cognitive activity during early and middle life was associated with reduced cortical amyloid deposition on PiB PET, especially in APOE4 carriers.	80
	Reas 2019	Acceleration of executive function decline was particularly pronounced in APOE4 carriers with lower education.	81
	Arenaza-Urquijo 2015	Higher education was associated with greater frontotemporal FDG−PET metabolism and higher performance on episodic memory tests only in APOE4 carriers.	82

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Table 1. continued

lifestyle/ environmental factor	study	main results	references
	Seeman 2005	APOE4 carriers with more than 8 years of education demonstrate greater cognitive decline.	83
	Van Gerven 2012	No associations were shown between APOE4 status and education in regard to cognitive impairment.	84
traumatic brain injury	Mayeux 1995	AD development was more likely among APOE4 carriers after TBI. TBI was not a risk factor for AD in APOE4 noncarriers.	89
	Crawford 2002	Memory performance was worse after TBI among APOE4 carriers, whereas executive function was not altered.	90
	Christensen 2008	The effects of the APOE4 genotype on some cognitive function tests were demonstrated only after adjusting for head injury.	159
	Jellinger 2004	There is no link between the APOE genotype, TBI, and AD.	92
pesticides	Richardson 2014	In the case of the highest serum DDE levels, the MMSE score in APOE4 carriers was significantly lower compared with that in noncarriers.	96
smoking	Ghebranious 2011	Ever smoking was associated with late-onset AD in APOE2 and APOE3 carriers but not in APOE4 carriers.	98
	Ott 1998 and Aggarwal 2006	Smoking did not affect cognition in APOE4 allele carriers, but it was a risk factor for AD in APOE4 noncarriers.	99 and 100
	Merchant 1999	Smokers displayed the highest AD risk in the case in which they did not carry the APOE4 allele.	101
	van Duijn 1995	In early onset AD, a potential protective role of smoking was restricted to APOE4 carriers with a positive family history.	102
	Kalapatapu 2013	Smoking duration and intensity did not differ between APOE4 carriers and noncarriers in both normal cognition and MCI groups.	103
	Reas 2019	APOE4 allele did not show any interaction with smoking in regard to cognitive decline during aging.	81
	Durazzo 2016	APOE4 carriers who ever smoked displayed reduced glucose metabolism, as evaluated by PET and worse cognitive performance, compared with never-smoker APOE4 carriers, never-smoker APOE4 noncarriers, and ever-smoker APOE4 noncarriers.	104
	Newhouse 2012	Transdermal nicotine could improve executive cognitive function in nonsmokers with MCI, and this was more profound among APOE4 carriers.	105
	Marchant 2010	Nicotine showed a greater cognitive enhancement in APOE4 carriers, especially at a younger age.	106
coffee	Kim 2019	Higher coffee consumption was associated with reduced abnormal cerebral amyloid-beta deposition in nondementia individuals, but APOE4 status did not affect this relationship.	113
alcohol	Dufouil 2000	Higher alcohol consumption was associated with a reduced risk of cognitive impairment for APOE4 noncarriers, whereas carriers of one or two APOE4 alleles showed the opposite trend.	120
	Anttila 2004	Increased alcohol intake could increase the dementia risk only among APOE4 carriers.	121
	Mukamal 2003	A trend toward a greater risk of dementia was associated with heavy alcohol usage in APOE4 carriers.	119
	Harwood 2010	Heavy alcohol usage and the APOE4 allele had additive effects on the age of onset of AD.	122
	Luchsinger 2004	Daily moderate wine consumption was associated with reduced AD risk restricted to elderly APOE4 noncarriers.	123
	Downer 2014	Light and moderate alcohol consumption was associated with greater cognitive impairment among APOE4 carriers, whereas among APOE4 noncarriers, light and moderate alcohol intake were associated with improved cognitive function. APOE allele status did not affect the impact of midlife alcohol consumption on learning and memory in late life.	118
	Kim 2020	APOE4 status did not alter the association between moderate lifetime alcohol consumption and amyloid-beta deposition.	124
	Reas 2019	Non-alcohol consumption accelerated memory impairment only in APOE4 carriers.	81
sunlight exposure, vitamin d levels	Maddock 2015	Elevated vitamin D levels were associated with better memory scores in participants with two APOE4 alleles, whereas memory function was slightly poorer with higher vitamin D concentration in those with one or no APOE4 allele.	140
	Dursun 2016	Serum vitamin D levels were lower in APOE4 noncarriers compared with APOE4 carriers only in the subgroup of patients with LOAD and not with EOAD. Serum vitamin D levels were lower in LOPD patients compared with those with MCI or healthy controls only in the subgroup of APOE4 noncarriers.	141
air pollution	Cacciottolo 2017	Exposure to particulate matter in ambient air has been associated with an increased risk of AD in older women, which is more pronounced in those carrying two APOE4 alleles.	142
	Daniels 2021	Prolonged exposure to the debris pile of the WTC was associated with MCI in responders carrying the APOE4 allele.	143

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3.10. Air Pollution. Epidemiological evidence shows that air pollution may increase the risk of cognitive impairment.[9] Exposure to particulate matter in the ambient air has been associated with an increased risk of AD development in older women, which was more pronounced in those carrying two APOE4 alleles.[142] Experimental evidence demonstrated that exposure to air pollutants in female transgenic mice increased cerebral amyloid-beta deposits, which was further enhanced by APOE4.[142] These findings suggest that APOE4 carriers might be more vulnerable to the detrimental effects of air pollution on cognition, although further research is needed to replicate these results.

Interestingly, individuals (workers, residents, responders) exposed to physical and psychological stressors due to the terrorist attacks at the World Trade Center (WTC) on September 11, 2001 have been demonstrated to have an increased risk of MCI.[143] In particular, prolonged exposure to the debris pile of the WTC for more than 15 weeks was associated with MCI in responders carrying the APOE4 allele.[143] Hence, air pollutants combined or not combined with other psychological factors might affect the MCI and dementia risk depending on APOE allele status.

4. DISCUSSION AND FUTURE PERSPECTIVES

Collectively, epidemiological evidence suggests that the APOE genotype may interact with several environmental factors and affect cognitive decline, highlighting the promising potential of lifestyle prevention strategies according to APOE allele status (Table 1). These studies support the "multi-hit" hypothesis, in which genetic susceptibility and environmental exposure synergistically promote the development and progression of neurodegenerative disorders under specific circumstances.[8] However, given the contradictory findings, the careful selection of participants, the time of intervention, and the methodological design of future studies are needed to clarify these relationships.

Although evidence is inconsistent, it seems that APOE4 carriers are rather more susceptible to the effects of environmental exposures on cognition, especially at a younger age and possibly in preclinical stages of AD. Because neurobiological alterations of AD may be initiated some decades before dementia develops,[45] it could be hypothesized that there is a critical time window during which preventive strategies would be beneficial among APOE4 carriers; however, after a specific time threshold, these lifestyle strategies may not affect cognitive impairment in this subgroup of individuals.

Given the complex APOE genotype−environment interactions that still remain obscure, future epidemiological studies aiming to investigate the effect of various lifestyle factors on cognition should include a sufficient sample size of individuals with diverse APOE genotypes and especially the APOE4 allele.[14] For valid results, gene−environment interaction studies usually require an uncommonly large sample size to attain the essential statistical power.[8] Longitudinal studies with many years of follow up will also aid in diminishing recall bias and potential reverse causation. Multimodal neuroimaging approaches combined with biochemical AD biomarkers are needed to more deeply understand the effects of APOE genotype−environment interactions on AD development. Because the effects of the interaction between the APOE genotype and several environmental factors depends on age, sex, cognitive impairment, menopause status, and possibly other related exposures or comorbidities such as obesity, dyslipidemia, and diabetes mellitus, these covariates should also be taken into consideration in future relevant epidemiological or interventional studies. In addition, objective and standardized measures, including timing, duration, intensity or dosing, and frequency of environmental exposures like physical exercise, education, or dietary habits are needed to obtain meaningful and comparable results. In this context, smartphone-based and wearable technologies may also allow for real-time, more accurate, and reliable exposures and lifestyle habits.[8] Experimental studies will also act synergistically with epidemiological evidence not only to confirm the biological role of environmental exposures in APOE genotype-related cognitive impairment but also to provide novel hypotheses to explore at a clinical level.[8]

Apart from the environmental factors previously described, the potential interaction between the APOE genotype and other factors, including metals, be should also explored in regard to cognitive decline. In this context, it has been shown that copper, zinc, and iron are implicated in the pathogenesis of AD,[95] and APOE isoforms can bind to these metals with different affinities.[144] For example, APOE4 has the lowest affinity for zinc, whereas APOE2 has the highest,[144] paving the way for future research.

An emerging role of infections has been increasingly recognized in AD development and progression. In this regard, a recent study demonstrated that immunoglobulin M (IgM) positivity or higher levels of IgG against herpes simplex virus (HSV) type 1 was associated with an increased risk for AD among APOE4 carriers, whereas no such association was found for APOE4 noncarriers.[145] Furthermore, the APOE4 allele has been related to worse memory function in patients with HIV[146] but to improved cognitive abilities in Amazonian forager−horticulturalists carrying a high parasite burden.[147] Hence, it seems that different pathogens may have diverse effects on the APOE4-mediated effects on cognition, and their relationships with AD need to be further investigated.

Vitamin C and E have been associated with reduced AD risk possibly via antioxidant mechanisms. Interestingly, the beneficial impact of vitamins C and E on lowering the risk of cognitive impairment was observed in APOE4 female carriers and APOE4 male noncarriers respectively, suggesting that the a gender−APOE genotype interaction may also affect the role of vitamin C and E on cognition.[148]

Depression has been also shown to affect cognitive function in various studies. Concerning the role of the APOE genotype in this relationship, a recent study has shown that depressive symptoms were associated with worse visual memory performance, in particular, among APOE4 carriers, suggesting that the APOE genotype may differentially affect the impact of depression on cognitive function.[149]

Specific sleep disturbances, including sleep apnea, have been related to dementia.[150] The APOE4 allele has been shown to elevate the risk of memory impairment in patients with obstructive sleep apnea.[151,152] Moreover, sleep disruption has been reported to be significantly more common in dementia patients carrying the APOE4 allele compared with noncarriers,[153] implying that the APOE genotype may be also involved in the relationship between sleep disturbances and cognitive impairment.

In addition, the APOE2 allele has been demonstrated to affect the natural history of AD in the case of the *PSEN1* E280A mutation, a genetic form of AD.[154] In particular, the

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presence of the APOE2 allele could delay the age at disease onset of E280A PSEN1 carriers, thus potentially acting in a neuroprotective manner. Hence, additional gene−gene interactions should also be considered in future studies in this field.

The elucidation of the impact of environmental factors on the effects of the APOE genotype in cognitive impairment may also aid in the development of potential targeted therapeutic approaches. Statins, β-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase inhibitors that are widely used to reduce cholesterol levels, have been associated with a reduced AD risk in some but not all studies.[27] This inconsistency might be at least partially attributable to the APOE genotype, and future work is needed toward this direction. Anti-APOE4 immunotherapies, antisense APOE oligonucleotide therapies, APOE mimetic peptides, inhibitors of APOE−amyloid-beta interaction, gene therapy and especially stimulating APOE expression via HDACi, as previously mentioned, represent some of the potential strategies that could be useful in the future.[27] The combination of these pharmaceutical strategies with lifestyle interventions may synergistically protect against cognitive impairment in specific APOE genotype subpopulations.

Apart from AD, the APOE genotype is also involved in other neurological disorders. For instance, it has been demonstrated that APOE4 may be associated with an earlier age of onset of Parkinson's disease (PD) and an increased risk of dementia.[155] Given that environmental factors including smoking and coffee consumption have been differentially associated with early onset and late-onset PD,[156] APOE4 allele status could also at least partially underlie these differences. Moreover, APOE4 homozygosity was shown to be associated with worse cognitive performance of patients with early relapsing remitting multiple sclerosis.[157] Given that smoking, obesity, and low vitamin D levels have been also associated with the risk for multiple sclerosis,[158] the APOE genotype could possibly be implicated in this relationship.

Future work will aid in the elucidation of the impact of these lifestyle and environmental factors on cognition and AD risk, pointing toward more effective, integrated, and personalized preventive and treatment approaches.

5. CONCLUSIONS

Increasing evidence suggests that several types of environmental exposure may interact with the APOE genotype and differentially affect cognitive decline. However, given the large inconsistency between studies, future larger longitudinal studies will aid in our deeper understanding of this relationship, which will lead to more effective and personalized preventive approaches against dementia and, in particular, AD. Informing the vulnerable population carrying the APOE4 allele about potential preventive strategies may have a major practical impact on altering the natural history of the disease.

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E.A. carried out the literature review and conceptualized and prepared the initial draft. Y.N.P. and S.G.B. edited and contributed to the final manuscript. C.P. provided critical input to, edited, and contributed to the final version of the manuscript. All authors read and approved the final manuscript.

Notes

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