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REVIEW

Apolipoprotein E ε-4 as a genetic determinant of Alzheimer's disease heterogeneity

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MJ Kotze[1]
HK Lückhoff[1]
T Brand[1]
J Pretorius[1]
SJ van Rensburg[2]

[1]Division of Anatomical Pathology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa; [2]Division of Chemical Pathology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University and the National Health Laboratory Service, Tygerberg Hospital, Tygerberg, South Africa

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Correspondence: MJ Kotze
Division of Anatomical Pathology, Department of Pathology, Faculty of Medicine and Health Sciences, University of Stellenbosch, PO Box 19063, Tygerberg, 7505, South Africa
Tel +27 21 938 9324
Email maritha@sun.ac.za

Abstract: Alzheimer's disease (AD) displays a high degree of heterogeneity in terms of its etiology, presentation, prognosis, and treatment response. This can partly be explained by high-penetrance mutations in the amyloid precursor protein, presenilin 1 and presenilin 2 genes causing amyloid beta aggregation, which is a major pathogenic mechanism in the development of early-onset AD in a small subgroup of patients. Late-onset AD is considered a polygenic disorder in which cumulative risk resulting from interaction with modifiable environmental risk factors may be responsible for the majority of cases. The ε-4 allele of the apolipoprotein E (*APOE*) gene has emerged as the most significant genetic risk factor for late-onset AD, influencing nearly every pathogenic domain affected in AD. It is a major risk factor for cerebral amyloid angiopathy, recognized as a common pathological finding in an AD subtype associated with white matter dysfunction. The *APOE* ε-4 allele is also a known risk factor for ischemic stroke, which can result in vascular dementia or contribute to subcortical vascular dysfunction. In this review, we evaluate the clinical relevance of *APOE* genotyping in relation to cholesterol metabolism and available evidence on risk reduction strategies applicable to AD.

Keywords: Alzheimer's disease, heterogeneity, APOE, cholesterol, polymorphism, pharmacogenetics

Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder associated with a significant disease burden that places tremendous emotional and financial strain on families, caregivers, and society at large. AD is largely underreported on death certificates and medical records, with the figure in the United States found to be six times higher than previously estimated.[1] Between 2006 and 2010, the global prevalence of AD increased by nearly 35% (going from 25.6 million to 35.6 million), and it is expected to increase threefold by 2050.[2] It is anticipated that AD will then affect ~1% of the global population, the majority (71%) of whom will reside in low- or middle-income countries.[3,4] The growing prevalence of AD globally has been attributed to a worldwide increase in life expectancy across different population groups. Intervention strategies aimed at delaying disease onset and progression by merely 1 year may result in more than 9 million people being spared this devastating diagnosis by 2050.[2]

In sub-Saharan Africa, dementia is set to become one of the major public health care challenges of the third millennium, as its prevalence is expected to increase dramatically from the current rate of ~2%–4% in the coming decades.[5,6] AD further places a significant strain on the global economy. In 2010, the direct and indirect health expenditure for AD worldwide exceeded 1% of the global gross domestic product, at $600

billion. Its total contribution to global health expenditure, including medical services and hospice care, is anticipated to reach $1.1 trillion in the near future.[7,8]

Diagnosis of AD

AD has conventionally been defined as a clinicopathological entity, with extracellular amyloid beta (Aβ) aggregation and intracellular neurofibrillary tangle formation being associated with its clinical symptomatic emergence. However, new diagnostic criteria for AD proposed by the National Institute on Aging and the Alzheimer's Association, which include a preclinical, asymptomatic stage, are in accord with the notion that characteristic neuropathology may arise years or even decades before clinical presentation. This shift from a definitive to a probabilistic diagnostic approach is assisted by the use of novel biomarkers and imaging methodology, which may identify asymptomatic individuals and enable the timely implementation of intervention strategies aimed at curbing disease onset.[9,10] Although intended primarily for research purposes, these criteria may be of immediate use to the clinician. As novel diagnostic tools are becoming increasingly available in general practice, accurate diagnosis facilitated by these emerging technologies may significantly optimize patient care.[11] However, this approach has been critiqued because of the concept of disease being inexorably related to impairment, clinical difficulty in differentiating preclinical AD from other neurodegenerative diseases such as Fronto-Temporal Dementia and Progressive Supranuclear Palsy, a failure to acknowledge overlapping pathological changes underlying disease onset, and the need for further validation of suggested biomarkers for AD.[12]

Genetic determinants of AD risk

Recent genomic advances have greatly increased our understanding of the underlying pathogenesis of AD, which is known to involve a significant heritability component (~60%–80%) as is evident from epidemiological and twin studies.[13] High-penetrance mutations in the amyloid precursor protein and presenilin 1 and presenilin 2 genes, which are inherited in a Mendelian pattern, result in excess cerebral accumulation of neurotoxic Aβ and are implicated in the development of early-onset AD, accounting for ~1% of cases. First-degree relatives of affected patients are also at a significantly increased risk of developing AD.

Although early-onset AD is relatively rare, late-onset AD has been linked to more than 600 genes, of which only a minority are supported by a sufficient level of evidence. This includes variation in the apolipoprotein E (*APOE*) gene that forms the focus of this review. The *APOE* gene is located on the long arm of chromosome 19 (q) at position 13.2 and consists of four exons and three introns totaling 3,597 base pairs. As a component of chylomicrons and intermediate-density lipoproteins, APOE plays a crucial regulatory role in lipid metabolism as well as the transport of cholesterol and fat-soluble compounds such as vitamins.[14] The *APOE* gene is highly polymorphic, with the two most extensively studied single nucleotide polymorphisms resulting in an interchangeable arginine (Arg) to cysteine (Cys) substitution at amino acid positions 112 and 158, corresponding to the ε-2 (rs7412) and ε-4 (rs429358) alleles (and therefore E2 and E4 protein isoforms), respectively.[15] Individuals with the *APOE* ε-4 allele are 15 times more likely to develop AD compared with noncarriers.

The *APOE* ε-4 allele is a major determinant of genetic predisposition for late-onset AD in different population groups and across boundaries for age and sex.[16] This supports the notion that the amyloid cascade hypothesis plays a central pathogenic role in sporadic as well as monogenic forms of the condition.[17] The *APOE* ε-4 allele affects nearly every pathological domain in AD, including Aβ aggregation, neurofibrillary tangle formation, regional and global cerebral atrophy, decreased synaptic plasticity, deranged lipid metabolism, and cholinergic dysfunction.[18] Coinheritance of deleterious genetic variants implicated in these processes associated with oxidative stress and inflammation may lead to an earlier age of onset in AD, suggesting a combined detrimental effect on AD pathology.[19,20] We hypothesized that the production of hydroxyl radicals contributing to lipotoxicity and oxidative stress in patients with AD needs to be counteracted by constantly providing the cells with antioxidants and other essential nutrients, and that a drug that would stimulate the regrowth of neurons may be beneficial.[21]

It is important to emphasize that the expression of low-penetrance polymorphic variants in genes such as *APOE* is highly context-dependent. The influence of modulating interactions with occupational exposures and other environmental risk factors (eg, smoking, low socioeconomic status, and poor dietary and lifestyle habits), together with associated medical comorbidities, may create a high-risk metabolic milieu conducive to disease development. Modifiable nongenetic factors are therefore an important focus for primary and secondary preventive strategies aimed at halting disease onset and progression.

Cholesterol metabolism, *APOE* genotype, and AD

The relationship between cholesterol and AD remains incompletely understood. Cholesterol plays a key role in

neurodevelopment, maintains the structural integrity of neuronal cell membranes, and ensures physiological extracellular messenger activity as well as neuronal repair. It has been proposed that the use of cholesterol and apolipoproteins as biomarkers may facilitate prognostication and guide therapeutic decision making in a broad spectrum of psychiatric illnesses, including autistic spectrum disorders, major depressive disorder, schizophrenia, and AD, as reviewed by Woods et al.[22] A reduction in neuronal cholesterol content promotes colocalization of beta-secretase 1 and amyloid precursor protein, disrupting plasmin generation and contributing to neurotoxic Aβ production and associated neurodegeneration.[23,24] However, elevated cholesterol levels also promote Aβ production and aggregation, as well as tau hyperphosphorylation, neuritic plaque formation, and cerebrovascular ischemia.[25,26] This apparent contradiction highlights the uncertainty regarding the molecular mechanisms implicated in cholesterol-mediated AD neuropathology.

Altered serum cholesterol levels may contribute to the pathogenesis of AD by modulating cerebral APOE mRNA expression.[27] Limited amounts of cholesterol are able to cross the blood–brain barrier (BBB) incorporated as high-density lipoproteins. Large lipoproteins are prohibited,[28] whereas oxidized derivatives of cholesterol (oxysterols), including 27-hydroxycholesterol, are able to cross the BBB. Oxysterol levels may be elevated in patients with AD, with these compounds being associated with increased cerebral Aβ production in vivo.[29,30] These findings may partly explain the link between elevated circulating cholesterol levels and neuropathological findings in AD. Limiting oxidative stress by means of health-promoting lifestyle or dietary adaptations, including smoking cessation and ensuring adequate dietary antioxidant intake, might prove more beneficial as a preventive measure than decreasing endogenous cholesterol synthesis.[80,82–84]

Epidemiological studies investigating the role of cholesterol in AD have reported mixed results. Many have correlated elevated cholesterol levels with an increased risk of developing mild cognitive impairment (MCI) and AD later in life, as well as an increased rate of cognitive decline in those with established dementia, independent of *APOE* genotype. However, conflicting studies have either failed to replicate these findings or demonstrated an inverse relationship between cholesterol levels and AD risk. The majority of positive findings note an increase in AD risk associated with elevated cholesterol levels during midlife, whereas similar changes during later life have been correlated with a decreased risk for dementia.[31–33] These conflicting findings may be explained by variation in the timing of cholesterol measurement with regard to age and the course of the underlying disease process.

In light of these findings, there is significant interest in the potential beneficial effects of lipid-lowering therapies, particularly statins, in mitigating the onset and progression of AD. Preclinical studies have clearly indicated that statins modulate the processing of amyloid precursor protein, correlating with a decrease in cerebral and cerebrospinal fluid levels of Aβ. Simvastatin in particular has been shown to improve cognitive functioning, protect against neurodegeneration in vivo, and promote cerebrovascular integrity in animal models.[34,35] However, results from human observational studies have been mixed. Multiple retrospective case-control studies suggest statins may prevent the onset of MCI and AD, as well as alter the course of disease progression.[36–40] A recent meta-analysis also concluded that statins may be beneficial in preventing AD.[41] Certain studies have shown that statin use in individuals at an increased risk for AD improves verbal fluency and working memory. However, others have proposed a detrimental effect on certain cognitive abilities,[42] and cohort studies have failed to associate statin use with a decreased risk of developing AD.[43]

Although an early randomized control trial (RCT) demonstrated significant improvement in cognitive performance and a decrease in serum Aβ levels in AD patients treated with statins,[44] subsequent larger trials have failed to demonstrate that statins alter the course or progression of established AD or offer additional neuroprotective benefits.[45,46] Another RCT also concluded that statin use does not improve cognition in established AD, and as such, is not currently recommended for AD prevention.[47] Other lipid-lowering agents including niacin, cholestyramine, and fibrates are also not effective in protecting against AD.[48] Various explanations have been put forth concerning such apparent negative findings evident for the majority of RCTs to date. Regarding study design, observational studies typically differ regarding the duration of statin use and period of observation, whereas discrepancy between the duration of statin use and the timing of clinical assessment is frequently noted between different studies. In addition, the distinction between preexisting and incident AD is often not apparent.[26] Various forms of bias, including mortality, indication, and cessation bias, also play a role. The role of cardiometabolic risk factors, inflammation, and the presence of coexisting vascular dementia may also not be fully considered. The type and dosage of statins administered may vary, whereas statins also differ in their BBB permeability and lipophilicity.

With the exception of their lipid-lowering properties, statins also improve BBB integrity; possess anti-inflammatory, antioxidant, and profibrinolytic properties, and improve endothelial dysfunction.[49] To what extent these factors contribute to the aforementioned findings remains incompletely understood.

Future investigation is required to elucidate the effect of statin therapy in ε-4 allele carriers with AD who are normocholesterolemic.[50] The beneficial role of statins in lowering dementia risk appears to be independent of *APOE* genotype, whereas the association between hyperlipidemia and increased dementia prevalence is only evident in patients without AD and in ε-4 allele noncarriers.[51] Young et al developed a Gaussian predictive model integrating multimodal data gathered from volumetric magnetic resonance imaging, fludeoxyglucose positron emission tomography, determination of cerebrospinal fluid t-tau, p-tau, and aβ42 levels, and *APOE* genotyping, which correlated with conversion rates from MCI to AD.[52] A higher frequency of the ε-4 allele observed in patients with primarily amnestic MCI further suggests an increased risk of conversion to AD in this subgroup.[53] These findings are in accordance with results reported by Fagan et al, who showed that baseline fludeoxyglucose positron emission tomography measurements and episodic memory loss predicted the rate of conversion from MCI to AD, whereas the p-tau181p/Aβ1-42 ratio predicted further cognitive decline.[54]

Statin-induced adverse effects, including myalgia, which occurs in approximately 2% of patients;[55] a benign elevation in liver enzyme levels,[56] and an increased risk for new-onset diabetes[57] are widely known. Cognitive effects such as memory loss and confusion have been associated with simvastatin in particular, tend to run a variable course, and significantly influence quality of life.[58] These cognitive adverse effects have come under recent scrutiny by the US Food and Drug Administration. At least one study has suggested statins might adversely affect cognition in AD patients;[59] however, a recent meta-analysis concludes that statins do not appear to adversely affect cognition in those with normal functioning at baseline.[60]

APOE genotype, cerebral vasculopathy, white matter pathology, and clinical heterogeneity in AD

A preponderance of evidence now suggests that AD, ischemic heart disease, and stroke share overlapping risk factors, including obesity, type 2 diabetes mellitus, hypertension, dyslipidemia, smoking, physical inactivity, oxidative stress, and hyperhomocysteinemia.[61,62] A multidisciplinary therapeutic approach centered on lifestyle-based interventions targeting shared disease pathways may decrease disease risk across the diagnostic spectrum.[63]

In addition to its multifunctional role in AD, the *APOE* ε-4 allele is also associated with accelerated atherogenesis and greater risk for ischemic stroke. Multiple cerebral infarctions may lead to vascular dementia, which commonly coexists with AD.[64,65] A recent meta-analysis clearly demonstrated a linear relationship between *APOE* genotype, serum low-density lipoprotein-cholesterol levels and carotid intimal media thickness, consistent with the view that ε-4 allele carriers are at an increased risk for ischemic stroke.[66] It should, however, be emphasized that even homozygosity for the ε-4 allele only partially accounts for vascular risk.[67]

White matter pathology is frequently encountered in AD, being associated with focal symptomatology as well as global cognitive impairment. Aβ deposition in cortical and leptomeningeal arteries is strongly correlated with the *APOE* ε-4 allele, resulting in cerebral amyloid arteriopathy (CAA). This common (80%–90%) neuropathological characteristic of AD is closely related to structural white matter abnormalities, arising secondary to endothelial dysfunction, basement membrane thickening, lobar hemorrhages, and vessel stenosis.[68,69] Vascular pathology underlying white matter dysfunction is observed in many forms of subcortical dementia, including extensive lacunar infarcts as well as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.[70] Hall et al[71] evaluated the relationship between a biomarker panel reflecting cardiovascular risk and inflammation, as well as microvascular dysfunction and neuropsychiatric symptomatology in mild AD. The authors found a significant positive association between cholesterol and all four items on the neuropsychiatric inventory, which was restricted to male patients, reflecting the importance of sex as a determinant of clinical heterogeneity. The presence of CAA in *APOE* ε-4 allele carriers may further play a synergistic role in AD progression.[69] However, other studies note that although white matter pathology originates secondary to vascular dysfunction, it is not directly related to *APOE* genotype, which rather influences the localization of CAA and thereby contributes to the emergence of focal cerebral pathology and corresponding clinical heterogeneity.[72,73] It has been suggested that the presence of capillary CAA in *APOE* ε-4 allele carriers might constitute a specific subtype of AD.[74] The localization of cerebral Aβ deposition

and CAA may account for a degree of clinical heterogeneity observed in AD.[75] Absence of the *APOE* ε-4 allele is further associated with an atypical clinical presentation in presenting at an earlier age, which merits further consideration of other risk factors for AD.[76,77] Given the reciprocal influence of *APOE* genotype and CAA on parenchymal as opposed to vascular Aβ aggregation, further investigation of whether the combined presence of these factors influences clinical and therapeutic heterogeneity in AD is also warranted.

AD typically first presents with episodic memory loss. However, some patients may present at an earlier age with atypical symptoms. This clinical heterogeneity is partly a reflection of focal cerebral pathology, including atrophy and hypoperfusion; executive dysfunction and visuospatial symptoms are associated with synucleinopathy and microvascular pathology, focal temporal atrophy with an amnestic picture, and parietal pathology with disordered visuospatial processing. It is interesting to note that although the *APOE* ε-4 allele accelerates disease progression in AD, patients who present atypically or at an earlier age seldom carry the risk-associated allele.[77,78] This suggests that the presence of such symptoms and associated pathology in ε-4 carriers might represent a distinct subtype of AD.

AD a paradigm shift from treatment to prevention

Health-promoting lifestyle changes are of proven benefit in ameliorating risk for cardiovascular disease and stroke. In line with a growing international health care focus on primary prevention of disease, dementia was identified as a major global health aim at the 2013 G8 summit. An international team of experts argued that public health policy should reflect current knowledge supporting the risk-modulating benefits of smoking cessation, regular physical exercise, a nutritional diet rich in fruits, vegetables, and fish; as well as adequate B vitamin intake in reducing the risk of AD and dementia.[79] The implementation of national policies aimed at preventing cumulative risk for chronic noncommunicable diseases by means of lifestyle-based intervention strategies has proven beneficial in resource-limited settings in the developing world.[80,81]

There is particular interest in the Mediterranean diet as an effective strategy to decrease cumulative risk for AD and dementia-related mortality.[82–84] Results from the Lyon Diet Heart Study showed an astonishing 70% reduction in mortality in patients randomly assigned to a Mediterranean-style diet compared with a low-cholesterol diet, despite only a 6% decrease in total cholesterol levels in the former group.[85] Benefits attributable to the Mediterranean diet therefore appear to be largely independent of its cholesterol-lowering effects, but are rather accredited to a higher dietary intake of folate, as well as the protective benefits of flavonoids, omega-3 fatty acids, antioxidants, and moderate alcohol intake.[86] We recently confirmed the cardiovascular health benefits of moderate polyphenol-rich red wine consumption in healthy volunteers participating in a 6-week crossover alcohol intervention study, where an increase in HDL cholesterol observed was less pronounced in *APOE* ε-4 carriers.[87]

Physical activity in middle age and later life may reduce the risk for progression from MCI to AD. However, results from epidemiological studies remain inconsistent, and no RCTs to date have been performed to definitely establish the value of lifestyle-based interventions aimed at improving neurocognitive performance in at-risk individuals.[88] In line with a growing shift toward the prevention of AD, there is a need to better define the exact duration, type, and intensity of physical activity required to effectively reduce cumulative AD risk.[89] The Exercise and Nutritional Interventions for Cognitive and Cardiovascular Health Enhancement (ENLIGHTEN) trial is set to establish the efficacy of physical exercise and the DASH (dietary approaches to stop hypertension) diet in patients at increased cardiometabolic risk, as well as assess the mechanisms whereby these interventions may improve neurocognitive performance.

Influence of *APOE* genotype on therapeutic decision making in AD

APOE genotyping, when performed as part of a comprehensive clinical risk assessment strategy considering environmental modulators of phenotypic expression, may facilitate the timely implementation of tailored lifestyle-centered treatment strategies and optimize pharmacotherapy in AD.[69] Differentiating between hypercholesterolemic patients with the monogenic disorder, familial hypercholesterolemia (FH), and those carrying the *APOE* ε-4 allele is important, as treatment strategies would differ. A relatively high incidence of mild cognitive impairment has recently been reported in FH patients, possibly due to early exposure to elevated cholesterol or low-density lipoprotein dysfunction.[90] The importance of the availability of a DNA test for diagnosis of FH as a high-risk cardiovascular subtype[91] is emphasized by the clinical variability of this condition, which complicates clinical diagnosis.[92,93] Although FH patients require lipid-lowering medication to reduce their risk of ischemic vascular disease, *APOE* ε-4 carriers are less responsive to statin therapy.[94] *APOE* ε-4 carriers appear

Table 1 Influence of *APOE* genotype on the efficacy of lifestyle-based interventions in relation to Alzheimer's disease

Study design	Lifestyle intervention	Interpretation	Reference
Prospective study	Physical activity	Physical activity attenuated the effects of genetic risk on episodic memory in individuals free of dementia at baseline	101
Prospective study	Dietary antioxidant intake (vitamin E)	Adequate dietary intake of vitamin E may reduce Alzheimer's disease risk in *APOE* ε-4 allele noncarriers in individuals free of dementia at baseline	102
Prospective study	Fish high in omega 3 fatty acids more than two times per week	Regular consumption of foods rich in omega 3 fatty acids reduces Alzheimer's disease risk in *APOE* ε-4 allele noncarriers	103
Randomized control trial	Omega 3 fatty acid (docosahexaenoic acid) supplementation	No effect on clinical outcomes in patients with mild to moderate Alzheimer's disease	104
Prospective cohort study	Dietary antioxidant intake	Higher dietary antioxidant intake decreases risk of Alzheimer's disease irrespective of *APOE* genotype	105

Abbreviation: *APOE, apolipoprotein E.*

to be more vulnerable to the deleterious effects of excessive alcohol consumption, cigarette smoking, a sedentary lifestyle, and high dietary intake of saturated fat, suggesting interventions targeting these risks may be beneficial in decreasing risk aimed at AD prevention.[95,96] Lowering of cumulative risk aimed at AD prevention is very important in *APOE* ε-4 allele carriers, as the benefits associated with many lifestyle-orientated interventions, including regular physical exercise and supplementation with omega-3 fatty acids, may be less pronounced or absent in AD patients carrying the *APOE* ε-4 allele (Table 1). This may be attributed to the attenuating effects of preclinical neuropathology, which can arise years or even decades before presentation. Furthermore, although a significant body of evidence implicates oxidative stress and chronic inflammation in the development and progression of AD, RCTs to date have failed to significantly associate antioxidant or omega-3 fatty acid supplementation with clinical improvement.[97]

Table 2 Influence of *APOE* genotype on the efficacy of acetylcholine-esterase inhibitors traditionally used in Alzheimer's disease

Medication	Reference
Interpretation: influence of *APOE* genotype on therapeutic response	
Donepezil	
Patients with Alzheimer's disease carrying the *APOE* ε-4 allele may respond better to donepezil than noncarriers	106
Tacrine	107
Faster rate of cognitive decline in *APOE* ε-4 allele carriers treated with tacrine	
Galantamine	
APOE genotype does not influence the efficacy of galantamine therapy in Alzheimer's disease	108
APOE genotype does not influence cognitive improvement related to galantamine treatment in Alzheimer's disease	109
Rivastigmine	
Moderately severe Alzheimer's disease patients with the *APOE* ε4 allele may respond more favorably to memantine plus rivastigmine patch than noncarriers	110

Abbreviation: *APOE, apolipoprotein E.*

Up to 80% of interpatient variation in the therapeutic response to medications commonly used to treat AD may be explained by genotype. Both *APOE* genotype and sex are important determinants of treatment response in AD.[98] Multiple studies,[99] have demonstrated that AD patients who carry the *APOE* ε-4 allele show a differential response to conventional pharmacotherapy (Table 2). Coinheritance of inactivating *CYP2D6* alleles, conferring ultrarapid or poor metabolizer status, appear to have an additive effect.[100]

Conclusion

AD is commonly viewed as a hopeless diagnosis, relegating patients to a life marked by feelings of uncertainty and fear. Providing a caregiver, family member, or physician with additional genetic information may be viewed as contributing to this prevailing aura of futility. However, a growing appreciation that the phenotypic expression of risk-associated variants of low-penetrance in genes such as *APOE* ε-4, implicated in the development of AD, is largely dependent on a conducive metabolic milieu creates hope that timely health-promoting lifestyle-centered intervention strategies may overcome an apparently insurmountable genetic predisposition. Growing insight into the multifunctional role of the *APOE* ε-4 allele in explaining a certain degree of the marked interpatient etiological, clinical, and therapeutic heterogeneity noted for this condition gives hope that the identification of distinct treatable subtypes of AD

may provide an opportunity for effective primary and secondary intervention. It may be viewed as the resilient duty of the physician to become increasingly knowledgeable about the therapeutic implications of personalized genotyping as a means to tailor treatment to the needs of the individual. A paradigm shift in thinking is required for genetic insights to be viewed as a beneficial avenue for intervention, rather than irrefutable confirmation of an incurable diagnosis.

A healthy lifestyle to prevent AD based on a similar approach applicable to cardiovascular risk reduction would be most beneficial when followed throughout life, rather than only after disease manifestation. This may be particularly important in individuals with a genetic predisposition to AD, to protect against disease development or reduce the risk of vascular disease and diabetes associated with this neurodegenerative condition.

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