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Review

Putative Survival Advantages in Young Apolipoprotein ε4 Carriers are Associated with Increased Neural Stress

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Abstract. Inheritance of a single copy of the apolipoprotein E (APOE) ε4 allele increases risk of Alzheimer's disease (AD) by 3-4-fold, with homozygosity associated with a 12-16-fold increase in risk, relative to ε3 allele homozygosity. There is a decreased risk associated with the APOE ε2 allele. The pathological consequence of APOE genotype has led to intense efforts to understand the mechanistic basis of the interplay between APOE status and loss of synapses. Numerous ε4 allele-related associations have been reported with the potential relevance of these associations to the pathogenesis of AD unknown at this time. In primarily young subjects, we have reviewed a representative body of literature on ε4 allele-associations related to the following: cardiovascular responses; impacts on reproduction and fetal development; co-morbidities; resistance to infectious disease; responses to head injury; biochemical differences possibly related to neural stress; and brain structure-function differences. In addition, the literature on the association between the ε4 allele and cognitive performance has been reviewed comprehensively. The weight-of-the-evidence supports the hypothesis that possession of the ancestral ε4 allele in youth is associated with improved fitness during fetal development, infancy, and youth relative to the more recently appearing ε3 allele, at the expense of decreased fitness in old age, which is substantially improved by the ε3 allele. However, possession of the ε4 allele is also associated with higher levels of synaptic macromolecular turnover, which likely stresses basic cellular neuroplasticity mechanisms. Clinical trials of potential AD therapeutics should consider APOE status as an enrollment criterion.

Keywords: Alzheimer's disease, apolipoprotein E, ε4 allele, improved performance, youth

INTRODUCTION

Alzheimer's disease (AD) is a pathological condition adversely affecting the brain. AD has a large genetic component. The neuropathology is characterized by the presence of neurofibrillary tangles (NFTs) and neuritic plaques [1, 2]. The modern conceptualization of AD pathology dates from 1968 when Blessed et al. showed in elderly individuals that the NFTs correlated with the severity of the dementia, though the neuritic plaques, which contain cerebral amyloid-β (Aβ), did not [2]. A major advance in understanding AD pathology was the demonstration that AD pathology predominantly affects the posterior-temporal, inferior parietal, posterior cingulate, and medial temporal region [3], with a characteristic pattern of progression beginning in the entorhinal cortex involving neurofibrillary (NF)

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and microtubule associated protein-tau pathology rather than senile plaque and cerebral Aβ pathology [4], consistent with the earlier findings of Blessed et al. [2].

Dementia is a condition involving impairment of cognitive function, which has deteriorated from a prior higher level, and causes social impairment. There are a few types of dementia, mostly frontotemporal (rare) and temporal-parietal (common). Patients with temporal-parietal dementia subdivide into approximately one third with pure AD, one third not AD, and one third being mixed, with the prevalence of mixed cases increasing with age. This progression of AD (NF/NFT/tau pathology) is clearly reflected by both altered cerebral blood flow [5] and cerebral metabolism [6, 7], as well as by PET tracers targeting tau [8, 9], with characteristic regional and stage-specific variations [9]. These changes in the brain are closely related to the impairments of memory function that are so typical of the dementia associated with AD and its progression [10, 11]. This pattern has strongly suggested that AD pathology selectively attacks those neuroplastic brain systems which perform the functions of episodic memory [12, 13]. The neuritic plaques and Aβ are consistent components of AD pathology [14], which is the predominant cause of dementia. However, the distribution pattern of Aβ pathology, which is found at least as early and diffusely in the neocortex as the tau pathology, is found first in most regions of the neocortex [15] but is generally not or much less related to cognitive changes than the tau pathology [16–18]. With a slowly progressing condition, mild cognitive impairment is a transition from normal cognition that precedes dementia, and is very poorly described [19].

Previously, we hypothesized that apolipoprotein E (APOE) ε4 allele-associated AD risk is consistent with increased lifetime exposure to a neurotoxic process [20]. Specifically, if the hippocampal neurons of two individuals possess the same susceptibility to an endogenous or exogenous stress factor, the neurons with the highest turnover of proteins, lipids, and other macromolecules might experience a larger integrated dose of detriment. Small differences in pharmacokinetic effects might be amplified by the extremely long pre-symptomatic phase of AD, i.e., average age of presentation for a homozygous ε4 is about 68 years of age [20]. Studies conducted across the age spectrum from infancy through senescence have suggested that APOE ε4-positive status is associated with increased brain activity and macromolecule turnover in young healthy individuals, with the reverse extant in elderly subjects. In the current study, we extend our analysis from the limited number of studies examined in Smith and Ashford [20] and attempt herein to comprehensively examine the literature on reported associations between clinical conditions, cognitive performance, and presence or absence of the ε4 allele in otherwise healthy young subjects.

The literature on associations between ε4 status in otherwise healthy young subjects falls into several categories including: cardiovascular responses (Table 1); reproduction and development (Table 2); co-morbidities (Table 3); resistance to infectious disease (Table 4); responses to head injury (Table 5); biochemical differences possibly related to neural stress (Table 6); brain structure-function (Table 7); and mental performance (Table 8). Possession of the ε4 allele is a strong risk factor for development of AD in the elderly, and all individuals possessing the ε4 allele are increasingly likely to develop AD the older they live, relative to those without this allele. An understanding of the clinical conditions and cognitive performance characteristics idiosyncratic to healthy young persons who possess the ε4 allele might assist in the complex task of disentangling the relative contributions of genetics and lifestyle that appear to play a role in how and when a given individual develops AD [21].

The mechanism through which inheritance of an allele of a protein associated with cholesterol metabolism, i.e., ε4, exerts an increased risk for the development of AD later in life is not understood. One current hypothesis emphasizes that vulnerability to AD is based on the very high rate of formation and removal of synapses in the brain. In healthy individuals, the number of synapses formed and actively removed is estimated to be one trillion per day, presumably associated with constant learning and establishment of new memories. The amyloid-beta protein precursor (AβPP) plays a central role in this aspect of neuroplasticity [13]. A considerable amount of evidence has related AβPP to AD [22], including a relationship between its Aβ product and APOE genotype [23]. AβPP can be cleaved either by the α-secretase, which leads to increased local synapse production and prevents formation of the synaptotoxic Aβ molecule or by the β-secretase, followed by γ-secretase, which leads to the removal of the affected synapse [22]. The control of the delicate balance between synapse creation and destruction is critical for learning and involves numerous mechanisms, with a positive neuronal action culminating in activation of the α-secretase, while activation failure leads

Table 1
Cardiovascular responses in young apolipoprotein ε4 carriers

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
Young adult Chinese men and women, approximate mean age = 32	ε3/4 (N = 60), ε4/4 (N = 13)	Mixed	Association of APOE polymorphism with maximal oxygen uptake after exercise training: a study of Chinese young adult	VO_2max after exercise training increased significantly in carriers of ε3/ε4 in males (OR = 0.60, 95% CI = 0.09,1.11; $p = 0.02$) and females (OR = 0.62, 95% CI = 0.09, 1.15; $p = 0.02$)	Yu et al. [51]	Moderate
Children from the Tasmanian Infant Health Survey; ε4 carriers, mean age = 8	ε4 carriers (N = 75)	Mixed	APOE genotype and cardio-respiratory fitness interact to determine adiposity in 8-year-old children	ε4 carriers had a lower BMI (mean difference –0.90 kg/m2) [95% CI –1.51, –0.28; $p = 0.004$] and the effect was more evident among the less fit (mean difference –1.78 kg/m^2) [95% CI –2.74, –0.83; $p < 0.001$]	Ellis et al. [50]	Moderate
Subjects from a supervised exercise training program in Black and White men and women, average age approximately 35	ε3/ε4 (N = 101), ε4/ε4 (N = 7)	Mixed	Association of APOE polymorphism with blood lipids and maximal oxygen uptake in the sedentary state and after exercise training (HERITAGE Family Study)	APOE polymorphism was not associated with VO_2max [maximal oxygen uptake] levels either in the sedentary state nor the VO_{2max} response to exercise training	Leon et al. [149]	Moderate
Healthy 13-month-old Finnish children	16 ε4 children and 20 ε3/ε3 children (N = 36)	Mixed	APOE phenotype regulates cholesterol absorption in healthy 13-month-old children (The STRIP Study)	16 ε4 children had 30% to 50% higher cholesterol-adjusted campesterol and sitosterol concentrations in serum than 20 ε3/3 children ($p = 0.002$ and $p = 0.02$, respectively)	Tammi et al. [45]	Moderate
7- and 13-month-old Finnish infants	ε4/ε4 (N = 36), ε3/ε4 (N = 209)	Mixed	APOE4 phenotype increases non-fasting serum triglyceride concentration in infants (The STRIP Study)	Triglyceride concentrations were higher in infants with ε4/ε4 or ε3/ε4 than in those with ε3/ε3 (p-value for difference 0.01 and 0.009, respectively)	Tammi et al. [44]	High
Caucasian males in Perth, Australia, eight pairs of ε3/ε3 and ε4/ε4 subjects matched for age and serum lipid levels; average age = ε3/ε3 = 45 and ε4/ε4 = 42	ε3/ε3, N = 16 and ε4/ε4, N = 16	Males	Comparison of the LDL-receptor binding of VLDL and LDL from APOE4 and APOE3 homozygotes	Inheritance of APOE4 was associated with an increased affinity of VLDL particles for LDL receptors on hepatocytes	Mamotte et al. [48]	Low
Finnish infants	ε4 carriers (N = 44)	Mixed	APOE phenotype determines serum cholesterol in infants during both high-cholesterol breast feeding and low-cholesterol formula feeding	In infants fed high-fat, high-cholesterol human milk, the total and LDL-cholesterol concentrations and the LDL apoB concentration of those with the APOE phenotype ε4/4 or ε3/4 rose faster and to higher levels than in other infants	Kallio et al. [46]	Moderate

(Continued)

Table 1
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Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
Healthy Finnish boys, 16 years old	ε4 carriers (N = 11); Controls N = 17	Males	APOE phenotypes and cardiovascular responses to experimentally induced mental stress in adolescent boys	ε3/ε2 or ε3/ε3 showed marginally significant greater heart rate reactivity and significantly greater task levels of heart rate and heart rate variability during mental stress than ε4/ε2, ε4/ε3, or ε4/ε4	Ravaja et al. [49]	Low
Healthy Finnish boys and girls, 16 years old	ε2/ε4 carriers (N = 28), ε3/ε4 carriers (N = 470), ε4/ε4 carriers (N = 49)	Mixed	The effect of physical activity on serum total and LDL cholesterol concentrations varies with APOE phenotype in male children and young adults (The Cardiovascular Risk in Young Finns Study)	Physical exercise does not affect LDL cholesterol, total cholesterol, or HDL/total cholesterol in ε4 carriers	Taimela et al. [47]	High
Finnish male and female newborns and 3-year-old children	ε2/ε4 (N = 5), ε3/ε4 (N = 147), ε4/ε4 (N = 8)	Mixed	APOE phenotypes and serum lipids in newborns and 3-year-old children: (The Cardiovascular Risk in Young Finns Study)	In 3-year-olds, the concentrations of serum total cholesterol and LDL cholesterol increased with APOE phenotype in the order of ε3/ε2, ε3/ε3, ε4/ε3, and ε4/ε4, in both males and females ($p < 0.001$)	Lehtimaki et al. [43]	Moderate
Finnish boys and girls ages 3, 6, 9, 12, 15, and 18.	ε2/ε4 carriers (N = 28), ε3/ε4 carriers (N = 483), ε4/ε4 carriers (N = 50)	Mixed	APOE phenotypes in Finnish youths: a cross-sectional and 6-year follow-up study	The concentrations of serum total cholesterol, LDL cholesterol, and apoB increased with APOE phenotype in the order of ε2/ε2, ε3/ε2, ε4/ε2, ε3/ε3, ε4/ε3, and ε4/ε4	Lehtimaki et al. [42]	High

APOE, apolipoprotein E; BMI, body mass index; 95% CI, 95% confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; VLDL, very-low-density lipoprotein.

Table 2
Reproduction and development in apolipoprotein ε4 carriers

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
100 women with a history of at least 2 first-trimester recurrent miscarriages in Tabriz, Iran, and 100 healthy women with at least 2 successful pregnancies and no miscarriages were the control group; Age not specified	N = 100 (Test Subjects) ε4 (N = 31); N = 100 (Control Subjects)	Female	Effect of APOE ε4 allele on survival and fertility in an adverse environment	ε4 was associated with higher fertility in women exposed to high pathogen levels. Compared with women not carrying an ε4 allele; those carrying one ε4 had on average one more child and those carrying two ε4 alleles had 3.5 more children ($p = 0.018$)	van Exel et al. [52]	Moderate
White, Black, and Hispanic neonates and infants	(N = 87) All ε4 carriers	Not specified	Validation of association of the APOE ε2 allele with neurodevelopmental dysfunction after cardiac surgery in neonates and infants	The ε2 allele was associated with a lower Psychomotor Development Index ($p = 0.038$)	Gaynor et al. [66]	Moderate
100 Iranian women with at least 2 first trimester recurrent miscarriages and 100 Iranian women with at least two successful pregnancies with no miscarriages; Age not specified	N = 100 (Test Subjects); ε4 (N = 31); N = 0 (Control Subjects)	Female	APOE genotyping in women with recurrent pregnancy loss: an *in silico* and experimental hybrid study	ε4 carriers and the frequency of the ε4 allele in the case group were statistically significantly higher than those in the control group ($p < 0.05$)	Zonouzzi et al. [65]	Low
81 Iranian women with 2 or more pregnancy losses; Age not specified	N = 81; ε4 Carriers (N = 22)	Female	Positive association of APOE E4 polymorphism with recurrent pregnancy loss in Iranian patients	Allelic frequency for ε4 was 13.5% in the patients with recurrent pregnancy loss and only 1% in the non-recurrent pregnancy loss group	Asgari et al. [63]	Low
90 Turkish women (45 women with >2 consecutive spontaneous abortions and no successful pregnancies and 45 fertile women with at least one live birth); Age not specified	N = 90, 45 Test, 45 Controls; ε4 Carriers (N = 16 in patients, N = 18 in controls)	Female	Study on potential role of APOE in recurrent pregnancy loss	ApoE genotypes and ε2, ε3, and ε4 allele frequency distribution were observed among recurrent pregnancy loss patients and controls	Korkmazer et al. [58]	Moderate
Meta-analysis of seven studies with combined ε4 carriers; Age not specified	N = 323 for the cases; N = 70 for the controls)	Female	Association between APOE gene polymorphism and the risk of recurrent pregnancy loss	Meta-analysis suggests an association [OR = 1.98, 95% CI 1.14–3.43] between ε4 and increased risk of recurrent pregnancy loss	Meng et al. [64]	High
Pregnant Romanian women, average age 28	ε4 Carriers (N = 46)	Female	APOE polymorphism as a risk factor in Romanian pregnant women with preeclampsia	Pregnant women with the ε4 allele were at increased risk to develop Pregnancy Induced Hypertension (OR 4.14, $p = 0.013$) and severe preeclampsia (OR 4.43, $p = 0.019$)	Procopciuc et al. [67]	Moderate

(Continued)

Table 2
Continued

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
Indian women with a history of three spontaneous abortions (mean 4, range 3–7) and no previous history of successful pregnancy, average age 28.4	ε4 Carriers (N = 11 in patients; N = 4 in controls)	Female	A case-control study of recurrent pregnancy loss and APOE gene polymorphisms in women from North India	Similar APOE genotypes and ε2, ε3, and ε4 allele frequency distribution were found among recurrent pregnancy loss patients and controls	Agarwal et al. [56]	Low
160 Italian women with recurrent pregnancy loss; Age not specified	ε4 Carriers (N = 23)	Female	The association between APOE polymorphisms and recurrent pregnancy loss	No association was seen between ε4 and recurrent pregnancy loss	Bianca et al. [57]	Low
Turkish women, average age 35	ε4 Carriers (N = 33)	Female	The apparent association of APOE codon 112 polymorphisms with recurrent pregnancy loss	Significantly more ε3/ε4 and ε4/ε4 genotypes were seen among individuals experiencing recurrent pregnancy loss and deep vein thrombosis than fertile controls ($p < 0.05$)	Ozornek et al. [62]	Low
69 American women with recurrent loss of pregnancy (average age 34.7), 69 control women, Average age 37	ε4 Carrier patients (N = 15), ε4 controls (N = 2)	Female	The association of APOE polymorphisms with recurrent pregnancy loss	Patients experiencing recurrent pregnancy loss had a significantly higher prevalence of APOE ε3/ε4, ε4/ε4 genotypes (21.7%) compared with control women (5.4%) ($p = 0.036$)	Goodman et al. [61]	Low
Scottish perinatal deaths	ε4 Carriers (N = 3 ε4/ε4; N = 16 ε2/ε4; N = 51 ε3/ε4)	Not specified	The distribution of APOE alleles in Scottish perinatal deaths	ε4 prevalence was raised in healthy liveborn infants (19%) compared with stillbirths (12%, OR = 1.59, 95% CI 1.11 to 2.26)	Becher et al. [60]	Moderate
CSF collected from 107 healthy Japanese subjects (70 males, 37 females) aged 1–86; 67 <20 years and 40 >20 years old	N = 107 (70 males, 37 females)	Mixed	Effect of APOE phenotype on the APOE content of CSF-HDL in children <20 years old	APOE phenotype does not affect composition or concentration of CSF HDL in children <20 years old	Hirayama et al. [68]	Moderate
Afro-Ecuadorian and Cayapa Indian women, average age 39	ε4 Carriers (ε3/4 = 16; ε4/4 = 6; ε4/2 = 5)	Female	A study of APOE polymorphism and fertility in pre-industrial populations	ε3/ε4 genotype frequency (0.50) in African-Ecuadorian women with 9–17 children was about 3-fold that of women with 0–8 children (0.14) ($p = 0.02$)	Corbo et al. [53]	Low
Asian, Black, and White, male and female infants under 6 months undergoing cardiac surgery in Philadelphia	ε4 Carriers (N = 52)	Mixed	APOE genotype and neurodevelopmental sequelae of infant cardiac surgery	Patients with an ε2 allele had approximately a 7-point decrease in the Psychomotor Developmental Index [Bayley Scales of Infant Development] ($p = 0.036$)	Gaynor et al. [69]	Moderate
81 Spontaneously aborted embryos and 100 adult controls from Crete; Age of adults not specified	N = 81 (4 ε3ε4) Test; N = 100 adult controls (17 ε3ε4)	Not applicable	Influence of the APOE ε4 allele on human embryonic development	ε4 allele was less frequent in the spontaneous abortion group than in the control group ($p = 0.009$), while the frequency of ε3 was increased ($p = 0.005$)	Zetterberg et al. [55]	Moderate
40-year-old married men residing in Aarhus, Denmark	ε4 Carriers (ε3/ε4 = 93; ε4/ε4 = 12; ε4/ε2 = 9); ε3 Carriers (ε3/ε3 = 212; ε3/ε4 = 93; ε3/ε2 = 48); ε2 Carriers (ε2/ε2 = 5)	Men	The fertility of men carrying the apolipoprotein ε4- or ε2 allele versus ε3/ε3 genotypes	Men with the ε3/ε3 genotype ($n = 212$) had 1.93 children, men with the ε3/ε4 or ε2/ε2 genotypes ($n = 53$) had 1.66 children ($p = 0.0026$), and men with the ε3/ε2 or ε2/ε2 genotypes ($n = 53$) had 1.66 children	Gerdes et al. [54]	Moderate

APOE, apolipoprotein E; 95% CI, 95% confidence interval; CSF, cerebrospinal fluid; HDL, high-density lipoprotein; OR, odds ratio.

Table 3
Co-morbidities in young apolipoprotein ε4 carriers

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
Meta-analysis of 28 studies on schizophrenia; Age of subjects not specified	Not specified	Mixed	Determine the association between APOE and schizophrenia: evidence of systematic review and updated meta-analysis	Protective effect was found for ε3 in the Asian population (OR = 0.73, 95% CI = 0.54–0.98)	Gonzalez-Castro et al. [70]	Moderate
Infants with hypoxic-ischemic encephalopathy	ε4 Carriers (N = 41)	Mixed	APOE genotype and outcome in infants with hypoxic-ischemic encephalopathy	Disability was not associated with APOE genotype in this cohort of hypoxic-ischemic encephalopathy patients	Cotton et al. [72]	Moderate
Pooled analysis of 15 studies on the association of APOE alleles with age-related macular degeneration; Age not specified	Not specified	Mixed	Evidence of association of APOE with age-related macular degeneration–a pooled analysis of 15 studies	Decrease in risk associated with each copy of ε4 in all age-related macular degeneration sub-phenotypes (Neovascular: OR = 0.74, CI 0.66–0.83; Geographic Atrophic: OR = 0.65, CI 0.55–0.77; Geographic Atrophic Neovascular: OR = 0.71, CI 0.59–0.85; early Age-Related Macular Degeneration: OR = 0.84, CI 0.77–0.92	McKay et al. [71]	High
Male and female patients, average age 46, from the dermatology clinic at Hospital Universitario Central Asturias, Spain	ε3/ε4 (N = 54), ε4/ε4(N = 3), ε2/ε4(N = 5)	Mixed	APOE4 allele is associated with psoriasis severity	ε4 carriers were significantly more common in patients with severe psoriasis compared to controls ($p = 0.003$) and to non-severe psoriasis ($p = 0.017$)	Coto-Segura et al. [150]	Moderate
Children in Brasilia Brazil with and without CP; Age not specified	ε4 Carriers (N = 139)	Mixed	Association of APOE genotype and CP	Presence of ε2 raised the probability of having cerebral palsy (OR 3.2; 95% CI 1.27–8.27). The presence of ε4 was not significantly different among groups	Braga et al. [73]	Moderate
Infants in Edinburgh Scotland	ε4 Carriers (N = 95)	Mixed	APOE ε4 and its prevalence in early childhood death due to sudden infant death syndrome or to recognized causes	Percentage of children with at least one ε4 allele was lower in non-SIDS compared to SIDS ($p = 0.016$)	Becher et al. [59]	Moderate
Caucasian (70%) and African-American children (30%) from Louisville, KY, area, average age 6.4 years	ε4 Carriers (N = 19)	Mixed	APOE ε4 allele, cognitive dysfunction, and obstructive sleep apnea in children	ε4 allele is more frequent in children with obstructive sleep apnea and particularly in children who develop neurocognitive deficits	Gozal et al. [151]	Low

(Continued)

Table 3
Continued

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
White, Black, and Hispanic children from the Chicago area; Age not specified	ε4 Carriers (N = 25 patients; N = 9 controls)	Mixed	Association of APOE genotype and CP in children	Overall risk for CP was elevated 3.4-fold among children carrying an ε4 allele	Kuroda et al. [75]	Low
40 patients with CP and 40 without, in S'ao Paulo, Brazil; Age not specified	Total N = 80, 40 with CP, 40 without CP; ε4 Carriers (N = 13 patients; N = 4 controls)	Mixed	Presence of APOE ε4 allele in CP	OR for correlation between CP and ε4 allele = 4.333	de Barros et al. [74]	Low

APOE, apolipoprotein E; 95% CI, 95% confidence interval; CP, cerebral palsy; OR, odds ratio; SIDS, sudden infant death syndrome.

Table 4
Resistance to infectious disease in apolipoprotein ε4 carriers

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
Patients from Charite Berlin and University of Leipzig with either chronic or self-limited HCV infection, average age = 48.7	ε4 Carriers (N = 205) in two cohorts combined	Mixed	APOE allele frequencies in chronic and self-limited hepatitis C suggest a protective effect of APOE4 in the course of HCV infection	ε4 alleles are underrepresented in chronically hepatitis C-infected patients (10.2%) compared to 13% in healthy controls ($p = 0.001$)	Mueller et al. [76]	High
Seven APOE ε4/ε4 and six APOE ε3/ε3 donors from Cleveland, OH, area; Age not specified (only adults)	ε4/ε4 Donors N = 7 and ε3/ε3 donors N = 6	Not specified	APOE ε4 prevents growth of malaria at the intraerythrocyte stage: implications for differences in racial susceptibility to AD	Human plasma samples from ε4/ε4 but not ε3/ε 3 donors inhibited growth and disrupted morphology of *P. falciparum* [malaria]	Fujioka et al. [82]	Low
Male and female Caucasian Italian patients with chronic hepatitis C, median age = 41	ε2/4 Carriers (N = 3), ε3/4 Carriers (N = 21), ε4/4 Carriers (N = 1)	Mixed	APOE genotypes modulate fibrosis progression in patients with chronic hepatitis C and persistently normal transaminases	Patients not carrying ε3, as well as carriers of a single ε3 with serum cholesterol concentration >190 mg/dL were more likely to have a favorable outcome regarding fibrosis progression with chronic hepatitis C	Fabris et al. [77]	Low
British and Irish Caucasian hepatitis C patients; Age not specified	ε2 Carriers (N = 48), ε4 Carriers (N = 84), 11 Carriers were both, i.e. ε2/ε4	Mixed	APOE ε3 allele is associated with persistent HCV infection	ε2 and ε4 alleles were both associated with a reduced likelihood of chronic hepatitis C infection. For ε2, OR = 0.39[95% CI = 0.211–0.728] ($p = 0.003$), and for ε4, OR = 0.6[95% CI = 0.38–0.96] ($p = 0.032$)	Price et al. [79]	Moderate
Italian male and female patients who underwent a cadaveric orthotopic liver transplantation, median age 55	ε4 Carriers (N = 34)	Mixed	The relationship with the blood lipid profile and low fibrosis progression of recurrent hepatitis C in APOE E4 carriers	Possession of an APOE ε4 allele is associated with low fibrosis progression in recurrent hepatitis C infection, and with an idiosyncratic APOE-associated lipid profile.	Fabris et al. [78]	Low
Gambian children, ages 1–10	ε4 Carriers (N = 244)	Mixed	Common APOE polymorphisms and risk of clinical malaria in the Gambia	For severe malaria cases subdivided into clinical categories, ε3/ε4 was more common in children with both cerebral malaria and severe malarial anemia (42.9%) than in controls (24.8%) and mild malaria cases (27.2%). When a correction factor is calculated for the number of clinical groups (4) compared with controls, this finding loses statistical significance	Aucan et al. [83]	High

(Continued)

Table 4
Continued

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
24 male and female patients, median age = 53.5, with recurrent hepatitis C following cadaveric orthotopic liver transplantation	ε4 Carriers (N = 12) of 48 donors, ε4 carriers (N = 17) of 48 recipients	Mixed	Carriage of the APOE ε4 allele and histologic outcome of recurrent hepatitis C after antiviral treatment	Recipient (but not donor) carriage of at least 1 ε4 allele was associated with improvement in staging score due exclusively to the contribution from male recipients	Toniutto et al. [80]	Low
Article is a commentary	Article is a commentary	Article is a commentary	Commentary on APOE polymorphisms and risk of malaria	APOE might compete with pathogens for entry into cells. Differences in isoform affinity for the binding sites/receptors could affect competition and pathogen entry, spread, and damage. APOE isoforms do have different affinities for certain cells. This might explain why a specific allele is protective in some cases but harmful, or else neutral, in others. Competition between APOE and the protozoon might be a factor also in very severe malaria.	Wozniak et al. [152]	Not applicable
Infants from Prampram 50 km east of Accra on south coast of Ghana	ε2/ε2 Carriers (N = 4), ε4 carriers (N = 47)	Mixed	The influence of APOE polymorphism on susceptibility to malaria	ε2 homozygotes became infected with malaria at an earlier age than those carrying other genotypes	Wozniak et al. [84]	Moderate
British men and women with HCV infection, mean age = 41	ε4 Carriers (N = 42)	Mixed	APOE ε4 protects against severe liver disease caused by HCV	In chronically HCV-infected patients grouped according to extent of fibrosis, necroinflammation, and total Knodell score, an overrepresentation of ε4 was found in those whose livers were mildly affected. ε4 protects against severe liver damage induced by HCV	Wozniak et al. [81]	Moderate
The study samples were specimens from the brain or spleen of 14 UK patients with HSE and from the CSF of seven UK patients with HSV1 in their CSF as detected by PCR; Age not specified	N = 14 for HSE samples; N = 7 for CSF	Mixed	HSE: involvement of APOE genotype	ε3 and ε4 allele frequencies did not differ significantly between the two groups. ε2 is a risk factor for HSE	Lin et al. [85]	Low

APOE, apolipoprotein E; 95% CI, 95% confidence interval; CSF, cerebrospinal fluid; HCV, hepatitis C virus; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; OR, odds ratio.

Table 5
Responses to head injury in young apolipoprotein ε4 carriers

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
Male football and male and female soccer players at University of South Carolina, Jacksonville University, Benedict College, College of Charleston, average age 19.85	All ε4 carriers (N = 35)	Mixed	A multicenter prospective cohort study on genetic polymorphisms associated with the risk of concussion in 1,056 college athletes	IL-6R cytokine was associated with a 3-fold greater concussion risk and ε4 with a 40% lower risk	Terrell et al. [86]	Low
Collegiate male football players and female soccer players, average age 19.7; [N.B. Participants completed a researcher-assisted paper and pencil assessment to indicate the athlete's concussion history.]	ε4 Carriers (N = 62)	Mixed	APOE genotype and concussion in college athletes	No significant association between carrying the ε4 allele and history of concussion was found	Tierney et al. [87]	Moderate
APOE genotype and concussion in college athletes	ε4 Carriers (N = 79)	Mixed	A prospective cohort study to determine if APOE ε4 allele predisposes varsity athletes to concussion	The unadjusted hazard ratio for concussion for ε4 carriers was 1.18 (95% CI: 0.52, 2.69) compared to non-carriers. Adjustment for sex, weight, height, and team type resulted in a similar hazard ratio of 1.06 (95% CI: 0.41, 2.72), showing little effect from confounding factors	Kristman et al. [88]	Low
Black and White, male and female, college athletes from 23 schools, average age 19.7; [N.B. Subjects self-report concussion history over the previous eight years]	ε3/ε4 (N = 225), ε4/ε4 (N = 20)	Mixed	APOE, APOE promoter, and tau genotypes and risk for concussion in college athletes	Substantial evidence of an association between history of concussion and APOE genotypes and haplotypes was not seen. Cell sizes for some of the APOE genotypes were small. Compared to those with ε3/ε3, those with ε2/ε3 were at a 60% higher risk for concussion. Results were not statistically significant (OR, 1.6; 95% CI, 0.5 to 4.8)	Terrell et al. [89]	Moderate
Active duty personnel with a recent history of mild to moderate traumatic brain injury, average age 22.6	ε4 Carriers (N = 16)	Mixed	APOE and traumatic brain injury in a military population: evidence of a neuropsychological compensatory mechanism	Comparable performances were seen on most neuropsychological measures and better performances by ε4 carriers on select measures of attention, executive functioning, and episodic memory encoding	Han et al. [90]	Low
Review paper of the childhood literature on APOE and brain injury up through 2005	Review paper	Review paper	APOE and brain injury: implications for children	Contrary to the adult experience, in children ε4 seemed to confer protection for the brain whereas ε2 posed a risk	Blackman et al. [95]	Review paper Not applicable

(Continued)

Table 5
Continued

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
Consecutive head injury admissions (men and women) to a regional neurosurgical unit in West Scotland, average age 35	ε4 Carriers (N = 324)	Mixed	The association between APOE ε4, age and outcome after head injury: a prospective cohort study	No overall association between APOE genotype and outcome, with 36% of ε4 carriers having an unfavorable outcome compared with 33% of non-carriers of ε4	Teasdale et al. [92]	High
Subjects recruited from Canadian traumatic brain injury clinic who experienced mild to moderate traumatic brain injury, mean age 33	ε3/ε4 (N = 16)	Mixed	Six-month recovery from mild to moderate traumatic brain injury: the role of APOE ε4 allele	No association was found between the presence of the ε4 allele and poor outcome across all measures	Chamelian et al. [94]	Low
Prospectively recruited series of patients admitted to West Scotland neurosurgical unit following head injury, median age 38	N = 89; 30 patients with ε4 and 59 patients without ε4	Mixed	Association of APOE polymorphism with outcome after head injury	17 (57%) of 30 patients with ε4 had an unfavorable outcome including death, vegetative state, or severe disability, compared with 16 (27%) of the 59 patients without ε4 (adjusted $p = 0.024$)	Teasdale et al. [93]	Low

APOE, apolipoprotein E; 95% CI, 95% confidence interval; OR, odds ratio.

Table 6
Biochemical differences possibly related to neural stress in apolipoprotein ε4 carriers

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
Subjects and ages varied. Original articles, systematic reviews, and meta-analyses of omega-3 studies in AD that were published before August 20, 2016.	Variable	Mixed	Association of DHA supplementation with AD stage in APOE ε4 carriers	Randomized clinical trials of omega-3 in symptomatic AD have had negative findings. Observational and clinical trials of omega-3 in the pre-dementia stage of AD suggest that omega-3 supplementation may slow early memory decline in ε4 carriers	Yassine et al. [33]	Review paper, not applicable
Middle-aged healthy adults (mean age 35 years, range 19–65 years)	N = 22	Mixed	DHA brain uptake and APOE ε4 status: a PET study with [1-^{11}C]-DHA	Mean global gray matter DHA incorporation coefficient, k*, was significantly higher (16%) among ε4 carriers ($n = 9$) than among non-carriers ($n = 13$, $p = 0.046$)	Yassine et al. [96]	Moderate
Mini-review of APOE genotype and stress responses	Variable	Mixed	APOE genotype and stress response – a mini review	Oxidative stress and, correspondingly, mitochondrial function is affected in an APOE isoform-dependent manner with ε4 usually showing an increased stress response	Dose et al. [98]	Review paper, not applicable
Autopsy specimens from young adults (18–39 years old)	11 ε 3/ε3 Carriers; 1 ε2/ε3 heterozygote; 11 ε3/ε4 heterozygotes; 2 ε4/ε4 homozygotes	Mixed	Altered energy metabolism pathways in the posterior cingulate in young adult APOE ε4 carriers	The authors state that their results suggest the presence of dysregulation of energy metabolism in young ε4 carriers. They noted that young adult ε4 carriers displayed upregulation of specific glucose (GLUT2, GLUT3) and moncarboxylate (MCT2) transporters, the glucose metabolism enzyme hexokinase, the SCOT & AACS enzymes involved in ketone metabolism, and complexes 1, II, and IV of the mitochondrial electron transport chain. The monocarboxylate transporter (MCT4) was found to be downregulated in ε4 carriers	Perkins et al. [153]	Low

(Continued)

Table 6
Continued

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
21 young and middle-aged participants with FAD and 12 Controls.	Six had the APOE ε2/ε3, 6 had the ε3/ε4, [Controls] and 21 had the ε3/ε3 genotype [Test]	Mixed	A study of the effect of familial AD mutations and APOE genotype on plasma signaling protein levels	Plasma levels of APOE and superoxide dismutase 1 were highest in ε2 carriers, lowest in ε4 carriers, and intermediate in ε3 carriers. Levels of multiple interleukins among the ε4 carriers demonstrated significant negative correlations with age	Ringman et al. [101]	Low
699 Subjects from Kiel Germany representing the general population of middle-aged adults, Age 63± years old. A sub-group of 93 subjects from the general population with Metabolic Syndrome; Age 45±11 years	For N = 699 Population - APOE ε4 = 195 and No APOE ε4 = 504; For N = 93 sub-group - APOE ε4 = 30 and No APOE ε4 = 63	Mixed	APOE ε4 is associated with higher vitamin D levels in targeted replacement mice and humans	Multivariate adjusted models calculated a positive association of the ε4 allele with 25(OH)D [vitamin D] levels in a subset of human subjects ($n = 93$; $p = 0.072$) and a general population sample ($n = 699$; $p = –0.003$)	Huebbe et al. [100]	High
Human brain tissue was obtained from the Douglas Hospital Research Centre Brain Bank, Canada, average age 75–79	ε4 Carriers (N = 18)	Mixed	Oxidative insults are associated with APOE genotype in AD brain	Within AD cases, the levels of thiobarbituric acid-reactive substances were higher among ε4 carriers while APOE protein concentrations were lower	Ramassamy et al. [99]	Low

AD, Alzheimer's disease; APOE, apolipoprotein E; DHA, docosahexaenoic acid; PET, positron emission tomography.

Table 7
Brain structure and brain function differences in young apolipoprotein ε4 carriers

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
A total of 97 participants (48 women/49 men) between 20 and 35 years of age (Medium age = 24.3 years) with 12–20 years of education	ε4 Carriers (N = 29)	Mixed	APOE ε4 is positively related to spatial performance but unrelated to hippocampal volume in healthy young adults	Two significant patterns observed: 1) specific structural covariance of the anterior hippocampus and posterior hippocampus in all other groups co-varied with frontal, parietal and cerebellar areas; and 2) opposite structural covariance of the posterior hippocampus in ε4 carriers and the anterior hippocampus of ε4 non-carriers co-varying with motor areas and the middle frontal gyrus	Stening et al. [119]	Low
Young group (average age 21) and a mid-age group (average age 50), right-handed males and females; ε4 carriers in young group (N = 21) and in mid-age group (N = 17)	ε4 Carriers in young group (N = 21) and in mid-age group (N = 17)	Mixed	Structural and resting-state MRI detects regional brain differences in young and mid-age healthy APOE-ε4 carriers	There were no detectable genotype-dependent differences in hippocampal volume for either the young or mid-aged adults. The cuneas appeared to be an important locus for genotype differences with greater functional connectivity among young ε3/ε3 individuals and greater white matter volume in young ε4+ individuals. Subtle cortical thickness measures in the parahippocampus of our young ε4+ individuals positively correlated with performance in a memory task	Dowell et al. [103]	Moderate
Right-handed subjects aged 20–40, average age 24, were recruited in Oxfordshire, UK	N = 18, all ε4	Mixed	Reduced cerebrovascular reactivity in young adults carrying the APOE ε4 allele	ε4 Carriers had the highest task-related hippocampal BOLD signal relative to non-carriers	Suri et al. [148]	Low
93 healthy young participants were recruited (age, 20; range 18–30; 64 women, 29 men), right-handed Caucasian undergraduates at the University of Sussex	Split population of young ε4 and homozygous ε3 carriers; exact N not specified	Mixed	MRI of carriers of the APOE ε4 allele-evidence for structural differences in normal-appearing brain tissue in ε4+ relative to ε4- young adults	Employing voxel-based morphometry of high-resolution structural MR images, a higher white matter volume ratio in ε4 relative to homozygous ε3 carriers was observed	Dowell et al. [104]	Moderate
33 healthy young German students, average age 24, carrying either the APOE ε2 or the ε4 allele	ε2/ε3 (N = 15), ε2/ε2 (N = 2), ε3/ε4 (N = 12), ε4/ε4 (N = 4)	Mixed	Hippocampal volume differences between healthy young APOE ε2 and ε4 carriers	Healthy young ε4 carriers have statistically smaller hippocampal volumes than ε2 carriers, while no differences were detected between the two groups in memory performance	Alexopoulos et al. [105]	Low

(Continued)

Table 7
Continued

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
Hemispheric and lateral ventricular volumes of 144 healthy individuals, aged 19–35 years, were measured using high resolution MRI and data were correlated with BDNF and APOE genotypes.	ε4 carriers (N = 20); ε4 Non-carriers (N = 124); BDNF Val homozygotes (N = 92); BDNF Met carriers (N = 52)	Mixed	Influence of brain-derived neurotrophic factor and APOE genetic variants on hemispheric and lateral ventricular volume of young healthy adults	No correlations between BDNF or APOE genotype and hemispheric or lateral ventricular volumes were seen	Sidiropoulos et al. [106]	Moderate
Students from University of Sussex, average age = 20.92	ε4 Carriers (N = 28); 26 non-ε4 carriers	Mixed	Disrupted neural activity patterns to novelty and effort in young adult APOE ε4 carriers performing a subsequent memory task	In ε4 carriers only, subsequently remembered words were linked to increased hippocampal activity. In the recognition phase, genotype status also modulated hippocampal activity. ε4 Carriers failed to show the conventional pattern of greater hippocampal activity to novel words	Evans et al. [110]	Moderate
Young healthy male and female subjects, age range 20–35 years	18 APOE ε4 carriers and 18 matched non-carriers	Mixed	Distinct patterns of brain activity in young carriers of the APOE ε4 allele	Resting fMRI imaged increased default mode network (involving retrosplenial, medial temporal, and medial-prefrontal cortical areas) co-activation in ε4 carriers relative to non-carriers. The encoding task induced higher hippocampal activation in ε4 carriers relative to non-carriers	Filippini et al. [107]	Low
Forty-one non-demented, HIV-1 seropositive adults, mean age = 45	15 ε4 Carriers and 26 ε4 non-carriers	Mixed	The APOE ε4 allele and memory performance in HIV-1 seropositive subjects: differences at baseline but not after acute oral lorazepam challenge	Acute lorazepam administration produced dose- and time-dependent impairments in measures of verbal recall. However, the ε4 allele did not modulate these adverse effects. An APOE ε4 group by time interaction was also found such that the APOE ε4-positive subjects had significantly better immediate and delayed verbal recall than the negative subjects at baseline assessment, but the groups did not significantly differ at any subsequent time point.	Pomara et al. [154]	Low

(Continued)

Table 7
Continued

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
Healthy right-handed adults recruited from Lebanon, NH, median age = 63	ε4 Carriers (N = 13)	Mixed	Increased brain activation during working memory in cognitively intact adults with the APOE ε4 allele	The ε3/ε4 group displayed greater activity during working memory in medial frontal and parietal regions bilaterally and in the right dorsolateral prefrontal cortex	Wishart et al. [155]	Low
20 healthy young adults performing non-verbal memory tasks, age 19 to 28 years	4 ε4 Carriers and 16 non-ε4 carriers	Mixed	APOE related alterations in cerebral activation even at college age	Using PET imaging, specific brain regions were imaged where ε4 carriers showed significantly lower or higher activation than non-carriers	Scarmeas et al. [108]	Low
Normal male and female volunteers, age was 20 to 39 years	12 ε4 heterozygotes, all with the ε3/ε4 genotype, and 15 noncarriers of the ε4 allele, 12 of whom were individually matched for sex, age, and educational level	Mixed	Functional brain abnormalities in young adults at genetic risk for late-onset AD	The young adult ε4 carriers and noncarriers did not differ significantly in their sex, age, educational level, clinical ratings, or neuropsychological test scores. Like previously studied patients with probable AD and late-middle-aged ε4 carriers, the young ε4 carriers had abnormally low rates of glucose metabolism bilaterally in the posterior cingulate, parietal, temporal, and prefrontal cortex.	Reiman et al. [109]	Low

AD, Alzheimer's disease; APOE, apolipoprotein E; BDNF, brain-derived neurotrophic factor; BOLD, blood-oxygenation-level-dependent; fMRI, functional magnetic resonance imaging; HIV-1, human immunodeficiency virus-1; MRI, magnetic resonance imaging; PET, positron emission tomography.

Table 8
Mental performance in young apolipoprotein ε4 carriers

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
Older Korean adults at risk for AD and 44 subjects with AD, Exact age not specified	N = 441 General population; N = 44 with AD	Mixed	Explore whether the size of the difference between carriers and noncarriers is a function of how well the tests measure general intelligence, so whether there are Jensen effects	On some neurocognitive tests, there are smaller differences between ε4 carriers and non-carriers, while other tests show larger differences. The method of correlated vectors on 441 Korean older adults at risk for AD and 44 with AD was used. Correlations between APOE status and test scores ranged from –0.05 to 0.11 (normal), and –0.23 to 0.54 (AD). The differences between carriers and non-carriers were Jensen effects (general intelligence): $r = 0.31$ and $r = 0.54$, respectively. A composite neurocognitive score may show a clearer contrast between APOE carriers and non-carriers than a large number of scores of single neurocognitive tests	Nijenhuis et al. [156]	Moderate
A total of 97 participants (48 women/49 men) between 20 and 35 years of age (Medium age = 24.3) with 12–20 years of education	ε4 Carriers (N = 29)	Mixed	Specific patterns of whole-brain structural covariance of the anterior and posterior hippocampus in young APOE ε4 carriers	ε4 Carriers performed better compared to non-carriers on Spatial Function and Memory ($F[70] = 6.67$, $p < 0.05$), but there no ε4-related differences on the Episodic Memory composite measure were observed	Stening et al. [102]	Moderate
Amazonian children from 28 villages aged 6–18.	ε4 Carriers (N = estimated 31 from 25% of 124 children)	Mixed	APOE ε4 is associated with improved cognitive function in Amazonian forager-horticulturists with a high parasite burden	After controlling for age, sex, education, and Spanish fluency, ε4 was positively associated with visual scan ($p = 0.037$) and spatial forward tasks ($p = 0.032$), and positively but not significantly associated with 6/8 cognitive outcomes in 124 children aged 6–18	Trumble et al. [120]	Moderate
Healthy men and women selected from the Oxford Biobank, Oxfordshire (mean age 45.5)	ε4 carriers (N = 20 ε3/4; N = 20 ε4/4)	Mixed	Sex and APOE: a memory advantage in male APOE ε4 carriers in midlife	Memory decay (forgetting) was slower in ε4 carriers, as measured by localization error and after controlling for misbinding errors. ε4 carriers made less misbinding errors. Findings were specific to male carriers only	Zokaei et al. [136]	Moderate

British male and female 18-year-olds	ε3/ε4 Carriers N = 542, ε4/ε4 Carriers N = 43	Mixed	Investigation of possible association of APOE genotype with working memory in young adults	There was no evidence of a genotype effect on accuracy when the two difficulty levels were examined separately. There was some evidence to support a deleterious effect of the ε4 allele on n-back accuracy in the multi-level regression. There was weak evidence that the ε2/ε2 group were less accurate, but the numbers were very low in this group. The ε3/ε4 group had faster reaction times than the reference ε3/ε3 group in all adjusted analyses but the ε4/ε4 group were only faster in the 3-back condition in multi-level analyses	Sinclair et al. [121]	Moderate
Young adults (mean age 23.8) recruited from Uppsala University	ε4 Carriers (N = 40)	Mixed	APOE ε4 is positively related to spatial performance but unrelated to hippocampal volume in healthy young adults	ε4 Carriers showed positive effects on spatial function and memory and object location memory, but no effect on word recognition	Stening et al. [119]	Moderate
Male and female college students from Oregon, average age = 19	ε4 Carriers (N = 40)	Mixed	Sex, but not APOE polymorphism, differences in spatial performances in young adults	No significant differences related to APOE types was observed on mental rotation, spatial span, and the Memory Island spatial navigation task	Yasen et al. [117]	Moderate
93 healthy young participants were recruited (age, 20; range 18–30; 64 women, 29 men), right-handed Caucasian undergraduates at the University of Sussex	Not specified	Mixed	MRI of carriers of the APOE ε4 allele-evidence for structural differences in normal-appearing brain tissue in ε4+ relative to ε4– young adults	In a verbal fluency task, ε4 carriers generated more words than non-carriers in the first two time periods for the second and third, but not the first, letter. Comparisons of means confirmed these differences to be significant only for the final letter [$t(38) = 2.00$, 1.70 for first and second time bins, respectively; $p < 0.03$, 0.05; one-tailed]	Dowell et al. [104]	Low

(Continued)

Table 8
Continued

Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
Subjects were aged between 19 and 24 years (Medium = 20.2 years, 14 male and 26 females.)	From the 98 volunteers, 40 volunteers were selected for further study. 20 of these were either homozygous or heterozygous for ε4. 20 were homozygous for ε3. Among the ε4 carriers, two participants were homozygous ε4 carriers.	Mixed	APOE ε4 carriers show prospective memory enhancement under nicotine, and evidence for specialization within medial BA10	fMRI explored performance on a PM task in young adults (age 18–30) using and not using nicotine using a within-subjects design. Participants performed an ongoing task while retaining a PM instruction to respond to specific stimuli embedded in the task. Nicotine effects varied according to APOE allelic status. Reaction times to the PM cue improved under nicotine in ε4 carriers, but not in ε3 carriers	Evans et al. [157]	Low
Dutch men and women (mean age = 57)	ε4 Carriers (N = 116)	Mixed	APOE ε4 differentially influences change in memory performance depending on age (The SMART-MR Study)	In persons ≤57, ε4+ showed increase in immediate recall and delayed recall	Jochemsen et al. [135]	Moderate
Poor Brazilian children with below median height (mean age = 8.6)	ε4 Carriers (N = 37)	Mixed	APOE ε4 influences growth and cognitive responses to micronutrient supplementation in shantytown children from northeast Brazil	ε4+ children receiving glutamine supplementation presented improved short-term gains in HAZ, WAZ, and WHZ that were correlated with better performance in long-term cognitive testing	Mitter et al. [141]	Low
Males and females, Caucasian Australians, age 20–24	ε4 Carriers (N = 530)	Mixed	Examine if the possession of APOE ε4 benefits cognitive function in healthy young adults	The ε4 allele did not benefit cognitive performance in younger persons, nor accompany cognitive deficits in older persons	Bunce et al. [115]	High
Predominately male, HIV seronegative, mean age 46 from Hawaii	ε4 Carriers (N = 16)	Male	Determine the impact of APOE ε4 and HIV on cognition and brain atrophy: antagonistic pleiotropy and premature brain aging	ε4+ seronegative controls scored higher (better) than APOE- seronegative controls on the Auditory Verbal Learning Test immediate recall ($p = 0.01$), memory domain ($p = 0.03$), and trends for better performance on the learning ($p = 0.09$) and fluency ($p = 0.10$) domains	Chang et al. [134]	Low

Students of the Friedrich-Alexander University of Erlangen-Nuremberg, average age = 24.1	ε4 Carriers (N = 18)	Mixed	Influence of brain-derived neurotrophic-factor and APOE genetic variants on hippocampal volume and memory performance in healthy young adults	Differences in memory function between participants possessing the ε4 allele and those without it were not detected	Schmidinger et al. [116]	Low
Avon Longitudinal Study of Parents and Children	ε3/ε4 = 709, ε4/ε4 = 58	Mixed	IQ, educational attainment, memory and plasma lipids: associations with APOE genotype in 5,995 children	IQ was 3.6 points higher for children who carried ε2/ε2 compared with those who carried ε3/ε3 and 2.6 points higher for ε4/ε4 compared with ε3/ε3. There was a consistent pattern that ε2/ε2 and ε4/ε4 girls had higher IQ scores (from 3 to 7 points) compared with ε3/ε3 girls	Taylor et al. [126]	High
Healthy 7-10-year-old boys and girls from Oregon	ε4 carriers (N = 12)	Mixed	APOE ε4 and sex affect neurobehavioral performance in primary school children	ε4+ subjects were ten times more likely to be placed in an ICU after birth. ε4+ subjects did not show a target preference in the Memory Island paradigm. Vocabulary score on WASI and immediate and visual recall on the Family Pictures assessment was better in ε4+ subjects	Acevedo et al. [132]	Low
Subjects from San Diego area charter middle and high schools (average age = 13.3)	ε4 Carriers (N = 33)	Mixed	APOE genotype is associated with left-handedness and visuospatial skills in children	Significant differences were found on the Rey-Osterrieth Complex Figure Test, with ε2-positive children (29.2%) relative to ε3/ε3 (8.9%) and ε4-positive children (6.1%; $p = 0.12$)	Bloss et al. [118]	Moderate
Healthy nonsmokers aged 18–30 recruited from Sussex University	ε4 Carriers (N = 27)	Mixed	Positive effects of cholinergic stimulation favor young APOE ε4 carriers	ε4 allele conferred a cognitive advantage on tasks mediated by the frontal lobe. Young carriers of the ε4 allele showed larger cognitive benefit from procholinergic nicotinic stimulation	Marchant et al. [140]	Low
Patients with PTA	Patients with the APOE ε4 [N = 17 in the PTA group and N = 9 in the out of PTA group]	Mixed	Patients with the APOE ε4 [N = 17 in the PTA group and N = 9 in the out of PTA group]	ε4+ patients showed enhanced verbal memory recovery during and after emergence from post-traumatic amnesia	Noe et al. [133]	Low
Brazilian shantytown children (mean age = 8.7)	ε4 Carriers (N = 31)	Mixed	APOE polymorphisms and diarrheal outcomes in Brazilian shanty town children	ε4 protected shanty town children against heavy diarrhea outcomes, and among those with heavy diarrhea it protected against long-term sequelae	Oria et al. [124]	Low

(Continued)

Table 8
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Subjects / Age	Sample Size	Sex	Study Scope	Major Finding	Citation	Quality of Evidence
Urban Spanish adolescents aged 13–18.5	ε4 Carriers (N = 76)	Mixed	Individual and combined effects of APOE and MTHFR 677C/T polymorphisms on cognitive performance in Spanish adolescents (The AVENA Study)	ε4 alone is not associated with cognitive performance on the Spanish version of the SRA-Test of Educational-Ability	Ruiz et al. [114]	Moderate
Lothian Birth Cohort 1936 comprising 1,091 surviving participants of the Scottish Mental Survey 1947	ε4 Carriers (N = 299)	Mixed	Cognitive ability at age 11 and 70 years, information processing speed, and APOE variation: The Lothian Birth Cohort 1936 Study	No significant difference seen between those with and without a copy of the ε4 allele in MHT IQ at age 11 years. The cognitive tests measured non-verbal endpoints	Luciano et al. [113]	High
Healthy Caucasian subjects from NY, Rhode Island, Nijmegen, Sydney, and Adelaide Australia, mean age = 27.4	ε4 Carriers (N = 91)	Mixed	The contribution of APOE alleles on cognitive performance and dynamic neural activity over six decades	ε4 group scored consistently higher on verbal fluency tasks than the ε3 group, across all age-bands	Alexander et al. [137]	Moderate
Young Swiss adults, average age 23	ε4 Carriers (N = 80 ε3/4; N = 6 ε4/4)	Mixed	Better memory and neural efficiency in young APOE ε4 carriers	ε4 carriers had better performance in delayed but not immediate recall of 30 studied words (OR = 1.6, $p = 0.009$). fMRI on 13 ε4+ subjects showed decreased brain activity over 3 runs while other alleles show increased brain activity	Mondadori et al. [131]	Moderate
Review paper on Brazilian shantytown children	Variable	Mixed	Role of APOE ε4 in protecting children against early childhood diarrhea outcomes and implications for later development	ε4 was important for cognitive development under the stress of heavy diarrhea	Oria et al. [123]	Review paper, Not applicable
Poor Brazilian children average age 10	ε4 Carriers (N = 21)	Mixed	APOE ε4 protects the cognitive development in children with heavy diarrhea burdens in northeast Brazil	ε4+ children with heavy diarrhea burdens showed protected cognitive development	Oria et al. [122]	Low
Han Chinese female nursing students aged 19–21	ε4 Carriers (N = 32)	Females	Personality traits in young female APOE ε4 and non-ε4 carriers	ε4+ status did not affect tridimensional personality questionnaire scores	Tsai et al. [128]	Low
Young Finnish men and women (mean age = 28)	ε4 Carriers (N = 20)	Mixed	The combined effects of APOE polymorphism and LDL cholesterol on cognitive performance in young adults	ε4+ status was associated with good performance in mental arithmetic and the association was dependent on LDL cholesterol level	Puttonen et al. [125]	Low

Infants in Mexico City	ε4 Carriers (N = 53)	Mixed	APOE genotype predicts 24-month Bayley Scales Infant Development Score	ε4+ status had 4.4 point higher 24-month Mental Development Index on Bayley Scale	Wright et al. [138]	Moderate
Czech men and women aged 25–64	ε4 Carriers (N = 23)	Mixed	A possible role of APOE polymorphism in predisposition to higher education	87% of ε4+ carriers reached higher education	Hubacek et al. [139]	Low
Caucasian children from Cleveland area	ε4 Carriers (N = 52)	Mixed	Study explored the hypothesis that variation in the gene encoding APOE is a factor modifying general cognitive ability	No association between APOE polymorphisms and general cognitive ability in children	Turic et al. [112]	Moderate
Han Chinese female nursing students aged 19–21	ε4 Carriers (N = 31)	Females	Intelligence and event-related potentials for young female human volunteer APOE ε4 and non-ε4 carriers	Modest increase in performance IQ and N100 amplitude	Yu et al. [127]	Moderate
Finnish children, adolescents, and young adults	ε4/ε3 Carriers (N = 483) and ε4/ε4 carriers (N = 50)	Mixed	Dependence between APOE phenotypes and temperament in children, adolescents, and young adults	Motor activity (even hyperactivity) in childhood and mental vitality in adolescence and young adulthood increased significantly with APOE phenotype in the order of ε2/ε2, ε3/ε2, ε4/ε2, ε3/ε3, ε4/ε3, and ε4/ε4.	Jarvinen et al. [129]	High

AD, Alzheimer's disease; APOE, apolipoprotein E; fMRI, functional magnetic resonance imaging; HAZ, height for age z-scores; HIV, human immunodeficiency virus; ICU, intensive care unit; IQ, intelligence quotient; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; OR, odds ratio; PM, prospective memory; PTA, post-traumatic amnesia; WASI, Wechsler Abbreviated Scale of Intelligence; WAZ, weight for age z-scores; WHZ, weight for height z-scores.

to the default action, β-secretase cleavage, then γ-secretase cleavage of the AβPP, with the end-products being fatal to that synapse. Note that the γ-secretase appears to act only on the β-secretase product and not on the α-secretase product, producing both the Aβ and an AβPP intracellular domain (AICD) [24]. The AICD protein, acting intracellularly, leads to hyperphosphorylation of the critical structural protein of neuronal processes, microtubule associated protein tau [25]. The hyperphosphorylated tau appears to disrupt the normal flow in neuronal processes, leading to amputation [26]. The initial memory impairment of AD is likely due to the failure of the process for establishing new memory, while the dementia appears to develop when synaptic slaughter destroys large numbers of synapses [27], and loss of synapses is the factor most closely associated with the late progression of dementia [28]. Cholesterol metabolism, transport and processing might play a role in this process by affecting the composition of the neuronal synaptic membrane thereby altering its thickness. The extracellular region of AβPP is much longer than the intracellular region. Small differences in the availability of enzymatic cleavage sites influenced by membrane thickness might have profound effects on the ultimate production of AβPP sub-fragments [29, 30].

IMPORTANCE OF THE APOE GENOTYPE

The APOE genotype accounts for the vast majority of AD risk [31, 32]. There are three common alleles of the APOE gene, i.e., APOE ε2, APOE ε3, and APOE ε4 [33]. In the general US population, the ε4 allele prevalence is approximately 13% [34], constituted by about 2% being ε4 homozygous (2% of the US population) and 11% being heterozygous (22% of the US population). Possession of one ε4 allele increases the risk of developing AD by 3 to 4-fold, and possession of two ε4 alleles increases risk by 15-fold, as compared with the ε3/ε3 genotype, with a large part of the variation being related to substantially early age of onset, and over 60% of patients with non-familial AD carry the ε4 allele [35, 36].

This profound difference in AD risk results from only minor changes in the structure of the APOE molecule. The three isoforms of APOE differ in amino acid sequence at only chain positions 112 and 158: the APOE ε2 allele has cysteine at both positions; the APOE ε4 allele has arginine at both positions; and the APOE ε3 allele has cysteine at position 112 and arginine at 158 [37]. These small changes in amino acid sequence alter the biological activity of the APOE proteins in multiple ways, one of which is increased liver catabolism of the APOE ε4 lipoprotein as compared with the APOE ε3 lipoprotein [38, 39].

The strong positive association between possession of the ε4 allele and the development of late-onset AD has stimulated extensive investigation on young, healthy subjects differing in APOE allele status. Numerous ε4 allele-related associations have been reported in a series of epidemiological and clinical investigations on a variety of conditions, with the potential relevance of these associations to the pathogenesis of AD poorly understood at this time. Over the last several decades, numerous and elaborate interactions have been demonstrated between the nervous, immune, and endocrine systems [40]. This sophisticated system of sometimes centrally mediated biochemical cross-talk opens the possibility that an association between possession of the ε4 allele and a particular clinical characteristic, condition, susceptibility or outcome might provide mechanistic information as to why allelic variation in a cholesterol metabolism gene is so strongly associated with the loss of synapses in the brain.

In primarily young subjects, we have attempted to review a representative body of literature on ε4 allele-associations related to the following: cardiovascular responses; impacts on reproduction and fetal development; co-morbidities; resistance to infectious disease; responses to head injury; biochemical differences possibly related to neural stress; and brain structure-function differences. In addition, the literature on the association between the ε4 allele and cognitive performance has been reviewed comprehensively. In each summary table, the ethnic composition, age, clinical diagnosis, and number of ε4 carriers of the cohort studied are included.

LITERATURE SEARCH STRATEGY

Using Google and PubMed of the National Library of Medicine, the search terms apolipoprotein E or ε4 allele were cross-matched against the terms: infant, youth, child, children, adolescent, or young. This initial search gathered a large number of potentially relevant citations that were categorized by clinical condition including cardiovascular responses; reproduction and development; co-morbidities; resistance to infectious disease; responses to head injury;

biochemical differences possibly related to neural stress; brain structure-function; and mental performance. Each citation was physically collected, and the reference sections were manually checked for additional relevant citations until no further citations were found. No papers on the relevant topics were excluded. A few studies on middle age subjects not yet presenting with mild cognitive impairment were included with the aberrant age ranges clearly marked in the tables. The studies in the tables were not amenable to meta-analysis as the protocols were too heterogeneous. There were four referenced articles ([15, 47, 53, 130]) that included a meta-analysis. Some of the individual papers in the meta-analyses were also separately included in the review because the details in the individual papers were important.

METHOD FOR GRADING QUALITY OF EVIDENCE

As noted previously, the literature on associations between ε4 status in otherwise healthy young subjects can be subdivided into several categories including: cardiovascular responses (Table 1); reproduction and development (Table 2); co-morbidities (Table 3); resistance to infectious disease (Table 4); responses to head injury (Table 5); biochemical differences possibly related to neural stress (Table 6); brain structure-function (Table 7); and mental performance (Table 8). Each table contains seven headings including sequentially: Subject/Age; Sample Size; Sex; Study Scope; Major Finding; Citation; and Quality of Evidence. The first six headings summarize the study characteristics, its results, and citation. The seventh heading provides the reader an estimate of the quality of evidence in the study based on a recognized evidence-based rating system.

A system developed by the Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) for ranking the quality of evidence and the strength of recommendations of scientific literature and clinical practice guideline was applied to rate the studies found in Tables 1–8 [41]. The method described by Adkins et al. [41] was used to estimate the degree of confidence that can be placed on the evidence from research and clinical studies. The studies in the tables of this review represent a wide range of data (high to low) based on quality of evidence regarding main outcomes. The quality of evidence for each study was evaluated based on the following criteria.

- Study design (e.g., observational versus randomized trials);
- Study quality (i.e., detailed study methods and execution);
- Consistency (similarity of estimates of effects across like studies); and
- Directness (i.e., the extent to which the subjects, interventions, and outcomes measures are similar to those of interest).

The following definitions from the GRADE Working Group were used in grading the quality of the evidence based on the criteria above [41]:

- High = Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low = Any estimate of effect is very uncertain.

It should be recognized that the ranking system is based on the quality of the evidence and not on the quality of the research, as all of the cited literature in this review was peer-reviewed.

CARDIOVASCULAR RESPONSES IN YOUNG APOLIPOPROTEIN ε4 CARRIERS (TABLE 1)

The relationship between APOE allele type and cardiovascular risk factors and responses has been extensively studied. In a large study on Finnish boys and girls (Table 1), ages 3, 6, 9, 12, 15, and 18, including 28 ε2/ε4 carriers, 483 ε3/ε4 carriers, and 50 ε4/ε4 carriers, the concentrations of serum total cholesterol, low density lipoprotein cholesterol, and apolipoprotein B increased with APOE phenotype in the order of ε2/ε2, ε3/ε2, ε4/ε2, ε3/ε3, ε4/ε3, and ε4/ε4 [42]. In a follow-up study on Finnish male and female newborns and 3-year-old children including five ε2/ε4, 147 ε3/ε4, and eight ε4/ε4 carriers, the concentrations of serum total cholesterol and LDL cholesterol increased with APOE phenotype in the order of ε3/ε2, ε3/ε3, ε4/ε3, and ε4/ε4, in both males and females ($p < 0.001$) in the 3-year-olds [43]. Another large study in 7- and 13-month-old Finnish infants included 36 ε4/ε4 and 209 ε3/ε4

carriers and reported that triglyceride concentrations were higher in infants with APOE ε4/ε4 or ε3/ε4 than in those with APOE ε3/ε3 (p-value for difference 0.01 and 0.009, respectively) [44]. A smaller follow-up study was conducted on healthy 13-month-old Finnish children and reported that 16 APOE ε4 children had 30% to 50% higher cholesterol-adjusted campesterol and sitosterol concentrations in serum than 20 APOE ε3/ε3 children ($p = 0.002$ and $p = 0.02$, respectively) [45]. In 44 ε4 carrier Finnish infants, fed high-fat, high-cholesterol human milk, the total and LDL-cholesterol concentrations and the LDL APOB concentration of those with the APOE phenotype ε4/ε4 or ε3/ε4 rose faster and to higher levels than in other infants [46]. In a large study on 16-year-old Finnish boys and girls including 28 ε2/ε4 carriers, 470 ε3/ε4 carriers, and 49 ε4/ε4 carriers, physical exercise did not affect LDL cholesterol, total cholesterol, or HDL/total cholesterol in APOE ε4 carriers [47]. In 1999, a study on Caucasian males in Perth, Australia, including eight pairs of ε3/ε3 and ε4/ε4 subjects matched for age and serum lipid levels, average age for the ε3/ε3 = 45 and ε4/ε4 = 42, suggested that inheritance of APOE ε4 is associated with an increased affinity of VLDL particles for LDL receptors on hepatocytes [48].

Cardiovascular endpoints in addition to blood lipid levels have also been examined. ε3/ε2 or ε3/ε3 carriers showed marginally significantly greater heart rate reactivity and significantly greater task levels of heart rate and heart rate variability during mental stress than ε4/ε2, ε4/ε3, or ε4/ε4 carriers among 28 healthy 16-year-old Finnish boys. The number of ε4 carriers in this study was limited at only 11 [49]. Ellis et al. [50] studied 8-year-old children from the Tasmanian Infant Health Survey including 75 ε4 carriers and found that the ε4 carriers had a lower body mass index and the effect was more evident among the less fit. In addition, Yu et al. [51] studied young adult Chinese men and women with an approximate mean age = 32; ε3/ε4 (N = 60), ε4/ε4 (N = 13). These authors found that VO_{2max} after exercise training increased significantly higher in carriers of ε3/ε4 in males (OR = 0.60, 95% CI = 0.09–1.11; $p = 0.02$) and females (OR = 0.62, 95% CI = 0.09–1.15; $p = 0.02$). In summary, as compared with ε3 carriers, young subjects possessing one or more ε4 alleles show significant differences in total serum cholesterol, LDL, triglycerides, heart rate variability during mental stress, and VO_{2max}. The directionality of the reported ε4-associated lipid profiles is consistent with an increased risk of atherosclerosis later in life.

Possible relationship of ε4-related cardiovascular responses and AD

As noted in the Introduction, cholesterol metabolism might play a role in slightly altering the thickness of the synaptic membrane. Synaptic membrane thickness could potentially affect the location of the cleavage site for γ-secretase [29, 30] AβPP sub-fragments possibly being more potent for synaptic remodeling and learning, including playing a role in tau phosphorylation for synapse retraction, could also possess increased pathogenicity for the elderly, leading to tau hyperphosphorylation, the creation of paired-helical filaments, neuropil threads, and NFTs, with amputations of neuritic processes and massive destruction of synapses.

REPRODUCTION AND DEVELOPMENT IN APOLIPOPROTEIN ε4 CARRIERS (TABLE 2)

A limited number of studies have examined potential associations between APOE ε4 carrier status and fertility. In 2017, van Exel et al. [52] studied 100 women with a history of at least two first-trimester recurrent miscarriages in Tabriz, Iran, and 100 healthy women with at least two successful pregnancies and no miscarriages. This study incorporated 31 ε4 carriers and showed that APOE ε4 was associated with higher fertility in women exposed to high pathogen levels. In 2004, Corbo et al. [53] reported similar results in a population of Afro-Ecuadorian and Cayapa Indian women, average age 39; ε4 carriers (ε3/ε4 = 16; ε4/ε4 = 6; ε4/ε2 = 5). These authors reported that the ε3/ε4 genotype frequency (0.50) in the African-Ecuadorian women with 9–17 children was about three times that of the women with 0–8 children (0.14) ($p = 0.02$). In contrast with these reportedly positive effects on fertility in populations without access to birth control methods, Gerdes et al. [54] studied a cohort of 40-year-old married men residing in Aarhus Denmark; ε4 carriers (ε3/ε4 = 93; ε4/ε4 = 12; ε4/ε2 = 9) and found that on average, men with the ε3/ε3 genotype ($n = 212$) had 1.93 children, men with the ε3/ε4 or ε2/ε2 genotypes ($n = 53$) had 1.66 children. The potential confounding effects of the widespread availability of birth control methods in Denmark and the low average number of children per couple questions the clinical relevancy of these findings as per the association of the ε4 allele and fertility.

Several studies have investigated the possible relationship between APOE ε4 carrier status and

occurrence of fetal miscarriages. A single study has reported a protective effect of the ε4 allele [55]. Some studies do not report an association between ε4 status and fetal loss [56–58]. At least five studies and one meta-analysis report a positive association between possession of the ε4 allele and fetal loss [59–65]. Several additional studies have examined the association between ε4 carrier status and a variety of pregnancy-related conditions. Gaynor et al. [66] studied White, Black, and Hispanic neonates and infants; ε4 carriers (N = 87) and reported that the APOE ε2 allele was associated with a lower Psychomotor Development Index ($p = 0.038$). Pregnant women with the ε4 allele displayed an increased risk to develop Pregnancy Induced Hypertension (OR 4.14, $p = 0.013$) and severe preeclampsia (OR 4.43, $p = 0.019$) in a group of pregnant Romanian women, average age 28; ε4 carriers (N = 46) [67]. Cerebrospinal fluid (CSF) was collected from 107 healthy Japanese subjects (70 males, 37 females) aged 1–86 by Hirayama et al. [68] who showed that the APOE phenotype does not affect the composition or concentration of CSF high density lipoprotein in children. In 2003, Gaynor et al. [69] studied Asian, Black, and White, male and female infants under 6 months undergoing cardiac surgery in Philadelphia; ε4 carriers (N = 52) and reported that patients with the ε2 allele had approximately a 7-point decrease in the Psychomotor Developmental Index [Bayley Scales of Infant Development] ($p = 0.036$).

In summary, the most notable findings related to fertility and the ε4 allele suggest a protective effect of $\varepsilon 4^{+}$ status and reproductive potential in populations exposed to high pathogen levels.

Possible relationship between ε-related reproduction and development and AD

The ε4 allele is the ancestral allele to the now more common ε3 allele. Protective effects on fertility and reproduction might help explain the original predominance of the ε4 allele. The impetus for the conversion from ε4 to ε3 predominance is currently not understood.

CO-MORBIDITIES IN YOUNG APOLIPOPROTEIN ε4 CARRIERS (TABLE 3)

A number of epidemiology studies have reported co-morbidities associated with possession of different APOE alleles (Table 1). Co-morbidities represent an important area of study as co-linearity in prevalence between clinical conditions of known etiology with clinical conditions whose current etiology is unknown (e.g., AD) might provide clues related to causation. A meta-analysis of 28 studies on schizophrenia reported a significant protective effect of ε3 in an Asian population [70]. Another meta-analysis found a significant decrease in risk associated with each copy of ε4 in all age-related macular degeneration sub-phenotypes [71]. A dermatology clinic in Spain reported that APOE ε4 carriers were significantly more frequent in patients with severe psoriasis compared to controls ($p = 0.003$) and to non-severe psoriasis ($p = 0.017$). Infants with hypoxic-ischemic encephalopathy did not show an association with APOE allele type [72]. In contrast, the percentage of children with at least one ε4 allele was significantly lower in non- Sudden infant death syndrome (SIDS) compared to SIDS ($p = 0.016$) in a study of infants from Scotland. Several studies have examined the potential relationship between APOE allele type and cerebral palsy. In children seen in Brasilia, Brazil, of whom 139 were ε4 carriers, the presence of the ε2 allele raised the probability of having cerebral palsy (OR 3.2; 95% CI 1.27–8.27) while the APOE ε4 allele was not significantly different among groups [73]. An earlier smaller study on Brazilian children that included only 13 ε4 carriers, reported a positive association between the ε4 allele and cerebral palsy [74], as did a study on children from Chicago that included 25 ε4 carriers [75].

Possible relationship between ε4-related co-morbidities and AD

The mechanism by which possession of the ε4 allele exerts its increase risk of AD is currently unknown. Concomitantly, the mechanistic relationships between co-morbid clinical conditions and the ε4 allele, and risk of AD, are also not understood. As mechanistic relationships on AD causation are elucidated in the future, ε4-related co-morbidities might provide additional mechanistic insights.

RESISTANCE TO INFECTIOUS DISEASE IN APOLIPOPROTEIN ε4 CARRIERS (TABLE 4)

The potential relationship between resistance to infectious diseases and APOE allele status represents an important area of investigation as this

environmental stressor can exert significant evolutionary pressures. The relationship between hepatitis C infection and APOE carrier status has been examined in several studies. Mueller et al. [76] enrolled 205 ε4 carriers in two combined cohorts selected from patients from Charite Berlin and the University of Leipzig diagnosed with either chronic or self-limited hepatitis C virus infection. The average age of the patients was 48.7. These authors found that APOE ε4 alleles were underrepresented in chronically hepatitis C-infected patients (10.2%) compared to 13% in healthy controls ($p = 0.001$).

Male and female Caucasian Italian patients with chronic hepatitis C, median age = 41; ε2/ε4 carriers (N = 3), ε3/ε4 carriers (N = 21), ε4/ε4 carriers (N = 1) were studied by Fabris et al. [77]. They reported that patients not carrying an ε3 allele, as well as carriers of a single ε3 allele with serum cholesterol concentration >190 mg/dL were more likely to have a favorable outcome regarding fibrosis progression with chronic hepatitis C. In an earlier study, Fabris et al. [78] investigated Italian male and female patients who underwent a cadaveric orthotopic liver transplantation, median age 55; ε4 carriers (N = 34). Their results showed that possession of an APOE ε4 allele to be associated with low fibrosis progression in recurrent hepatitis C infection, and with an idiosyncratic APOE-associated lipid profile. Price et al. [79] found that the APOE ε2 and APOE ε4 alleles were both associated with a reduced likelihood of chronic infection (hepatitis C virus). For ε2, OR = 0.39[95% CI = 0.211–0.728] ($p = 0.003$), and for ε4, OR = 0.6[95% CI = 0.38–0.96] ($p = 0.032$), in a study population of British and Irish Caucasian hepatitis C patients; ε2 carriers (N = 48), ε4 carriers (N = 84), 11 carriers were both, i.e., ε2/ε4. Twenty-four male and female patients, median age = 53.5, with recurrent hepatitis C following cadaveric orthotopic liver transplantation; ε4 carriers (N = 12) of 48 donors, ε4 carriers (N = 17) of 48 recipients were studied by Toniutto et al. [80]. These authors found that recipient (but not donor) carriage of at least one ε4 allele was associated with improvement in the staging score due exclusively to the contribution given by male recipients. Similarly, Wozniak et al. [81] observed British men and women with hepatitis C viral infection, mean age = 41; ε4 carriers (N = 42) and concluded that in chronically hepatitis C virus-infected subjects grouped according to extent of fibrosis, necroinflammation, and total Knodell score, an overrepresentation of the APOE ε4 allele was found in those whose livers were mildly affected. These authors suggested that carriage of an APOE4 ε4 allele protects against severe liver damage induced by hepatitis C virus.

Although not as extensively studied as hepatitis C infection, the relationship between resistance to malaria and APOE allele status has also been examined in several studies. Fujioka et al. [82] showed that human plasma samples from APOE ε4/ε4 but not APOE ε3/ε3 donors inhibited growth and disrupted morphology of *P. falciparum* (malaria) in seven APOE ε4/ε4 and six APOE ε3/ε3 donors from Cleveland, OH, USA. Aucan et al. [83] observed Gambian children ages 1–10; ε4 carriers (N = 244) and concluded that the APOE ε3/ε4 genotype was found to be more common in children with both cerebral malaria and severe malarial anemia (42.9%) than in controls (24.8%) and mild malaria cases (27.2%). When corrected for the number of clinical groups (4) compared with controls in this study, this finding was not statistically significant. An earlier study on African infants was reported by Wozniak et al. [84]. This group studied infants from Prampram, 50 km east of Accra on the south coast of Ghana; ε2/ε2 carriers (N = 4), ε4 carriers (N = 47). Based on small numbers, APOE ε2 homozygotes became infected with malaria at an earlier age than those carrying other genotypes.

At least one study on a potential relationship between APOE allele status and risk for development of herpes simplex encephalitis has been conducted in the United Kingdom [85]. These authors examined specimens from the brain or spleen of 14 patients with herpes simplex encephalitis and from the CSF of seven patients with HSV1 in their CSF detected by PCR. Lin et al. [85] concluded that APOE ε3 and ε4 allele frequencies did not differ significantly between the two groups, and that APOE ε2 is a risk factor for herpes simplex encephalitis. In summary, possession of the ε4 allele might provide some measure of protection against hepatitis C and malaria.

Possible relationship between ε4-related resistance to infectious disease and AD

ε4 allele-associated resistance to infectious diseases endemic in prehistoric populations is consistent with the ancestral predominance of the ε4 allele. Evolutionary pressures or mechanisms that influenced the conversion of human populations from ε4 predominance to ε3 predominance remain unexplained.

RESPONSES TO HEAD INJURY IN YOUNG APOLIPOPROTEIN ε4 CARRIERS (TABLE 5)

Several studies have been conducted on the association between APOE allele frequency and either susceptibility to head injury, or recovery from head injury. In a 2018 study by Terrell et al. [86] on a cohort of male football and male and female soccer players (average age 19.85) from four US southern universities that enrolled 35 ε4 carriers, IL-6R CC was associated with a three times greater concussion risk and APOE ε4 with a 40% lower risk. In a similar cohort with 62 ε4 carriers, Tierney et al. [87] found no significant association between carrying the ε4 allele and history of concussion. However, Tierney et al. [87] stated that they assessed the medical history via researcher-assisted paper and pencil assessment, attempting to indicate the athlete's concussion history. Collegiate student athletes from the University of Toronto, average age 20.5, with 79 ε4 carriers were studied by Kristman et al. [88] with a small statistically significant positive association reported as stated by the authors of an unadjusted hazard ratio for concussion in the APOE ε4 carriers of 1.18 (95% CI: 0.52, 2.69) compared to non-carriers. Adjusting for sex, weight, height, and team type resulted in an only slightly lower hazard ratio of 1.06 (95% CI: 0.41, 2.72), indicating little effect from confounding factors. A somewhat larger study that relied upon self-reported concussion history over the previous eight years was conducted by Terrell et al. [89] on Black and White, male and female, college athletes from 23 schools, average age 19.7; ε3/ε4 (N = 225), ε4/ε4 (N = 20). Terrell et al. [89] summarized their results as showing no substantial evidence of an association between a history of concussion and APOE genotypes and haplotypes. However, the authors also noted that the cell sizes for some of the APOE genotypes were so small that meaningful analysis was not possible. Also, compared to those with the APOE ε3/ε3 genotype, those with the ε2/ε3 genotype were at a 60% higher risk for concussion, but the results were not statistically significant (OR, 1.6; 95% CI, 0.5 to 4.8). In summary, the association between possession of the APOE ε4 allele and risk of concussion is unclear at this time due to methodological limitations in determination of concussion history and limited sample sizes.

Han et al. [90] conducted a study on active duty military personnel with a recent history of mild to moderate traumatic brain injury, average age 22.6; ε4 carriers (N = 16). Their analysis showed comparable performances on most neuropsychological measures and better performances by ε4 carriers on select measures of attention, executive functioning and episodic memory encoding. Merritt et al. [91] reported data on 53 veterans with a history of mild traumatic brain injury and 46 military controls and found that traumatic brain injury ε4 carriers had relative impairments in memory function and speed of processing but not on executive function relative to traumatic brain injury-affected veterans without an ε4 allele. However, there was no ε4-related difference among the non-traumatic brain injury military controls.

In a relatively large study (ε4 carriers N = 324) enrolling consecutive head injury admissions (men and women) to a regional neurosurgical unit in West Scotland, average age 35, Teasdale et al. [92] found no overall association between APOE genotype and outcome. Thirty-six percent of APOE ε4 carriers had an unfavorable outcome compared with 33% of non-carriers of APOE ε4. This relatively large study was a follow-up to a smaller study conducted by Teasdale et al. in 1997 [93] on only 30 ε4 carriers. Another small study on 16 ε3/ε4 subjects recruited from a Canadian traumatic brain injury clinic who experienced mild to moderate traumatic brain injury, mean age 33, was conducted by Chamelian et al. [94]. These authors reported no association between the presence of the APOE ε4 allele and poor outcome across all measures. In 2005, Blackman et al. [95] reviewed the childhood literature on APOE and brain injury up through 2005 and concluded that results from the limited studies in children were contrary to the adult experience with ε4 seeming to confer protection for the brain whereas ε2 posed a risk. Further larger studies are needed to definitively determine the role of APOE status on recovery from brain injury in young subjects.

Possible relationship between ε4-related responses to head injury and AD

To date, a definitive relationship between ε4 status and recovery from head injury has not been established. If ε4 possession was established as associated with poor recovery from head injury, poor recovery could be consistent with an ε4-associated increase in neural stress. Damage from accumulated neural stress might be a contributing factor to AD.

BIOCHEMICAL DIFFERENCES POSSIBLY RELATED TO NEURAL STRESS IN APOLIPOPROTEIN ε4 CARRIERS (TABLE 6)

The strongest direct evidence that some of the macromolecular components comprising the synapses of ε4 carriers might be turned over at a higher rate than comparable macromolecular synaptic components in non-ε4 carriers has been provided by Yassine et al. [96]. This group studied 22 middle-aged healthy adults (mean age 35 years, range 19–65 years) and found that k*, the mean global gray matter DHA incorporation coefficient, was significantly higher (16%) among ε4 carriers ($n = 9$) than among non-carriers ($n = 13$, $p = 0.046$). Also in 2017, the same group [13] reviewed original articles, systematic reviews, and meta-analyses of omega-3 studies in AD that were published before August 20, 2016 and concluded that while randomized clinical trials of omega-3 in symptomatic AD reported negative findings, several observational and clinical trials of omega-3 in the pre-dementia stage of AD suggest that omega-3 supplementation might slow early memory decline in ε4 carriers. Tambini et al. [97] conducted an *in vitro* experiment whose results are consistent with the increased lipid metabolism observed by Yassine et al. [96]. Using an astrocyte-conditioned media model, this group measured the synthesis of phospholipids and cholesteryl esters and reported a significant increase in cells treated with APOE ε4-containing astrocyte-conditioned media as compared to those treated with APOE ε3-containing-astrocyte-conditioned media.

Dose et al. [98] conducted a mini-review of APOE genotype and stress responses. From their analysis of the evidence on APOE isoform-dependent oxidative stress and mitochondrial function these authors concluded that APOE4 is associated with an increased stress response. Ramassamy et al. [99] conducted a brain tissue study whose results are consistent with the observations of Dose et al. [98]. They obtained human brain tissue from the Douglas Hospital Research Centre Brain Bank, Canada, average age 75–79; ε4 carriers (N = 18). Among ε4 carriers with AD, the levels of thiobarbituric acid-reactive substances were found to be higher among ε4 carriers while the APOE protein concentrations were lower.

At least one small study has examined the potential association between vitamin D and APOE allele status [100]. In a sub-group of 93 subjects from a general population sample of 699 subjects (age of subjects unknown), multivariate adjusted modeling showed a positive association ($p = 0.072$) of the APOE ε4 allele with 25(OH)D [vitamin D] levels. Another small study was conducted in 2012 by Ringman et al. [101] wherein thirty-three subjects were studied including six ε2/ε3, six ε3/ε4, and 21 ε3/ε4 allele combinations. Plasma levels of APOE and superoxide dismutase 1 were lowest in ε4 carriers, intermediate in ε3 carriers, and highest in the ε2 carriers. In contrast, multiple plasma interleukins were highest in ε4 carriers and demonstrated significant negative correlations with age. Larger studies similar to those conducted by Yassine et al. would be helpful in clarifying the association of neural stress/macromolecular turnover rate with allele subtype.

Possible relationship between ε4-related biochemical changes related to neural stress and AD

If the hippocampal neurons of two individuals possess the same susceptibility to an endogenous or exogenous stress factor, the neurons with the highest turnover of proteins, lipids, and other macromolecules might experience a larger integrated dose of detriment.

BRAIN STRUCTURE-FUNCTION DIFFERENCES IN YOUNG APOLIPOPROTEIN ε4 CARRIERS (TABLE 7)

Studies on brain structure

Several studies have reported subtle differences in brain structure in association with APOE allele status. Stening et al. [102] studied 29 ε4 carriers in their subject population of 97 participants (48 women/49 men) between 20 and 35 years of age (M = 24.3) with 12–20 years of education (M = 15). These authors reported the emergence of two different patterns. The first pattern showed that specific structural covariance of the anterior hippocampus and posterior hippocampus in all other groups co-varied with frontal, parietal and cerebellar areas. The second pattern displayed an opposite structural covariance of the posterior hippocampus in ε4 carriers and the anterior hippocampus of ε4 non-carriers co-varying with motor areas and the middle frontal gyrus. Given the small subject numbers, and uncertainty of the clinical significance of these differences in anatomic ratios,

the relevance to the development of AD pathology and the later appearance of dementia is unknown.

A young group (average age 21) and a mid-age group (average age 50), of right-handed males and females with 21 ε4 carriers in the young group and 17 in the mid-age group (N = 17) was investigated by Dowell et al. [103]. They found no detectable genotype-dependent differences in hippocampal volume for either the young or mid-aged adults. Also, the cuneus appeared to be an important locus for genotype differences with greater functional connectivity among young ε3/ε3 individuals and greater white matter volume in young $\varepsilon4^+$ individuals. These authors also reported subtle cortical thickness measures in the parahippocampus in the young $\varepsilon4^+$ individuals positively correlated with performance in a memory task. This 2016 study was a follow-up to an earlier study published by Dowell et al. [104]. The earlier 2013 study enrolled 93 healthy young participants (age, 20; range 18–30; 64 women, 29 men), right-handed Caucasian undergraduates at the University of Sussex. The authors summarized their results using voxel-based morphometry of high-resolution structural MR images as identifying a higher white matter volume ratio in ε4 relative to homozygous ε3 carriers.

In 2011, Alexopoulos et al. [105] reported that healthy young APOE ε4 carriers have statistically smaller hippocampal volumes than APOE ε2 carriers. No differences were detected between the two groups in memory performance. The study population in Alexopoulos et al. [105] consisted of 33 healthy young German students, average age 24, carrying either the APOE ε2 or the ε4 allele: ε2/ε3 (N = 15), ε2/ε2 (N = 2), ε3/ε4 (N = 12), ε4/ε4 (N = 4).

In a study incorporating 20 ε4 carriers, Sidiropoulos et al. [106] found no correlations between brain derived neurotrophic factor (BDNF) or APOE genotype and hemispheric or lateral ventricular volumes. The study measured the hemispheric and lateral ventricular volumes of 144 healthy individuals, aged 19–35 years, using high resolution magnetic resonance imaging (MRI) and data were correlated with BDNF and APOE genotypes.

Studies on brain function

In addition to imaging studies that have been conducted on brain morphology, several studies have examined brain function in association with ε4 carrier status. In 2009, Filippini et al. [107] conducted resting functional MRI (fMRI) on 18 young healthy male and female APOE ε4 carriers and 18 matched non-carriers (age range 20–35). These authors observed increased default mode network (involving retrosplenial, medial temporal, and medial-prefrontal cortical areas) co-activation in ε4 carriers relative to non-carriers. Also, the encoding task produced greater hippocampal activation in ε4 carriers relative to non-carriers. Scarmeas et al. [108] studied 20 healthy young adults (age 19 to 28 years; four ε4 carriers and 16 non-ε4 carriers) during a non-verbal memory task. Using PET imaging, brain regions were identified where ε4 carriers showed significantly lower or higher activation than non-carriers. Young ε4 carriers had abnormally low rates of glucose metabolism bilaterally in the posterior cingulate, parietal, temporal, and prefrontal cortex in 139 20–39 age range, normal male and female volunteers, average age 31; ε4 carriers (N = 12) [109]. The small subject numbers, high cost and labor intensity of imaging modalities, and heterogeneity of protocol design renders definitive interpretation of these structure and function studies problematic. However, lower brain metabolism in association with task performance can reasonably be assumed to represent a lower level of neural stress per unit time. Perhaps protocol design of imaging studies on metabolic demand should consider studying the brain areas recruited for tasks showing the greatest performance differential between ε3 and ε4 carriers.

Evans et al. [110] examined students from the University of Sussex, average age = 20.92; ε4 carriers (N = 28). In ε4 carriers only, these authors found that subsequently remembered words were linked to increased hippocampal activity. Additionally, Evans et al. reported that genotype status modulated hippocampal activity in the recognition phase [110]. Carriers of ε4 did not show the conventional pattern of greater hippocampal activity to novel words.

Dennis et al. [111] enrolled 24 healthy young adults, 12 carriers and 12 non-carriers of the APOE ε4 allele, and scanned them in a subsequent memory paradigm, using event-related fMRI. These authors reported that the APOE ε4 allele carriers exhibited greater bilateral medial temporal lobe activity relative to the non-carriers to accomplish the same encoding task. In addition, ε4 carriers demonstrated greater functional connectivity of encoding success activity-related medial temporal lobe activity with the posterior cingulate and other peri-limbic regions, with overall connectivity reductions found across anterior and posterior cortices.

Possible relationship between ε4-related brain structure and brain function and AD

Preliminary imaging data suggest that certain brain regions related to memory processes might contain fewer neurons in carriers of the ε4 allele than in non-carriers. Studies suggest the presence of increased mental performance in young healthy subjects who possess the ε4 allele. Increased mental performance elicited from a reduced population of neurons might be exposing the young healthy $\varepsilon4^+$ brain to neural stress. The process of synaptic formation and normal homeostatic synaptic loss might be adversely impacted by long-term neural stress.

MENTAL PERFORMANCE IN YOUNG APOLIPOPROTEIN ε4 CARRIERS (TABLE 8)

At least 32 studies or meta-analyses have examined mental performance in young APOE ε4 carriers. No effect of the APOE allele was reported in six studies [112–117]. All six of the study populations reporting no effect were Caucasian and lived in the United States, United Kingdom, or Western Europe. A single study [118] on only 33 ε4 carriers reported inferior performance associated with possession of ε4. Significant differences were found on the Rey-Osterrieth Complex Figure Test, with ε2-positive children scoring 29.2% relative to ε3/3 at 8.9% and ε4-positive children at 6.1% ($p = 0.12$).

Three studies reported improved performance in spatial tasks in ε4 carriers [102, 119, 120]. A large British study (ε3/4 = 542, ε4/4 = 43) showed faster reaction times in association with the ε4 allele [121]. In a series of studies, Oria et al. [122–124] have shown that possession of the ε4 allele protects against long-term cognitive deficits associated with severe diarrhea in Brazilian shanty-town children. In young Finnish men and women (mean age = 28), ε4 carriers (N = 20), $\varepsilon4^+$ status was associated with good performance in mental arithmetic and the association was dependent on LDL cholesterol level [125].

Two studies have reported a higher IQ in ε4 carriers. In a large British study [126], there was a consistent pattern that ε2/ε2 and ε4/ε4 girls had higher IQ scores (from 3 to 7 points) compared with ε3/ε3 girls. A small study (31 ε4 carriers) on Han Chinese female nursing students showed a modest increase in performance IQ and N100 amplitude for ε4 carriers ($p = 0.038$ and 0.068, respectively) [127]. Using the same cohort of nursing students reported in Yu et al. [127], $\varepsilon4^+$ status did not affect tridimensional personality questionnaire scores [128]. In contrast with the lack of correlation with personality reported in the small cohort of Tsai et al. [128], a large study on Finnish children, adolescents, and young adults [ε4/ε3 (N = 483) and ε4/ε4 (N = 50)] reported that motor activity and even hyperactivity in childhood, and mental vitality in adolescence and young adulthood increased significantly in the order of ε2/ε2, ε3/ε2, ε4/ε2, ε3/ε3, ε4/ε3, and ε4/ε4 [129]. In addition, ε4 carriers displayed a wider field of attention in two tasks [130].

Several studies have reported better performance on memory tasks in young subjects possessing the ε4 allele [131–136]. Comparatively enhanced verbal fluency has also been observed in ε4 allele carriers [137, 104]. In a study on 53 infants in Mexico City who were ε4 carriers, $\varepsilon4^+$ status had a 4.4 point higher 24-month Mental Development Index on the Bayley Scale [138]. A small study from the Czech Republic on 23 $\varepsilon4^+$ subjects suggested that early life cognitive advantages might persist through young adulthood as 87% of $\varepsilon4^+$ carriers reached higher education [139].

The results from two studies suggest that the cognitive response to particular pharmacologic agents might be affected by APOE ε4 status. Twenty-seven ε4 carriers who were healthy nonsmokers, aged 18–30 recruited from Sussex University demonstrated that the ε4 allele confers a cognitive advantage on tasks mediated by the frontal lobes. In addition, young carriers of the ε4 allele show larger cognitive benefit from procholinergic nicotinic stimulation [140]. In the second study, poor Brazilian children with below median height (mean age = 8.6), including 37 ε4 carriers reported that $\varepsilon4^+$ children receiving glutamine supplementation showed short-term gains in HAZ (height for age Z score), WAZ (weight for age Z score) and WHZ (weight for height Z score) that were correlated with better performance in long-term cognitive testing [141].

In this review of cognition and APOE allele genotype, our emphasis has been on ε-related clinical and performance associations in young rather than middle-age subjects. Several recent studies on middle age cohorts might address the issue of transition from ε4-associated cognitive advantage to cognitive deficit. In an older cohort with an average age for ε4 carriers of 58.0 and non-carriers of 61.4, Caselli et al. [142] sought to determine the age at presentation of ε4-related declines in memory. They enrolled 815 subjects: 317 ε4 carriers, 79 of whom were ε4/ε4 and 238 ε3/ε4. The non-carrier group

contained 498 subjects. Carriers were followed for a longer period (5.3 versus 4.7 years, $p = 0.01$), with an equivalent duration of formal education (15.4 years) and proportion of women (69%). Longitudinal decline in memory in ε4 carriers began before age 60 and showed greater acceleration than in non-carriers ($p = 0.03$). There was a possible ε4 dose effect ($p = 0.008$). In 2017, Lancaster et al. published a systematic and meta-analytic review of 36 studies on subjects ranging from 35–60 years old investigating APOE-related differences in cognition in mid-adulthood [143]. The average effect size of ε4 status was non-significant across cognitive domains. Sinclair et al. [144] studied 114 participants with the allelic combinations of ε3/ε3 (39 subjects), ε3/ε4 (27 subjects), ε4/ε4 (15 subjects), ε3/ε2 (26 subjects), and ε2/ε2 (7 subjects). The primary outcome was performance on the Rey Auditory Verbal Learning Test (RAVLT). ε2 carriers displayed slightly better episodic memory performance ($p = 0.016$), somewhat improved n-back accuracy and better executive functioning ($p = 0.005$).

Possible relationship between ε4-related increases in mental performance and AD

The observation of increased mental performance in young healthy carriers of the ε4 allele is consistent with the observation of increased brain lipid metabolism. Taken together, these observations suggest that macromolecular turnover rates related to synapse formation and loss might be elevated in these young ε4 carriers. It is possible that a higher rate of synaptic turnover leads to increased accumulation of non-repaired molecular errors.

CONCLUSIONS

The weight-of-the-evidence presented in Tables 1–8 supports the hypothesis that the possession of the ε4 allele in youth may have a positive differential impact on fitness during different life stages [145]. Young subjects having at least one copy of the ε4 allele reportedly possess a number of advantages that might facilitate survival in harsh environments including the following among others: more rapid improvement in VO_{2max} following exercise [51]; increased fertility at high pathogen burdens [52, 53]; more rapid infant development [105]; prophylaxis against cognitive deficits associated with severe diarrhea [122–124]; resistance to certain infections, e.g., hepatitis [76] and malaria [83]; faster reaction times [121]; better spatial memory [111, 102, 119, 120]; and slight superiority in direct or indirect measures of IQ [135, 134, 126, 141]. Some of these advantages appear to come at the expense of differences in neural processing that might place higher metabolic demands per unit time on the brains of young ε4 carriers [143, 111, 96].

Until 300,000 years ago, ancestors of modern humans were ubiquitously ε4/ε4 and then the ε3 allele mutated from the ancestral ε4 allele [146]. The ε3 allele displayed a competitive survival advantage sufficiently robust to result in the current predominance of the ε3/ε3 genotype which is now found in over 60% of the US population, presumably because of its protection for memory loss and dementia in progressively older age ranges [23]. Similarly, the ε2 allele mutated from the ε3 allele about 200,000 years ago, but this protective allele has remained relatively rare with the homozygous ε2/ε2 variant less than 1%, and the ε3/ε2 heterozygote in about 11% of the population [144].

Given the ancestral primacy of the ε4 allele, and the evolutionary trade-off of superior performance in youth versus additional years beyond historical lifespans, the abnormality of the ε4 allele is somewhat a matter of perspective. If part of the APOE ε4-associated neurotoxic susceptibility is based on pharmacokinetic rather than toxicant receptor interactions on a per mole basis [20], future therapies that slow down synaptic pruning might carefully consider differential effects based on APOE allele subtype. Current knowledge of potential sources of AD patient heterogeneity is lacking. Reducing at least one important source of inter-subject heterogeneity, i.e., APOE ε4 allele carrier status, is advisable. Early attempts at shifting the balance away from synaptic pruning might consider enrolling early stage AD patients possessing at least one ε4 allele.

DISCLOSURE STATEMENT

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/18-1089r3).

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