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Review

The effect of *APOE* genotype on Alzheimer's disease risk is influenced by sex and docosahexaenoic acid status

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ABSTRACT

An apolipoprotein E ε4 (*APOE*-ε4) genotype is the strongest common genetic determinant of Alzheimer's disease (AD). The pleiotropic nature of apolipoprotein E has made elucidation of the aetiological basis difficult to establish, which is further complicated by the fact that the penetrance of the *APOE*-ε4 allele is modulated by sex, age, and nutrition. A greater metabolic consequence of the *APOE*-ε4 allele is likely to contribute to the fact that two-thirds of AD patients are female. A higher tissue status of the marine n-3 fatty acid docosahexaenoic acid (DHA) is associated with a lower AD risk. However, *APOE*-ε4 carriers appear less sensitive to the neurocognitive benefits, which may be due to defective blood-brain barrier transport of DHA exacerbated by aging and possibly sex. This suggests higher DHA requirements in this large population subgroup. This narrative review will consider the influence of sex and DHA in modulating *APOE*-ε4–mediated AD risk.

1. Introduction

Dementias, of which Alzheimer's disease (AD) is the most common, are complex multifactorial disorders that manifest progressively over time, with deleterious behaviors and genetic predisposition contributing to compromised cognitive function. The apolipoprotein E ε4 (*APOE*-ε4) allele is the strongest prevalent genetic risk factor for sporadic late-onset AD with possession of 1 or 2 *APOE*-ε4 conferring 3- to 4- and 8- to 12-fold increased risk, respectively, and reduced age of onset (Davidson et al., 2007; Heffernan et al., 2016). While a significant risk factor, possession of an *APOE*-ε4 does not categorically determine AD outcome (Corder et al., 1993; Liu et al., 2013). *APOE*-ε4 prevalence within global AD populations varies considerably ranging from 41% to 61% (Corbo and Scacchi, 1999; Crean et al., 2011; Farrer et al., 1997) and only half of *APOE*-ε4 homozygotes develop AD by age 90 years (Henderson et al., 1995). This indicates that the penetrance of the ε4 allele, its influence on the rate of cognitive decline and the likelihood of transitioning to mild cognitive impairment (MCI) and AD, is variable and potentially modifiable (Fenesi et al., 2017; Moser and Pike, 2017; Singh et al., 2006; Ward et al., 2012).

Because of the pleiotropic nature of apolipoprotein E (apoE), possession of the deleterious *APOE*-ε4 allele influences multiple biological processes, including inflammation, amyloid beta deposition, neurogenesis, synaptic function, and lipid metabolism (including cholesterol and docosahexaenoic acid [DHA]) (Alata et al., 2015; Holtzman et al., 2012; Huang and Mahley, 2014; Theendakara et al., 2016). Originally described for its role in lipid transport, in contrast to the systemic circulation, apoE is the almost exclusive lipid transporter within the central nervous system (Bu, 2012).

Regular consumption of long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFAs), eicosapentaenoic acid, and DHA, found in high concentrations in oily fish is associated with reduced AD risk (Barberger-Gateau et al., 2007; Zhang et al., 2016). Current evidence suggests that the cognitive responsiveness to DHA intake is lower in *APOE*-ε4 individuals (Childs et al., 2014; Davis et al., 2017; Kofler et al., 2012; Metherel et al., 2009; Minihane, 2016; Slim et al., 2017; Walker et al., 2014).

Furthermore, the pathological impact of *APOE*-ε4 carrier status appears to be modified by sex, with female carriers found to have increased MCI or AD risk between the ages of 55 and 70 years compared to their male counterparts (Farrer et al., 1997; Neu et al., 2017), suggesting a possible role of menopausal transition.

Therefore, those with an *APOE*-ε4 genotype, particularly postmenopausal females, are a large "at-risk" population group who should be targeted for preventive intervention, such as LC n-3 PUFA supplementation. Strategies capable of delaying disease onset by as

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little as 2 years would have profound implications on current disease burden (Brookmeyer et al., 1998). Recent predictive UK models suggest that achieving a 2- or 5-year delay would result in a respective 19% or 33% reduction in the predicted AD prevalence by 2050 (Lewis et al, 2014) and alleviate the social and economic pressures associated with this debilitating disease.

This review will consolidate the current evidence of the interactive role of *APOE* genotype, DHA status and sex in the development of AD, highlighting research gaps and directions for future investigation.

2. Contribution of APOE genotype to AD risk

The human *APOE* gene, located on chromosome 19, has 3 common alleles, ε2, ε3, and ε4. Relative to the most common isoform *APOE*-ε3 (allele frequency 78%), the rarer *APOE*-ε2 (allele frequency 7%) is considered protective (Liu et al., 2013), whereas the *APOE*-ε4 isoform (allele frequency 14%) predisposes to AD. Systematic reviews and meta-analyses consistently describe strong *APOE*-ε4 AD associations. For example, using the *AlzGene* database, increased odds ratios (ORs) for both *APOE*-ε4 heterozygotes (OR: 2.8, 95% confidence interval: 2.3–3.5) and homozygotes (OR: 11.8, 95% confidence interval: 7.0–19.8) relative to "neutral" *APOE*-ε3 homozygotes were reported (Bertram et al., 2007). The *APOE*-ε4 allele is concentrated within the AD population, with prevalence reaching in excess of 50% relative to the global frequency estimated at 14% (in people aged <65 years) (Eisenberg et al., 2010; Hallman, 1991; Ward et al., 2012). Such associations are also apparent in MCI. *APOE*-ε4 carriers are 3.0–3.7 times more likely to develop MCI compared to all other groups (Viticchi et al., 2017) and *APOE*-ε4 MCI are more likely to convert to a more severe state of MCI or AD (Scarabino et al., 2016). *APOE*-ε4 has been associated with hippocampal, amygdala, and medial-temporal lobe atrophy (Lupton et al., 2016; Manning et al., 2014), which underlies the greater development and conversion rates in this genotype subgroup.

A consensus is developing that the impact of the *APOE*-ε4 allele on AD risk diminishes on reaching extreme ages (>90 years) (Corrada et al., 2013), (Valerio et al., 2014), which is reflected by the reduced allele frequency within the AD population (Corrada et al., 2013). Such a trend is unexpected given that the APOE-ε4 variant is attributed to an increased risk and reduced age of onset. The phenomenon has been attributed to the survivor effect, and the fact that these individuals have other phenotypic attributes that offer protection with many *APOE*-ε4 carriers reaching extreme ages with normal cognition (Corder et al., 1994; Rebeck et al., 1994). The study of such individuals is likely to provide valuable insights into strategies to mitigate the effect of genotype at younger ages.

3. Impact of sex on AD risk

3.1. Sex disparity in MCI and AD incidence

Sex influences dementia risk and prevalence (Podcasy and Epperson, 2016). Above age 65 years, there are approximately twice as many female AD cases (Seshadri et al., 1997). Although the higher prevalence has been attributed to longevity, the global 5-year longer lifespan in females (2017) can arguably only partially explain this phenomenon (Snyder et al., 2016). The reasons for this are still unclear, although it has been suggested that increased incidence in women may be related to the loss, after menopause, of the neuroprotective effect of estrogens, important in maintaining synaptic plasticity, neurotransmission, and blood-brain barrier (BBB) integrity (Karp et al., 2017; Maggioli et al., 2016; McEwen and Milner, 2017). However, current clinical trials using hormone replacement therapy have failed to yield any promising results (Marjoribanks et al., 2017). Interestingly, analysis of murine hippocampal expression profiles reveals that key AD-associated genes affecting energy and amyloid deposition are considerably altered prematurely in females, predisposing them to the development of the disease (Zhao et al., 2016).

A greater penetrance of an *APOE*-ε4 genotype in females, first reported in the early 90s (Payami et al., 1994), could also explain these higher AD rates. A subsequent meta-analysis, found that carrying 1 *APOE*-ε4 allele had a substantial effect on AD risk in females relative to noncarriers (OR: ≈4 at 65 years), whereas their male counterparts remained at similar risk (OR: ≈1 at 65 years) (Farrer et al., 1997) (Table 1 and Fig. 1). This somewhat "understudied" association, has been reiterated over the years (Bretsky et al., 1999; Gao et al., 1998; Holland et al., 2013; Xing et al., 2015), including work conducted by Altmann et al. who observed that the conversion of healthy controls to MCI/AD in *APOE*-ε4 carriers was stronger in women (hazard ratio: female = 1.81 and male = 1.27), with female *APOE*-ε3/ε4 more likely converting from MCI to AD (hazard ratio: female = 2.17 and male = 1.51 vs. *APOE*-ε3/ε3) (Fig. 1) (Altmann et al., 2014). A contemporary meta-analysis from the Global Alzheimer's Association Interactive Network (n = 27 studies, 58,000 participants) has offered novel insight into this interaction. Despite no overall significant difference between men and women on *APOE*-ε4 AD in 55–85 year olds, the influence of sex emerged as being age-dependent. *APOE*-ε4 females were at higher risk of MCI at ages 55–70 years and of AD at 65–75 years relative to *APOE*-ε4 males, with the sexual dimorphism disappearing after 75 years (Neu et al., 2017). This indicates that a higher susceptibility to the *APOE*-ε4 allele in females is most evident in the decade(s) following menopause. As with the overall reduction of penetrance of genotype on AD risk at older ages described above, a loss of effect of sex may be due to selective survival of those females less sensitive to genotype or the effect of genotype being lessened by an overall higher AD risk profile.

3.2. Female sex exacerbates the neurocognitive impact of an APOE-ε4 genotype

Limited human cognitive and biomarker data support the sexual dimorphism evident in epidemiological (incident disease) studies, indicating earlier onset and more extensive pathology in female *APOE*-ε4 carriers. Differences in cerebrospinal fluid tau and $A\beta_{42}$ load (Altmann et al., 2014; Li et al., 2017) along with aberrant Aβ/secretase profiles in autopsy samples (Nyarko et al., 2018) and brain hypometabolism and cortical thinning (Sampedro et al., 2015) have been observed between female and male *APOE*-ε4. Fleisher et al. observed reduced hippocampal volume and memory performance in female relative to male *APOE*-ε4 carriers, in whom significant pathological changes only occurred when in possession of 2 *APOE*-ε4 alleles (Fleisher et al., 2005). Analysis of >5000 brain samples of varying ages found that women carrying the *APOE*-ε4 gene had more extensive neurofibrillary tangles and senile plaques, with onset of pathology beginning considerably earlier (Corder et al., 2004). Neuroprotective immune cell (Aβ-specific CD4+ T cell) decline was found to occur 10–15 years earlier in female carriers compared to that of male carriers (Begum et al., 2014). Finally, levels of brain-derived neurotrophic factor, an important modulator of neuron survival and growth in areas associated with memory, have been found to be significantly reduced in *APOE*-ε4 females relative to age matched *APOE*-ε4 males and correlate to poorer mini mental state examination scores (Alvarez et al., 2014).

Rodent studies also highlight such a trend. It is widely accepted that female *APOE*-ε4 mice present a more extreme phenotype (Raber et al., 1998; Rodriguez et al., 2013), with greater cognitive decline evident from their poorer performance on a battery of