ELSEVIER

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring ■ (2018) 1-10

Alzheimer's & Dementia

Genetics

Sex differences in the association between apolipoprotein E-ε4 and Alzheimer's disease markers

Erin E. Sundermann[a,*], My Tran[b], Pauline M. Maki[c], Mark W. Bondi[a,d], for the Alzheimer's Disease Neuroimaging Initiative[1]

[a]Department of Psychiatry, University of California, San Diego, San Diego, CA, USA
[b]Department of Psychology, San Diego State University, San Diego, San Diego, CA, USA
[c]Departments of Psychiatry and Psychology, University of Illinois at Chicago, Chicago, IL, USA
[d]Veterans Affairs San Diego Healthcare System, San Diego, CA, USA

Abstract

Introduction: We determined whether the effect of apolipoprotein E (APOE)-ε4 genotype on Alzheimer's disease (AD) markers differs in men and women across AD stages.

Methods: Among participants with normal cognition (NC; N = 702), mild cognitive impairment (N = 576), and AD (N = 305), we examined the associations of sex and APOE-ε4 carrier status with cortical amyloid-beta (Aβ) burden, hippocampal volume to intracranial volume ratio (HpVR), brain glucose metabolism, and verbal memory.

Results: In NC, APOE-ε4 related to greater Aβ burden and poorer verbal memory across sex but to smaller HpVR and hypometabolism in men only. In mild cognitive impairment, APOE-ε4 related to smaller HpVR, hypometabolism, greater Aβ burden, and poorer verbal memory across sex. In AD, APOE-ε4 related to greater Aβ burden in men only and smaller HpVR across sex and showed no association with hypometabolism or verbal memory.

Discussion: Sex differences in the association between APOE-ε4 and AD markers vary by disease stage.

Keywords: APOE; Sex differences; Amyloid-β plaque deposition; Hippocampal volume; Brain glucose metabolism; Verbal memory

1. Background

The ε4 allele of the apolipoprotein E gene (APOE-ε4) is the most common genetic risk factor for Alzheimer's disease (AD) [1,2]. APOE-ε4 is associated with AD-related biological and clinical markers including cortical amyloid-beta (Aβ) plaque burden, hippocampal atrophy [3–5], and accelerated cognitive decline in healthy aging [6–8]. However, there have been conflicting/mixed findings with some reporting that APOE-ε4 is not associated with hippocampal volume [9,10] or cognitive decline in healthy aging [9,10] or with risk of converting from mild cognitive impairment (MCI) to AD [11,12]. These inconsistencies may be due to the potentially critical modulating role of sex in the association between APOE-ε4 and AD.

Conflict of interest: Dr. M.W.B. is paid royalties from the Oxford University Press and serves as a consultant for Eisai and Novartis. The other authors report no conflicts of interest.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

*Corresponding author. Tel.: (858)552-8585x7286; Fax: ■■■.
E-mail address: esundermann@einstein.yu.edu

https://doi.org/10.1016/j.dadm.2018.06.004

Early cross-sectional studies indicated that APOE-ε4 confers a greater risk for AD in women than in men [13–15]. These early findings are supported by a longitudinal study [16] and a meta-analysis that reported an increased risk of incident AD in female APOE-ε4 heterozygotes versus male heterozygotes among adults aged 65 to 75 years [17]. Among healthy older adults, the adverse effect of APOE-ε4 on AD biomarkers including cerebrospinal fluid total tau levels [18], brain metabolism [19], cortical thinning [19], and functional brain connectivity in the default mode network [18] was stronger in women versus men, although not consistently [19,20]. In MCI, the effect of APOE-ε4 on brain atrophy [21], total tau levels [16], and the tau/Aβ ratio [16] was stronger in women versus men. To our knowledge, only one study examined sex differences in the effects of APOE-ε4 in AD patients and reported a stronger association between APOE-ε4 and Aβ burden in parietal, cingulate, and frontal regions in men versus women [22], suggesting a possible reversal in the moderating role of sex on APOE-ε4 in the MCI-to-AD transition that warrants further exploration.

Surprisingly, few studies have examined the interactive effects of sex and APOE-ε4 on cognitive performance [21,23,24], particularly verbal memory, even though verbal memory is the cognitive domain that shows the earliest and most severe deficits in AD [25]. Among community-dwelling older adults, the association between APOE-ε4 and accelerated cognitive decline, as measured by a global cognitive measure, was stronger in women versus men [23,24]. In a MCI sample, female heterozygous or homozygous APOE-ε4 carriers showed worse performance on a delayed (5 minute) word recall task from the Alzheimer's Disease Assessment Scale Cognitive Subscale compared with female noncarriers, whereas the APOE-ε4 effect was only evident in homozygous men [21]. In addition, few studies have examined the sex by APOE interaction across the AD continuum [22] despite evidence of a temporal ordering of AD markers, whereby Aβ deposition occurs first, followed by neurodegenerative biomarkers and cognitive impairment [26,27]. We systematically examined the separate and interactive effects of sex and APOE on multiple AD-related markers including Aβ deposition, hippocampal volume, brain glucose metabolism, and verbal memory performance in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Effects were examined in each disease stage (NC, MCI, AD), in which MCI versus NC was defined using the Jak/Bondi diagnostic method, an actuarial, neuropsychological diagnostic approach that has produced more discernible cognitive phenotypes, more stable diagnoses, stronger associations with AD biomarkers, and better predication of progression to dementia than conventional diagnostic criteria [28,29]. Consistent with the broader literature, we predicted that the adverse effects of APOE-ε4 would be stronger in women versus men, and inline with the temporal sequence of AD-related markers [26,27], this sex difference in the APOE-ε4 effect will manifest at the NC stage for earlier AD events (Aβ deposition) and in MCI for later events (hippocampal atrophy, brain hypometabolism, and memory deficits).

2. Methods

2.1. Participants and data source

Data were extracted from the ADNI database (adni.loni.usc.edu). ADNI is a longitudinal, multisite cohort study that began in 2003 as a public-private partnership. Information about ADNI can be found at www.adni-info.org. ADNI study visits involve neuroimaging, neuropsychological, and clinical assessments. We included participants who had APOE genotype and baseline data on one of the AD-related markers examined herein. We limited our sample to ADNI's largest race/ethnic group, Caucasians, to minimize potential population stratification bias that could complicate interpretation of genetic data. Analyses were repeated while excluding APOE-ε2 allele carriers because the protective effect of APOE-ε2 could mask the adverse effect of APOE-ε4.

2.2. Verbal memory assessment

Our verbal memory measure was the Rey Auditory Verbal Learning Test (AVLT) [30]. The AVLT is a multitrial Q8 list learning and memory test with immediate and delayed recall and recognition outcomes. Immediate recall scores (range: 0–75) were the primary outcome because they were not used in diagnostic criteria, and learning deficits may better discriminate preclinical AD from normal controls than retention deficits [31,32].

2.3. Biomarkers

Biomarkers included neuroimaging measures of hippocampal volume, brain glucose metabolism, and cortical Aβ deposition. Structural MRI scans were collected on a 1.5T scanner according to a standardized protocol [33]. Hippocampal volume data were analyzed using FreeSurfer version 4.3 (https://surfer.nmr.mgh.harvard.edu) at the University of California–San Francisco (http://adni.loni.ucla.edu/wp-content/uploads/2010/12/UCSF-FreeSurfer-Overview-and-QC_-Template_Format.pdf) [34]. To control for sex differences in head size, we calculated a hippocampal volume ratio (HpVR) using the formula, hippocampal/intracranial volume $\times 10^3$.

Brain glucose metabolism was measured by [^{18}F]fludeoxyglucose (FDG)-PET. Images were preprocessed following Q9 a standard procedure described in http://adni.loni.usc.edu/methods/pet-analysis/pre-processing/. ADNI investigators at the University of California, Berkeley, established a "MetaROI" of brain regions that commonly demonstrate metabolic changes in MCI/AD which correlate with cognitive performance in a meta-analysis [11,35]. The "MetaROI" was comprised of bilateral posterior cingulate