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Sex-Specific Association of Apolipoprotein E With Cerebrospinal Fluid Levels of Tau

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IMPORTANCE The strongest genetic risk factor for Alzheimer disease (AD), the apolipoprotein E (APOE) gene, has a stronger association among women compared with men. Yet limited work has evaluated the association between APOE alleles and markers of AD neuropathology in a sex-specific manner.

OBJECTIVE To evaluate sex differences in the association between APOE and markers of AD neuropathology measured in cerebrospinal fluid (CSF) during life or in brain tissue at autopsy.

DESIGN, SETTING, AND PARTICIPANTS This multicohort study selected data from 10 longitudinal cohort studies of normal aging and AD. Cohorts had variable recruitment criteria and follow-up intervals and included population-based and clinic-based samples. Inclusion in our analysis required APOE genotype data and either CSF data available for analysis. Analyses began on November 6, 2017, and were completed on December 20, 2017.

MAIN OUTCOMES AND MEASURES Biomarker analyses included levels of β-amyloid 42, total tau, and phosphorylated tau measured in CSF. Autopsy analyses included Consortium to Establish a Registry for Alzheimer’s Disease staging for neuritic plaques and Braak staging for neurofibrillary tangles.

RESULTS Of the 1798 patients in the CSF biomarker cohort, 862 were women, 226 had AD, 1690 were white, and the mean (SD) age was 70 (9) years. Of the 5109 patients in the autopsy cohort, 2813 were women, 4953 were white, and the mean (SD) age was 84 (9) years. After correcting for multiple comparisons using the Bonferroni procedure, we observed a statistically significant interaction between APOE-ε4 and sex on CSF total tau (β = 0.41; 95% CI, 0.27-0.55; P < .001) and phosphorylated tau (β = 0.24; 95% CI, 0.09-0.38; P = .001), whereby APOE showed a stronger association among women compared with men. Post hoc analyses suggested this sex difference was present in amyloid-positive individuals (β = 0.41; 95% CI, 0.20-0.62; P < .001) but not among amyloid-negative individuals (β = 0.06; 95% CI, −0.18 to 0.31; P = .62). We did not observe sex differences in the association between APOE and β-amyloid 42, neuritic plaque burden, or neurofibrillary tangle burden.

CONCLUSIONS AND RELEVANCE We provide robust evidence of a stronger association between APOE-ε4 and CSF tau levels among women compared with men across multiple independent data sets. Interestingly, APOE-ε4 is not differentially associated with autopsy measures of neurofibrillary tangles. Together, the sex difference in the association between APOE and CSF measures of tau and the lack of a sex difference in the association with neurofibrillary tangles at autopsy suggest that APOE may modulate risk for neurodegeneration in a sex-specific manner, particularly in the presence of amyloidosis.

Published online May 7, 2018.
Apolipoprotein E (APOE) is the strongest genetic risk factor for sporadic Alzheimer disease (AD), explaining approximately 13% of the phenotypic variance. The ε4 allele increases risk for AD in a dose-dependent manner, and the strength of the association varies by age and sex. The effect of APOE-ε4 is strongest prior to age 70 years, declines after age 85 years, and is more robust among women compared with men, especially women between age 55 and 70 years. Although this sex difference has been well established after a 2017 comprehensive meta-analysis, very little is known about the underlying mechanism. APOE has been implicated in a variety of neuropathological cascades relevant to AD, including alterations in cerebral glucose metabolism, cerebrovascular disease, amyloidosis, neurodegeneration, and tau tangle pathology. This article will focus on amyloid and tau as potential contributors to sex differences in the clinical effects of APOE.

In the case of amyloid pathology, APOE-ε4 has a strong association with amyloidosis, even among older adults without dementia, likely through its role in amyloid clearance. Research leveraging in vivo biomarkers of amyloid has indicated that the association between APOE-ε4 and amyloidosis is consistent across sexes, yet other work has found evidence of age-dependent sex differences in the effects of APOE-ε4 on amyloidosis. In the case of tau pathology, APOE-ε4 is associated with higher levels of cerebrospinal fluid (CSF) tau and more neurofibrillary tangles at autopsy, although these associations are relegated to individuals with high levels of amyloid pathology. The evidence of a sex difference in the association between APOE and tau pathology is also mixed, with some biomarker and autopsy work suggesting women show a more robust association between APOE-ε4 and tau, while other work has reported no sex difference.

Collectively, the amyloid and tau findings to date provide mounting, although inconclusive, evidence of a sex difference in the association between APOE and both of the primary neuropathological hallmarks of AD. The objective of this study was to provide a comprehensive understanding of the sex-specific associations between APOE and AD neuropathology in older adulthood. The pooled data resources for this project provide the opportunity to evaluate sex differences across the spectrum of normal aging and AD including a broad range of age and cognitive status. The first set of analyses focused on 4 in vivo data sets that include CSF biomarkers of AD neuropathology. The second set focused on 6 autopsy data sets of AD leveraging direct measures of AD neuropathology. Together, these analyses provide a thorough and needed investigation into sex-specific effects of APOE on AD neuropathology.

**Methods**

Data were acquired from well-characterized studies of AD (Tables 1 and 2). The biomarker database included 4 cohort studies. The Vanderbilt Memory & Aging Project (VMAP), launched in 2012, recruited participants 60 years and older from the community who were magnetic resonance imaging eligible and free of dementia and clinical stroke. The Wisconsin Registry of Alzheimer’s Prevention began in 2001, recruiting participants aged 40 to 65 years. Seventy-two percent (n = 1112) have a parent with either probable AD dementia ascertained through medical history review or autopsy-confirmed AD. The Biomarkers of Cognitive Decline Among Normal Individuals study began in 1995. Enrollees were middle age at baseline and cognitively intact; 75% of participants (n = 266) had a first-degree relative with AD. The study stopped in 2005 and was reestablished in 2009, with annual assessments. The Alzheimer’s Disease Neuroimaging Initiative (ADNI) launched in 2003 and includes more than 1500 adults aged 55 to 90 years with normal cognition, mild cognitive impairment, or AD (http://adni-info.org).

The autopsy database was derived from data published by Beecham et al evaluating genetic markers of AD neuropathology, which includes cohort descriptions. The Translational Genomics Research Institute, National Institute on Aging Late-Onset Alzheimer’s Disease Family Study, and Mayo Clinic were analyzed directly from the published data. The data set was updated using data from the Religious Orders Study and Rush Memory and Aging Project, the Adult Changes in Thought study, and the National Alzheimer’s Coordinating Center data set. Briefly, the Religious Orders Study began in 1994 and involves older Catholic nuns, priests, and brothers recruited from across the United States. Rush Memory and Aging Project began in 1997 and involves older lay persons recruited from retirement communities, subsidized housing facilities, and social service agencies in the Chicago, Illinois, metropolitan area. Persons in both studies enrolled without dementia and agreed to annual clinical evaluations and organ donation at death. The Adult Changes in Thought began in 1994 and recruited a random sample of older adults without dementia from the Seattle, Washington, metropolitan area. A subset of participants in Adult Changes in Thought (25%-30%) also agreed to brain donation. The National Alzheimer’s Coordinating Center maintains a database of participant information collected from 34 past and present National Institute of Aging-funded Alzheimer’s Disease Centers. In 2005, the National Alzheimer’s Coordinating Center implemented a standard protocol (ie, Uniform Data set) including clinical, medical, neurological, and cognitive data. We only included autopsy participants who were 60 years and older at...
Table 1. Participant Characteristics for Biomarker Data Sets

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BIOCARD (n = 275)</th>
<th>WRAP (n = 154)</th>
<th>ADNI (n = 1213)</th>
<th>VMAP (n = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Total No. (%)</td>
<td>113 (41)</td>
<td>162 (59)</td>
<td>53 (34)</td>
<td>101 (66)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>62 (10)</td>
<td>59 (9)</td>
<td>62 (6)</td>
<td>63 (7)</td>
</tr>
<tr>
<td>White race/ethnicity</td>
<td>110 (97)</td>
<td>157 (97)</td>
<td>51 (96)</td>
<td>95 (94)</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal cognition</td>
<td>101 (90)</td>
<td>159 (99)</td>
<td>44 (83)</td>
<td>88 (87)</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>11 (10)</td>
<td>2 (1)</td>
<td>9 (17)</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>APOE ε4 count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 ε4 Alleles</td>
<td>75 (66)</td>
<td>104 (64)</td>
<td>36 (68)</td>
<td>62 (61)</td>
</tr>
<tr>
<td>1 ε4 Allele</td>
<td>29 (26)</td>
<td>51 (31)</td>
<td>17 (32)</td>
<td>34 (34)</td>
</tr>
<tr>
<td>2 ε4 Alleles</td>
<td>9 (8)</td>
<td>7 (4)</td>
<td>0</td>
<td>5 (5)</td>
</tr>
<tr>
<td>APOE ε2 carriers</td>
<td>11 (10)</td>
<td>24 (15)</td>
<td>7 (13)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Amyloid positive</td>
<td>55 (49)</td>
<td>60 (37)</td>
<td>5 (9)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Tau positive</td>
<td>38 (43)</td>
<td>51 (31)</td>
<td>4 (8)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Aβ42, pg/mL, mean (SD)</td>
<td>370 (89)</td>
<td>395 (99)</td>
<td>714 (179)</td>
<td>736 (217)</td>
</tr>
<tr>
<td>Total tau, pg/mL, mean (SD)</td>
<td>68 (35)</td>
<td>70 (32)</td>
<td>308 (116)</td>
<td>321 (116)</td>
</tr>
<tr>
<td>Phosphorylated tau, pg/mL,</td>
<td>38 (13)</td>
<td>40 (17)</td>
<td>45 (16)</td>
<td>48 (15)</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ42, β-amyloid 42; ADNI, Alzheimer’s Disease Neuroimaging Initiative; BIOCARD, Biomarkers of Cognitive Decline Among Normal Individuals; VMAP, Vanderbilt Memory and Aging Project; WRAP, Wisconsin Registry of Alzheimer’s Prevention.

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By the same laboratory using the same procedure. Given known batch effects, we analyzed variables as continuous square-root-transformed outcomes within each data set individually and used an analysis based on standardized coefficients to summarize results across data sets.

**Quantification of Neuropathology Outcomes**

Within the autopsy data sets, we used a measure of neurofibrillary tangles (Braak staging) and a measure of neuritic plaques (Consortium to Establish a Registry for Alzheimer’s Disease [CERAD] neuritic plaque score) in each data set. Both measures were analyzed as binary outcomes and as ordinal outcomes. The binary neuritic plaque positive score was defined based on CERAD, whereby scores of none or sparse neuritic plaques were considered neuritic plaque negative, and scores of moderate or frequent neuritic plaques were considered neuritic plaque positive. The binary neurofibrillary tangles positive score was defined based on Braak staging, whereby stages none, I, or II were considered neurofibrillary tangle negative and stages III, IV, V, or VI were considered neurofibrillary tangle positive.

**Statistical Analyses**

Statistical analyses were completed using RStudio, version 1.0.136 (RStudio). The threshold for statistical significance was set a priori at P less than .001 using a 2-sided test correcting for 35 total comparisons. For the neuropathology analyses, 2 primary models were run. The first was a binary logistic regression with tangle positivity or neuritic plaque positivity set as the outcome. The second model was a proportional odds
Table 2. Participant Characteristics for Autopsy Data Sets

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NACC (n = 2225)</th>
<th>ROS/MAP (n = 1259)</th>
<th>ACT (n = 381)</th>
<th>LOAD-Braak (n = 277)</th>
<th>LOAD-CERAD (n = 207)</th>
<th>Mayo Clinic (n = 392)</th>
<th>TGEN-Braak (n = 575)</th>
<th>TGEN-CERAD (n = 175)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Total No. (%)</td>
<td>1133 (51)</td>
<td>1092 (49)</td>
<td>435 (35)</td>
<td>824 (65)</td>
<td>179 (47)</td>
<td>202 (53)</td>
<td>99 (36)</td>
<td>178 (64)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>82 (9)</td>
<td>85 (9)</td>
<td>87 (7)</td>
<td>90 (6)</td>
<td>85 (4)</td>
<td>86 (5)</td>
<td>84 (8)</td>
<td>77 (9)</td>
</tr>
<tr>
<td>White race/ethnicity</td>
<td>1082 (95)</td>
<td>1021 (93)</td>
<td>427 (98)</td>
<td>798 (97)</td>
<td>148 (34)</td>
<td>260 (32)</td>
<td>15 (15)</td>
<td>29 (16)</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td>Normal cognition</td>
<td>167 (15)</td>
<td>228 (21)</td>
<td>148 (34)</td>
<td>260 (32)</td>
<td>116 (66)</td>
<td>128 (63)</td>
<td>15 (15)</td>
</tr>
<tr>
<td></td>
<td>Mild cognitive impairment</td>
<td>113 (10)</td>
<td>104 (10)</td>
<td>116 (27)</td>
<td>202 (25)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>853 (75)</td>
<td>760 (70)</td>
<td>171 (39)</td>
<td>362 (44)</td>
<td>61 (34)</td>
<td>74 (37)</td>
<td>84 (85)</td>
</tr>
<tr>
<td>APOE ε4 count</td>
<td>0 ε4 Alleles</td>
<td>585 (52)</td>
<td>603 (55)</td>
<td>319 (73)</td>
<td>608 (74)</td>
<td>133 (74)</td>
<td>145 (72)</td>
<td>31 (31)</td>
</tr>
<tr>
<td></td>
<td>1 ε4 Allele</td>
<td>427 (38)</td>
<td>402 (37)</td>
<td>110 (25)</td>
<td>199 (24)</td>
<td>45 (25)</td>
<td>50 (25)</td>
<td>48 (48)</td>
</tr>
<tr>
<td></td>
<td>2 ε4 Alleles</td>
<td>121 (11)</td>
<td>87 (8)</td>
<td>6 (1)</td>
<td>17 (2)</td>
<td>1 (1)</td>
<td>7 (4)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>APOE ε2 carriers</td>
<td>101 (9)</td>
<td>126 (12)</td>
<td>61 (14)</td>
<td>130 (16)</td>
<td>26 (15)</td>
<td>15 (7)</td>
<td>6 (6)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Neuritic plaque positive (CERAD ≥ moderate)</td>
<td>798 (70)</td>
<td>754 (69)</td>
<td>317 (73)</td>
<td>652 (79)</td>
<td>82 (46)</td>
<td>103 (51)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tangle positive (Braak ≥ III)</td>
<td>908 (80)</td>
<td>879 (80)</td>
<td>323 (74)</td>
<td>708 (86)</td>
<td>104 (58)</td>
<td>129 (64)</td>
<td>91 (92)</td>
<td>159 (89)</td>
</tr>
</tbody>
</table>

Abbreviations: ACT, Adult Changes in Thought; AD, Alzheimer disease; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; LOAD, Late-Onset Alzheimer’s Disease Family Study; NA, not applicable; NACC, National Alzheimer’s Disease Coordinating Center; ROS/MAP, Religious Orders Study and Rush Memory and Aging Project; TGEN, Translational Genomics Research Institute.
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Original Investigation Research

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 ordinal logistic regression, setting either Braak stage or CERAD neuritic plaque score as the ordinal outcome. Predictors in the model included age at death, sex, APOE, and a sex by APOE interaction. APOE-ε2 and APOE-ε4 were evaluated in separate models, and the main effect models were assessed excluding the sex by APOE interaction term. We used a dominant model for ε2 and an additive model for ε4. Follow-up analyses were run stratified by sex. All models were run within each data set individually.

For the biomarker analyses, the same prediction models and covariates were assessed using linear regression with baseline CSF β-amyloid42, CSF total tau (t-tau), or CSF phosphorylated tau set as the continuous outcome. Age at CSF acquisition was used as the age covariate term. Follow-up models were run stratified by sex. All models were run within each data set individually.

Analyses within the CSF and autopsy cohorts were completed separately using the metafor package in R (R Programming), including estimation of fixed effects and heterogeneity across data sets. Correction for multiple comparisons was performed using the Bonferroni procedure accounting for main effects and interactions on 3 biomarker outcomes (CSF β-amyloid42, t-tau, and phosphorylated tau) and 4 autopsy outcomes (ordinal and binary outcomes of CERAD and Braak staging), resulting in 35 independent tests (corrected α = .0014).

Post hoc analyses evaluated sex by APOE-ε4 interactions on CSF t-tau and phosphorylated tau among amyloid-positive and amyloid-negative individuals. Additional post hoc analyses restricted the sample to cognitively normal individuals, stratified by age group, covaried for education level, restricted autopsy results to longitudinal cohort studies, removed ADNI from the CSF analyses, and restricted to APOE-ε4 homozygotes.

Results

Participant characteristics are presented in Tables 1 and 2. The biomarker data set included individuals who were, on average, younger, with a higher percentage of men than the autopsy data sets.

Sex Differences and Main Effects of APOE

Main effect results are presented in Table 3. Women showed higher levels of CSF t-tau, CERAD neuritic plaque score, and Braak tau tangle stage. Similarly, APOE-ε4 was associated with higher levels of biomarker levels and pathology and ε2 was associated with lower biomarker levels and pathology for all metrics.

Sex by APOE Interactions: CSF Biomarker Results

Interaction results are presented in Table 3. A sex by APOE-ε4 interaction was observed on both t-tau (Figure 1) and phosphorylated tau wherein the association between APOE-ε4 and tau levels was stronger in women than in men (Figure 2).

Sex by APOE Interactions: Autopsy Results

Autopsy interaction results are also presented in Table 3. There were no significant interactions between sex and APOE on neuropathology.
Post Hoc Analyses

In post hoc analyses stratified by amyloid status, the sex by APOE-ε4 interaction was present among amyloid-positive individuals (β = 0.41; 95% CI, 0.20 to 0.62; P < .001; eTable 1 in the Supplement) but not amyloid-negative individuals (β = 0.06; 95% CI, −0.18 to 0.31; P = .62; eTable 2 in the Supplement). Additional post hoc analyses stratified by age, restricting the sample to cognitively normal individuals, adjusting for education, restricted to longitudinal cohort studies, removing the ADNI data set, and restricted to APOE-ε4 homozygotes are presented in eTables 3-9 in the Supplement.

Discussion

These findings provide, to our knowledge, the most robust evidence to date of sex differences in the association between APOE-ε4 and CSF tau levels, whereby the effect of APOE is stronger among women compared with men. The observed sex difference was driven by amyloid-positive individuals, suggesting APOE may confer sex-specific risk for downstream neurodegeneration in the presence of enhanced amyloidosis. In contrast to CSF tau levels, we did not observe sex differences in the association between APOE and any biomarkers of amyloidosis or autopsy measures of neurofibrillary tangles.

These analyses provide strong evidence of an enhanced association between APOE-ε4 and CSF tau levels among women compared with men, particularly among amyloid positive women. Previous work in ADNI has reported similar sex differences in CSF tau, although results have been somewhat mixed depending on the sample included and had never been replicated in an independent cohort. We were able to replicate the sex difference of APOE effects on CSF tau in 3 additional data sets that differ substantially in baseline age and diagnostic status. We also provide evidence of a comparable sex difference in the association between APOE-ε4 and CSF phosphorylated tau for the first time. Several mechanisms could underlie this sex difference in tau, and the hormonal changes that take place during and following menopause represent 1 strong candidate pathway. For example, there is evidence that changes in estrogen levels among women could drive a more severe downstream response to amyloidosis, an effect that could be enhanced among ε4 carriers given evidence that estradiol treatment drives APOE release from microglia. A second possibility is that late-life changes in estrogen levels among women have a direct effect on tau. For example, estradiol appears to protect against tau hyperphosphorylation, particularly among female rats, and estrogen receptor α colocalizes with neurofibrillary tangles at autopsy. Interestingly, the α receptor also appears to be responsible for the estrogen-mediated upregulation of APOE expression, suggesting a third possible mechanism in which estrogen and APOE act synergistically in postmenopausal women. Thoughtful, modern experimental approaches are needed to better understand the potential contribution of gonadal hormone differences between men and women in driving the observed APOE sex differences.

In contrast to the CSF biomarker results, we did not observe a sex difference in the association between APOE and neurofibrillary tangle load at autopsy. There are a few potential explanations for this counterintuitive observation. Notably, there is growing evidence that CSF tau is a better marker...
of the intensity of neurodegeneration than the stage of neurofibrillary tangle deposition, suggesting the autopsy and biomarker metrics may represent 2 distinct processes. Therefore, 1 possibility is that sex-specific effects of APOE contribute to differences in neurodegeneration that are not directly mediated by changes in neurofibrillary tangle burden. Other markers of neurodegeneration, including hippocampal volume and cerebral hypometabolism, show sex-specific effects of APOE-ε4 that may underlie the observed differences in CSF tau levels. A second possibility is that the age difference between the autopsy cohorts and biomarker cohorts in this analysis contribute to the observed discrepancy between CSF and autopsy measures of tau. Evidence indicates that both the detrimental effect of APOE-ε4 and the sex difference in APOE-ε4 effect diminishes among the oldest elderly individuals, suggesting that subtle age differences could have a large influence on results. In support of such a possibility, we do observe the strongest effects on CSF tau in the younger individuals when stratifying the CSF sample into younger elderly and older elderly adults (eTables 3 and 4 in the Supplement). However, even among the younger elderly adults, we did not observe a sex-specific effect of APOE on autopsy metrics, suggesting this age difference does not fully account for the discrepancy.

In all analyses, we observed a strong association between APOE and amyloidosis that was consistent across men and women. APOE appears to drive risk for clinical AD through an amyloid clearance pathway, so it is not surprising that both here and previously APOE shows a stronger association with amyloid deposition than tau. Notably, we did not observe differences in the APOE association when comparing younger elderly with older elderly individuals (eTables 3 and 4 in the Supplement), although age differences have been reported. The larger sample (and enhanced power) in this analysis likely explains the discrepant findings because Ghemreldin et al observed patterns consistent with our findings but failed to observe a statistically significant association in the younger group. Importantly, our primary and post hoc analyses support the notion that APOE shows a consistent association with amyloidosis across sex and age and is unlikely to drive observed sex differences in the association between APOE and clinical AD.

### Strengths and Limitations

This study has multiple strengths, including the large sample size, the integration of both CSF biomarker data and autopsy data, and the extensive sensitivity analyses including explorations into diagnostic status, age, amyloid status, and educational attainment. However, the study is not without limitations. One important limitation is the potential influence of sex differences in survival to older adulthood, which could contribute to a robust survivor effect among men compared with women. As others have previously highlighted, selective survival of men with substantially lower cardiovascular risk profiles may contribute to sex differences in AD risk in older adulthood. It is also notable that the sex-specific effect of APOE-ε4 on microbleeds is actually in the inverse direction, with men showing a stronger association than women, suggesting that sex-specific effects of APOE-ε4 may have differential effects on AD and non-AD pathologies, even in the face of potential survivor bias. Future work is needed to develop and integrate modern statistical approaches to estimate and account for the effect of survival bias, particularly in analyses of sex-specific molecular drivers of AD and non-AD neuropathologies. The cross-sectional nature of the biomarker and autopsy data also limits our ability to make causal inferences, particularly with respect to the sequential ordering of neuropathologies or CSF biomarker deposition. Finally, the cohorts were relatively homogeneous across race and ethnicity, with some cohorts being exclusively white. Thus, findings may not be generalizable to other racial and ethnic groups that may be at greater risk of AD. Results will need to be extended to cohorts with greater diversity.

### Conclusions

These results provide strong evidence of sex differences in the association between APOE and CSF tau levels that do not appear to reflect differences in neurofibrillary tangle deposition. Future work should evaluate the genetic drivers of plaques, tangles, neurodegeneration, and cognitive impairment in a sex-specific manner to identify novel pathways of risk.
Sex-Specific Association of Apolipoprotein E With Cerebrospinal Fluid Levelsof Tau

Research  
Original Investigation  

Department of Neurology, the Johns Hopkins University School of Medicine, Baltimore, Maryland (Albert).

Author Contributions: Dr Hohman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Hohman, Barnes, Larson, Jefferson.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Hohman, Dumitrescu, Thambisetty.

Critical revision of the manuscript for important intellectual content: Hohman, Dumitrescu, Barnes, Beecham, Kunkle, Gifford, Bush, Chibnik, Mukherjee, De Jager, Kukul, Crane, Resnick, Keene, Montine, Schellenberg, Haines, Zetterberg, Blennow, Bennis, Larson, Albert, Bennett, Schneider, Jefferson.

Statistical analysis: Hohman, Dumitrescu, Bush, Chibnik, Haines.

Obtained funding: Hohman, Montine, Schellenberg, Haines, Blennow, Larson, Johnson, Bennett, Schneider.

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Supervision: Hohman, Barnes, Montine, Schellenberg, Bennett, Jefferson.

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