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

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 Supplemental content

**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  $\beta$ -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*- $\epsilon$ 4 and sex on CSF total tau ( $\beta = 0.41$ ; 95% CI, 0.27-0.55;  $P < .001$ ) and phosphorylated tau ( $\beta = 0.24$ ; 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 ( $\beta = 0.41$ ; 95% CI, 0.20-0.62;  $P < .001$ ) but not among amyloid-negative individuals ( $\beta = 0.06$ ; 95% CI, -0.18 to 0.31;  $P = .62$ ). We did not observe sex differences in the association between *APOE* and  $\beta$ -amyloid 42, neuritic plaque burden, or neurofibrillary tangle burden.

**CONCLUSIONS AND RELEVANCE** We provide robust evidence of a stronger association between *APOE*- $\epsilon$ 4 and CSF tau levels among women compared with men across multiple independent data sets. Interestingly, *APOE*- $\epsilon$ 4 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.

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**A**polipoprotein E (*APOE*) is the strongest genetic risk factor for sporadic Alzheimer disease (AD),<sup>1</sup> explaining approximately 13% of the phenotypic variance.<sup>2</sup> The  $\epsilon 4$  allele increases risk for AD in a dose-dependent manner, and the strength of the association varies by age and sex.<sup>3</sup> The effect of *APOE*- $\epsilon 4$  is strongest prior to age 70 years, declines after age 85 years, and is more robust among women compared with men,<sup>3</sup> especially women between age 55 and 70 years.<sup>4</sup> Although this sex difference has been well established after a 2017 comprehensive meta-analysis,<sup>4</sup> 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,<sup>5,6</sup> cerebrovascular disease,<sup>7</sup> amyloidosis,<sup>8,9</sup> neurodegeneration,<sup>10</sup> and tau tangle pathology.<sup>11</sup> 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*- $\epsilon 4$  has a strong association with amyloidosis,<sup>8,9</sup> even among older adults without dementia,<sup>12</sup> likely through its role in amyloid clearance.<sup>13</sup> Research leveraging in vivo biomarkers of amyloid has indicated that the association between *APOE*- $\epsilon 4$  and amyloidosis is consistent across sexes,<sup>8,14-16</sup> yet other work has found evidence of age-dependent sex differences in the effects of *APOE*- $\epsilon 4$  on amyloidosis.<sup>17,18</sup> In the case of tau pathology, *APOE*- $\epsilon 4$  is associated with higher levels of cerebrospinal fluid (CSF) tau<sup>19</sup> and more neurofibrillary tangles at autopsy,<sup>11</sup> although these associations are relegated to individuals with high levels of amyloid pathology.<sup>16</sup> The evidence of a sex difference in the association between *APOE* and tau pathology is also mixed, with some biomarker<sup>15,19</sup> and autopsy<sup>18</sup> work suggesting women show a more robust association between *APOE*- $\epsilon 4$  and tau, while other work has reported no sex difference.<sup>14,20,21</sup>

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.<sup>22</sup> The Wis-

## Key Points

**Question** Does the association between apolipoprotein E (*APOE*) and Alzheimer disease neuropathology differ by sex?

**Findings** In this multicohort study, women showed a stronger association between *APOE* and cerebrospinal fluid tau levels when compared with men, particularly among amyloid-positive individuals. There was no sex difference in the association between *APOE* and amyloidosis or between *APOE* and autopsy measures of neurofibrillary tangles.

**Meaning** The sex difference in the association between *APOE* and cerebrospinal fluid measures of tau and the lack of a sex difference in the association with neurofibrillary tangles at autopsy suggests that *APOE* may modulate risk for neurodegeneration in a sex-specific manner, particularly in the presence of amyloidosis.

consin 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.<sup>23</sup> 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.<sup>24</sup> 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://www.adni-info.org>).

The autopsy database was derived from data published by Beecham et al<sup>25</sup> evaluating genetic markers of AD neuropathology, which includes cohort descriptions.<sup>25</sup> 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.<sup>25</sup> 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.<sup>26,27</sup> 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.<sup>28</sup> 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

Characteristic	No. (%)							
	BIOCARD (n = 275)		WRAP (n = 154)		ADNI (n = 1213)		VMAP (n = 156)	
	Men	Women	Men	Women	Men	Women	Men	Women
Total No. (%)	113 (41)	162 (59)	53 (34)	101 (66)	665 (55)	548 (45)	105 (67)	51 (33)
Age, mean (SD), y	62 (10)	59 (9)	62 (6)	63 (7)	74 (7)	72 (7)	72 (6)	72 (7)
White race/ethnicity	110 (97)	157 (97)	51 (96)	95 (94)	624 (94)	508 (93)	99 (94)	47 (92)
Clinical diagnosis								
Normal cognition	101 (90)	159 (99)	44 (83)	88 (87)	175 (26)	199 (36)	58 (55)	25 (49)
Mild cognitive impairment	11 (10)	2 (1)	9 (17)	12 (13)	358 (54)	255 (47)	46 (45)	26 (51)
Alzheimer disease	0	0	0	0	132 (20)	94 (17)	0	0
APOE $\epsilon$ 4 count								
0 $\epsilon$ 4 Alleles	75 (66)	104 (64)	36 (68)	62 (61)	357 (54)	297 (54)	68 (65)	35 (69)
1 $\epsilon$ 4 Allele	29 (26)	51 (31)	17 (32)	34 (34)	234 (35)	203 (37)	29 (28)	10 (20)
2 $\epsilon$ 4 Alleles	9 (8)	7 (4)	0	5 (5)	70 (11)	47 (9)	8 (8)	6 (12)
APOE $\epsilon$ 2 carriers	11 (10)	24 (15)	7 (13)	15 (15)	59 (9)	57 (10)	9 (9)	8 (16)
Amyloid positive	55 (49)	60 (37)	5 (9)	13 (13)	426 (64)	334 (61)	21 (20)	16 (31)
Tau positive	38 (43)	51 (31)	4 (8)	14 (14)	217 (33)	224 (41)	33 (31)	21 (41)
A $\beta$ 42, pg/mL, mean (SD)	370 (89)	395 (99)	714 (179)	736 (217)	172 (55)	178 (54)	751 (247)	634 (226)
Total tau, pg/mL, mean (SD)	68 (35)	70 (32)	308 (116)	321 (116)	86 (49)	96 (61)	404 (190)	474 (282)
Phosphorylated tau, pg/mL, mean (SD)	38 (13)	40 (17)	45 (16)	48 (15)	38 (21)	41 (27)	59 (23)	66 (30)

Abbreviations: A $\beta$ 42,  $\beta$ -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.

death. The collection of VMAP data and secondary analyses of all data were approved by the Vanderbilt University Medical Center institutional review board. All study participants provided written consent to the data collection and laboratory analyses proposed as part of their participation in the primary studies.

### APOE Genotyping

As previously reported,<sup>29</sup> APOE haplotypes ( $\epsilon$ 2,  $\epsilon$ 3, and  $\epsilon$ 4) were determined using single-nucleotide polymorphisms rs7412 and rs429358 in Adult Changes in Thought, Biomarkers of Cognitive Decline Among Normal Individuals, Mayo Clinic, National Alzheimer's Coordinating Center, National Institute on Aging Late-Onset Alzheimer's Disease Family Study, VMAP, and the Wisconsin Registry of Alzheimer's Prevention. Pyrosequencing, restriction fragment length polymorphism analysis, and high-throughput sequencing of APOE codons 112 and 158 were performed in ADNI, the Religious Orders Study and Rush Memory and Aging Project, and Translational Genomics Research Institute data sets to derive APOE haplotypes.

### Quantification of Biomarker Outcomes

Cerebrospinal fluid biomarkers have been measured in ADNI, Biomarkers of Cognitive Decline Among Normal Individuals, the Wisconsin Registry of Alzheimer's Prevention, and VMAP previously. The ADNI<sup>30</sup> and Biomarkers of Cognitive Decline Among Normal Individuals<sup>31</sup> were analyzed by the same laboratory using the same procedure. Similarly, the Wisconsin Registry of Alzheimer's Prevention<sup>32</sup> and VMAP<sup>22</sup> were analyzed

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)<sup>33</sup> and a measure of neuritic plaques (Consortium to Establish a Registry for Alzheimer's Disease [CERAD] neuritic plaque score)<sup>34</sup> 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

Characteristic	NACC (n = 2225)		ROS/MAP (n = 1259)		ACT (n = 381)		LOAD-Braak (n = 277)		LOAD-CERAD (n = 207)		Mayo Clinic (n = 392)		TGEN-Braak (n = 575)		TGEN-CERAD (n = 175)	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Total No. (%)	1133 (51)	1092 (49)	435 (35)	824 (65)	179 (47)	202 (53)	99 (36)	178 (64)	84 (41)	123 (59)	224 (57)	168 (43)	226 (39)	349 (61)	81 (46)	94 (54)
Age, mean (SD), y	82 (9)	85 (9)	87 (7)	90 (6)	85 (4)	86 (5)	84 (8)	77 (9)	76 (9)	79 (9)	72 (5)	73 (6)	79 (8)	83 (8)	80 (8)	83 (9)
White race/ethnicity	1082 (95)	1021 (93)	427 (98)	798 (97)	178 (99)	201 (100)	99 (100)	178 (100)	84 (100)	123 (100)	224 (100)	168 (100)	226 (100)	349 (100)	81 (100)	94 (100)
Clinical diagnosis																
Normal cognition	167 (15)	228 (21)	148 (34)	260 (32)	116 (66)	128 (63)	15 (15)	29 (16)	19 (23)	31 (25)	123 (55)	71 (42)	97 (43)	88 (25)	36 (44)	37 (39)
Mild cognitive impairment	113 (10)	104 (10)	116 (27)	202 (25)	0	0	0	0	0	0	0	0	0	0	0	0
AD	853 (75)	760 (70)	171 (39)	362 (44)	61 (34)	74 (37)	84 (85)	149 (84)	65 (77)	92 (75)	101 (45)	97 (58)	129 (57)	261 (75)	45 (56)	57 (61)
APOE ε4 count																
0 ε4 Alleles	585 (52)	603 (55)	319 (73)	608 (74)	133 (74)	145 (72)	31 (31)	68 (38)	29 (35)	49 (40)	127 (57)	96 (57)	117 (52)	160 (46)	47 (58)	54 (57)
1 ε4 Allele	427 (38)	402 (37)	110 (25)	199 (24)	45 (25)	50 (25)	48 (48)	88 (49)	37 (44)	58 (47)	82 (37)	56 (33)	85 (38)	137 (39)	26 (32)	29 (31)
2 ε4 Alleles	121 (11)	87 (8)	6 (1)	17 (2)	1 (1)	7 (4)	20 (20)	22 (12)	18 (21)	16 (13)	15 (7)	16 (10)	24 (11)	52 (15)	8 (10)	11 (12)
APOE ε2 carriers	101 (9)	126 (12)	61 (14)	130 (16)	26 (15)	15 (7)	6 (6)	16 (9)	8 (10)	10 (8)	21 (9)	21 (12)	26 (12)	36 (10)	10 (12)	10 (11)
Neuritic plaque positive (CERAD ≥ moderate)	798 (70)	754 (69)	317 (73)	652 (79)	82 (46)	103 (51)	NA	NA	67 (80)	94 (76)	99 (44)	97 (58)	NA	NA	46 (57)	59 (63)
Tangle positive (Braak ≥ III)	908 (80)	879 (80)	323 (74)	708 (86)	104 (58)	129 (64)	91 (92)	159 (89)	NA	NA	119 (53)	106 (63)	134 (59)	268 (77)	NA	NA

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.

Table 3. Results

Predictor	CSF Biomarker Results			Autopsy Results					
	Total Tau	Phosphorylated Tau	A $\beta$ 42	Braak	CERAD	NFT Positivity <sup>a</sup>	Neuritic Plaque Positivity <sup>b</sup>		
	$\beta$ (95% CI)	$\beta$ (95% CI)	$\beta$ (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)		
Female sex	0.11 (0.06 to 0.15)	0.07 (0.02 to 0.11)	0.04 (0.01 to -0.03 to 0.05)	1.32 (1.19 to 1.47)	1.29 (1.15 to 1.44)	1.34 (1.16 to 1.54)	1.22 (1.07 to 1.40)		
APOE $\epsilon$ 2	-0.10 (-0.15 to -0.06)	-0.10 (-0.15 to -0.06)	0.14 (0.10 to 0.19)	<.001 <sup>c</sup>	0.38 (0.32 to 0.45)	0.46 (0.38 to 0.57)	0.38 (0.31 to 0.46)		
APOE $\epsilon$ 4	0.28 (0.24 to 0.33)	0.28 (0.24 to 0.33)	-0.48 (-0.52 to -0.44)	<.001 <sup>c</sup>	2.96 (2.66 to 3.29)	3.64 (3.13 to 4.24)	3.11 (2.73 to 3.55)		
Sex $\times$ APOE $\epsilon$ 2	-0.10 (-0.25 to 0.05)	-0.10 (-0.25 to 0.05)	0.01 (-0.14 to 0.16)	.88	0.94 (0.67 to 1.32)	0.88 (0.59 to 1.32)	0.94 (0.63 to 1.39)		
Sex $\times$ APOE $\epsilon$ 4	0.41 (0.27 to 0.55)	0.24 (0.09 to 0.38)	0.01 (-0.12 to 0.14)	.87	1.12 (0.91 to 1.38)	0.83 (0.61 to 1.12)	1.16 (0.89 to 1.52)		

Abbreviations: A $\beta$ 42,  $\beta$ -amyloid 42; CSF, cerebrospinal fluid; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; NFT, neurofibrillary tangle; OR, odds ratio.

<sup>a</sup> Neurofibrillary tangle positivity was defined as Braak stage III, IV, V, or VI.

<sup>b</sup> Neuritic plaque positivity was defined as CERAD neuritic plaque stage of "moderate" or "frequent."

<sup>c</sup> Associations that remain statistically significant after correcting for multiple comparisons.

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- $\epsilon$ 2 and APOE- $\epsilon$ 4 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  $\epsilon$ 2 and an additive model for  $\epsilon$ 4. 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  $\beta$ -amyloid 42, 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  $\beta$ -amyloid 42, t-tau, and phosphorylated tau) and 4 autopsy outcomes (ordinal and binary outcomes of CERAD and Braak staging), resulting in 35 independent tests (corrected  $\alpha = .0014$ ).

Post hoc analyses evaluated sex by APOE- $\epsilon$ 4 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- $\epsilon$ 4 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- $\epsilon$ 4 was associated with higher levels of biomarker levels and pathology and  $\epsilon$ 2 was associated with lower biomarker levels and pathology for all metrics.

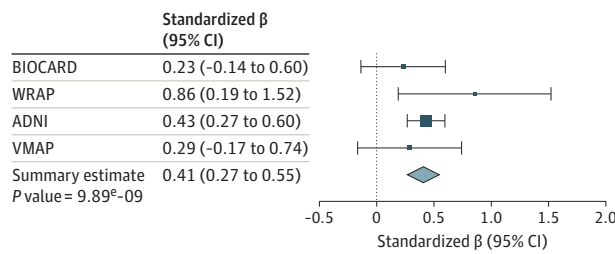
### Sex by APOE Interactions: CSF Biomarker Results

Interaction results are presented in Table 3. A sex by APOE- $\epsilon$ 4 interaction was observed on both t-tau (Figure 1) and phosphorylated tau wherein the association between APOE- $\epsilon$ 4 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.

Figure 1. APOE Interaction With Sex on CSF Total Tau



Forest plot summarizing the analysis of *APOE*  $\epsilon 4 \times$  sex interactions on CSF total tau modeled as a continuous outcome. Squares represent standardized  $\beta$  of the interaction term within each data set; confidence interval is represented by the line segment. The size of the square indicates precision of the estimate based on study variance. The fixed-effect  $\beta$  is represented by the diamond at the bottom of the figure. BIOCARD indicates Biomarkers of Cognitive Decline Among Normal Individuals; WRAP, Wisconsin Registry of Alzheimer's Prevention; ADNI, Alzheimer's Disease Neuroimaging Initiative; VMAP, Vanderbilt Memory and Aging Project.

### Post Hoc Analyses

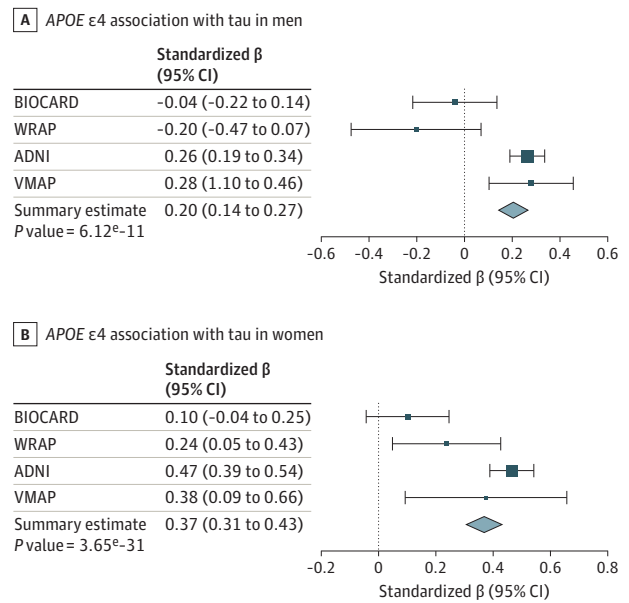
In post hoc analyses stratified by amyloid status, the sex by *APOE*- $\epsilon 4$  interaction was present among amyloid-positive individuals ( $\beta = 0.41$ ; 95% CI, 0.20 to 0.62;  $P < .001$ ; eTable 1 in the Supplement) but not amyloid-negative individuals ( $\beta = 0.06$ ; 95% CI, -0.18 to 0.31;  $P = .62$ ; 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*- $\epsilon 4$  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*- $\epsilon 4$  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*- $\epsilon 4$  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,<sup>14,20</sup> although results have been somewhat mixed depending on the sample included<sup>21</sup> 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*- $\epsilon 4$  and CSF phosphorylated tau for the first time. Several mechanisms could

Figure 2. APOE Association With CSF Total Tau Stratified by Sex



A, *APOE*- $\epsilon 4$  association with CSF tau in men. B, *APOE*- $\epsilon 4$  association with CSF tau in women. Forest plot summarizing the sex-stratified analysis of *APOE*  $\epsilon 4$  on CSF total tau modeled as a continuous outcome. Squares represent standardized  $\beta$  of the *APOE*  $\epsilon 4$  term within each data set; confidence interval is represented by the line segment. The size of the square indicates precision of the estimate based on study variance. The fixed-effect  $\beta$  is represented by the diamond at the bottom of the figure. BIOCARD indicates Biomarkers of Cognitive Decline Among Normal Individuals; WRAP, Wisconsin Registry of Alzheimer's Prevention; ADNI, Alzheimer's Disease Neuroimaging Initiative; VMAP, Vanderbilt Memory and Aging Project.

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,<sup>35-37</sup> an effect that could be enhanced among  $\epsilon 4$  carriers given evidence that estradiol treatment drives *APOE* release from microglia.<sup>38</sup> 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,<sup>39</sup> and estrogen receptor  $\alpha$  colocalizes with neurofibrillary tangles at autopsy.<sup>40</sup> Interestingly, the  $\alpha$  receptor also appears to be responsible for the estrogen-mediated upregulation of *APOE* expression,<sup>41</sup> 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.<sup>42</sup>

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,<sup>43</sup> 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<sup>44,45</sup> and cerebral hypometabolism,<sup>21</sup> 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,<sup>3,4</sup> 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,<sup>13</sup> so it is not surprising that both here and previously<sup>46</sup> *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.<sup>47</sup> The larger sample (and enhanced power) in this analysis likely explains the discrepant findings because Ghebremedhin et al<sup>47</sup> 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.<sup>48</sup>

## 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.<sup>49</sup> It is also notable that the sex-specific effect of *APOE-ε4* on microbleeds is actually in the inverse direction,<sup>50</sup> 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.

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