Title
Sex-chromosome dosage effects on gene expression in humans.

Journal
Proceedings of the National Academy of Sciences of the United States of America, 115(28)

ISSN
0027-8424

Authors
Raznahan, Armin
Parikshak, Neelroop N
Chandran, Vijay
et al.

Publication Date
2018-07-01

DOI
10.1073/pnas.1802889115

Peer reviewed

JAMA Neurology | Original Investigation

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

Timothy J. Hohman, PhD; Logan Dumitrescu, PhD; Lisa L. Barnes, PhD; Madhav Thambisetty, MD, PhD; Gary Beecham, PhD; Brian Kunkle, PhD, MPH; Katherine A. Gifford, PsyD; William S. Bush, PhD; Lori B. Chibnik, PhD; Shubhabrata Mukherjee, PhD; Philip L. De Jager, MD, PhD; Walter Kukull, PhD; Paul K. Crane, MD; Susan M. Resnick, PhD; C. Dirk Keene, MD, PhD; Thomas J. Montine, MD, PhD; Gerard D. Schellenberg, PhD; Jonathan L. Haines, PhD; Henrik Zetterberg, MD, PhD; Kaj Blennow, MD, PhD; Eric B. Larson, MD, MPH; Sterling C. Johnson, PhD; Marilyn Albert, PhD; David A. Bennett, MD; Julie A. Schneider, MD; Angela L. Jefferson, PhD; for the Alzheimer's Disease Genetics Consortium and the Alzheimer's Disease Neuroimaging Initiative

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.

JAMA Neurol. 2018;75(8):989-998. doi:10.1001/jamaneurol.2018.0821
Published online May 7, 2018.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the Alzheimer's Disease Genetics Consortium and the Alzheimer's Disease Neuroimaging Initiative appear at the end of the article.

Corresponding Author: Timothy J. Hohman, PhD, Vanderbilt Memory and Alzheimer's Center, Vanderbilt University Medical Center, 1207 17th Ave S, Nashville, TN 37212 (timothy.j.hohman@vanderbilt.edu).

Apolipoprotein E (*APOE*) is the strongest genetic risk factor for sporadic Alzheimer disease (AD),[1] explaining approximately 13% of the phenotypic variance.[2] The ε4 allele increases risk for AD in a dose-dependent manner, and the strength of the association varies by age and sex.[3] 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,[3] especially women between age 55 and 70 years.[4] Although this sex difference has been well established after a 2017 comprehensive meta-analysis,[4] 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,[5,6] cerebrovascular disease,[7] amyloidosis,[8,9] neurodegeneration,[10] and tau tangle pathology.[11] 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,[8,9] even among older adults without dementia,[12] likely through its role in amyloid clearance.[13] Research leveraging in vivo biomarkers of amyloid has indicated that the association between *APOE*-ε4 and amyloidosis is consistent across sexes,[8,14-16] yet other work has found evidence of age-dependent sex differences in the effects of *APOE*-ε4 on amyloidosis.[17,18] In the case of tau pathology, *APOE*-ε4 is associated with higher levels of cerebrospinal fluid (CSF) tau[19] and more neurofibrillary tangles at autopsy,[11] although these associations are relegated to individuals with high levels of amyloid pathology.[16] The evidence of a sex difference in the association between *APOE* and tau pathology is also mixed, with some biomarker[15,19] and autopsy[18] work suggesting women show a more robust association between *APOE*-ε4 and tau, while other work has reported no sex difference.[14,20,21]

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.

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.

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.[22] 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.[23] 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.[24] 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[25] evaluating genetic markers of AD neuropathology, which includes cohort descriptions.[25] 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.[25] 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.[26,27] 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.[28] 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 ε4 count								
0 ε4 Alleles	75 (66)	104 (64)	36 (68)	62 (61)	357 (54)	297 (54)	68 (65)	35 (69)
1 ε4 Allele	29 (26)	51 (31)	17 (32)	34 (34)	234 (35)	203 (37)	29 (28)	10 (20)
2 ε4 Alleles	9 (8)	7 (4)	0	5 (5)	70 (11)	47 (9)	8 (8)	6 (12)
APOE ε2 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)
Aβ42, 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: 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.

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,[29] *APOE* haplotypes (ε2, ε3, and ε4) 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[30] and Biomarkers of Cognitive Decline Among Normal Individuals[31] were analyzed by the same laboratory using the same procedure. Similarly, the Wisconsin Registry of Alzheimer's Prevention[32] and VMAP[22] 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)[33] and a measure of neuritic plaques (Consortium to Establish a Registry for Alzheimer's Disease [CERAD] neuritic plaque score)[34] 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	No. (%)													
	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		Aβ42		Braak		CERAD		NFT Positivity[a]		Neuritic Plaque Positivity[b]	
	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Female sex	0.11 (0.06 to 0.15)	<.001[c]	0.07 (0.02 to 0.11)	.004	0.01 (−0.03 to 0.05)	.60	1.32 (1.19 to 1.47)	<.001[c]	1.29 (1.15 to 1.44)	<.001[c]	1.34 (1.16 to 1.54)	<.001[c]	1.22 (1.07 to 1.40)	.004
APOE ε2	−0.10 (−0.15 to −0.06)	<.001[c]	−0.10 (−0.15 to −0.06)	<.001[c]	0.14 (0.10 to 0.19)	<.001[c]	0.44 (0.38 to 0.51)	<.001[c]	0.38 (0.32 to 0.45)	<.001[c]	0.46 (0.38 to 0.57)	<.001[c]	0.38 (0.31 to 0.46)	<.001[c]
APOE ε4	0.28 (0.24 to 0.33)	<.001[c]	0.28 (0.24 to 0.33)	<.001[c]	−0.48 (−0.52 to −0.44)	<.001[c]	2.62 (2.39 to 2.86)	<.001[c]	2.96 (2.66 to 3.29)	<.001[c]	3.64 (3.13 to 4.24)	<.001[c]	3.11 (2.73 to 3.55)	<.001[c]
Sex × *APOE* ε2	−0.10 (−0.25 to 0.05)	.20	−0.10 (−0.25 to 0.05)	.19	0.01 (−0.14 to 0.16)	.88	0.89 (0.65 to 1.22)	.47	0.94 (0.67 to 1.32)	.72	0.88 (0.59 to 1.32)	.53	0.94 (0.63 to 1.39)	.74
Sex × *APOE* ε4	0.41 (0.27 to 0.55)	<.001[c]	0.24 (0.09 to 0.38)	.001[c]	0.01 (−0.12 to 0.14)	.87	0.85 (0.72 to 1.01)	.07	1.12 (0.91 to 1.38)	.30	0.83 (0.61 to 1.12)	.22	1.16 (0.89 to 1.52)	.26

Abbreviations: Aβ42, β-amyloid 42; CSF, cerebrospinal fluid; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; NFT, neurofibrillary tangle; OR, odds ratio.

[a] Neurofibrillary tangle positivity was defined as Braak stage III, IV, V, or VI.

[b] Neuritic plaque positivity was defined as CERAD neuritic plaque stage of "moderate" or "frequent."

[c] 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*-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-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 β-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 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.

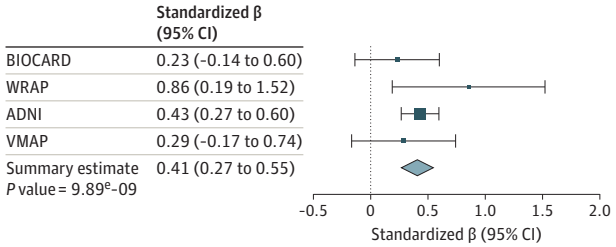
Sex by *APOE* Interactions: CSF Biomarker Results

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

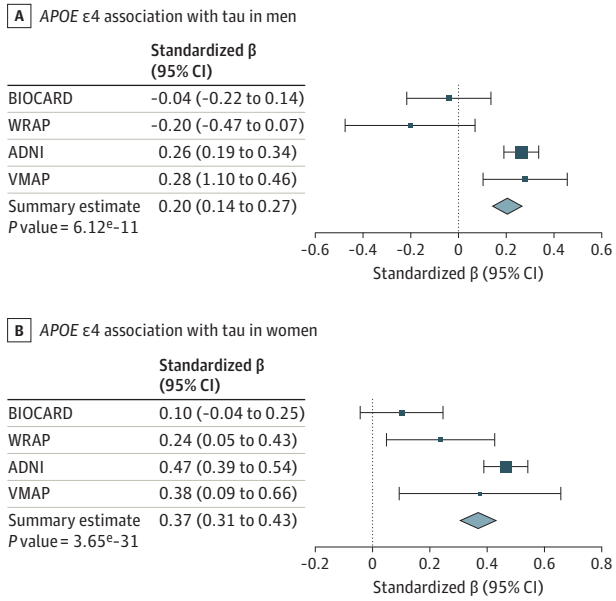
Autopsy interaction results are also presented in Table 3. There were no significant interactions between sex and *APOE* on neuropathology.

Figure 1. *APOE* Interaction With Sex on CSF Total Tau



Forest plot summarizing the analysis of *APOE* ε4 × sex interactions on CSF total tau modeled as a continuous outcome. Squares represent standardized β 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 β 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.

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



A, *APOE*-ε4 association with CSF tau in men. B, *APOE*-ε4 association with CSF tau in women. Forest plot summarizing the sex-stratified analysis of *APOE* ε4 on CSF total tau modeled as a continuous outcome. Squares represent standardized β of the *APOE* ε4 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 β 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*-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,[14,20] although results have been somewhat mixed depending on the sample included[21] 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,[35-37] an effect that could be enhanced among ε4 carriers given evidence that estradiol treatment drives *APOE* release from microglia.[38] 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,[39] and estrogen receptor α colocalizes with neurofibrillary tangles at autopsy.[40] Interestingly, the α receptor also appears to be responsible for the estrogen-mediated upregulation of *APOE* expression,[41] 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.[42]

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,[43] 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[44,45] and cerebral hypometabolism,[21] 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,[3,4] 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,[13] so it is not surprising that both here and previously[46] *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.[47] The larger sample (and enhanced power) in this analysis likely explains the discrepant findings because Ghebremedhin et al[47] observed patterns consistent with our findings but failed to observe a statistically significance 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.[48]

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 amongmen 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.[49] It is also notable that the sex-specific effect of *APOE*-ε4 on microbleeds is actually in the inverse direction,[50] 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.

ARTICLE INFORMATION

Accepted for Publication: February 8, 2018.

Published Online: May 7, 2018. doi:10.1001/jamaneurol.2018.0821

Author Affiliations: Vanderbilt Memory and Alzheimer's Center, Vanderbilt University Medical Center, Nashville, Tennessee (Hohman, Dumitrescu, Gifford, Jefferson); Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois (Barnes, Bennett, Schneider); Unit of Clinical and Translational Neuroscience, Laboratory of Behavioral Neuroscience, National Institute on Aging, National Institutes of Health, Baltimore, Maryland (Thambisetty, Resnick); John T MacDonald Foundation Department of Human Genetics, University of Miami, Miami, Florida (Beecham); Hussman Institute for Human Genomics, University of Miami School of Medicine, Miami, Florida (Beecham, Kunkle); Department of Population and Quantitative Health Sciences, Institute for Computational Biology, Case Western Reserve University, Cleveland, Ohio (Bush); Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Chibnik, Haines); Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, Massachusetts (Chibnik); Department of Medicine, University of Washington, Seattle (Mukherjee, Crane, Larson); Center for Translational and Computational Neuroimmunology, Department of Neurology, Columbia University Medical Center, New York, New York (De Jager); Cell Circuits Program, Broad Institute, Cambridge, Massachusetts (De Jager); Department of Epidemiology, School of Public Health, University of Washington, Seattle (Kukull); Department of Pathology, University of Washington, Seattle (Keene); Department of Pathology, Stanford University, Stanford, California (Montine); Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Schellenberg); Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg, Mölndal, Sweden (Zetterberg, Blennow); Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden (Zetterberg, Blennow); Department of Molecular Neuroscience, University College London Institute of Neurology, Queen Square, London, England (Blennow); UK Dementia Research Institute, London, England (Zetterberg); Kaiser Permanente Washington Health Research Institute, Seattle (Larson); Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, Madison (Johnson);

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, Kukull, Crane, Resnick, Keene, Montine, Schellenberg, Haines, Zetterberg, Blennow, Larson, Johnson, Albert, Bennett, Schneider, Jefferson.
Statistical analysis: Hohman, Dumitrescu, Bush, Chibnik, Haines.
Obtained funding: Hohman, Montine, Schellenberg, Haines, Blennow, Larson, Johnson, Bennett.
Administrative, technical, or material support: Barnes, Thambisetty, Gifford, Mukherjee, Crane, Keene, Montine, Schellenberg, Zetterberg, Larson, Bennett, Schneider.
Supervision: Hohman, Barnes, Montine, Schellenberg, Bennett, Jefferson.

Conflict of Interest Disclosures: Dr Larson reports royalties from UpToDate. Dr Schneider reports personal fees from Avid Radiopharmaceuticals and Navidea Biopharmaceuticals outside the submitted work. Dr Zetterberg has served at advisory boards of Eli Lilly, Roche Diagnostics, and Pharmasum Therapeutics and is one of the founders of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures–based platform company at the University of Gothenburg. Dr Blennow has served at advisory boards of Alzheon, Eli Lilly, IBL International, Fujirebio, Merck, and Roche Diagnostics and is one of the founders of Brain Biomarker Solutions in Gothenburg AB.

Funding/Support: This research was supported in part by grants K01 AG049164, K12 HD043483, K24 AG046373, HHSN311201600276P, R01 AG034962, R01 HL111516, R01 NS100980, R01 AG056534, P30 AG10161, RF1 AG15819, R01 AG17917, R01 AG30146, R01 AG019085, R01 AG15819, R01 AG17917, R01 AG30146, R01 AG027161, R01 AG021155, R01 AG037639, U01 AG46152, U01 AG006781, U01 AG032984, U01 HG004610, U01 HG006375, U24 AG021886, and U24 AG041689 from the Intramural Research Program, the National Institute on Aging, the National Institutes of Health, and the Vanderbilt Memory and Alzheimer's Center. The National Alzheimer's Coordinating Center database is funded by the National Institute on Aging and National Institutes of Health grant U01 AG016976. National Alzheimer's Coordinating Center data are contributed by the National Institute of Aging–funded Alzheimer's Disease Centers: P30 AG019610 (principal investigator [PI], Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI, Scott Small, MD), P50 AG025688 (PI, Allan Levey, MD, PhD), P30 AG010133 (PI, Andrew Saykin, PsyD), P50 AG005146 (PI, Marilyn Albert, PhD), P50 AG005134 (PI, Bradley Hyman, MD, PhD), P50 AG016574 (PI, Ronald Petersen, MD, PhD), P50 AG005138 (PI, Mary Sano, PhD), P30 AG008051 (PI, Steven Ferris, PhD), P30 AG013854 (PI, M. Marsel Mesulam, MD), P30 AG008017 (PI, Jeffrey Kaye, MD), P30 AG010161 (PI, David Bennett, MD), P30 AG010129 (PI, Charles DeCarli, MD), P50 AG016573 (PI, Frank LaFerla, PhD), P50 AG016570 (PI, David Teplow, PhD), P50 AG005131 (PI, Douglas Galasko, MD), P50 AG023501 (PI, Bruce Miller, MD), P30 AG035982 (PI, Russell Swerdlow, MD), P30 AG028383 (PI, Linda Van Eldik, PhD), P30 AG010124 (PI, John Trojanowski, MD, PhD), P50 AG005133 (PI, Oscar Lopez, MD), P50 AG005142 (PI, Helena Chui, MD), P30 AG012300 (PI, Roger Rosenberg, MD), P50 AG005136 (PI, Thomas Grabowski, MD, PhD), P50 AG033514 (PI, Sanjay Asthana, MD, FRCP), and P50 AG005681 (PI, John Morris, MD). Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (National Institutes of Health grant U01 AG024904) and US Department of Defense ADNI award number W81XWH-12-2-0012). The ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from AbbVie, Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Araclon Biotech, BioClinica Inc, Biogen, Bristol-Myers Squibb Company, CereSpir Inc, Cogstate, Eisai Inc, Elan Pharmaceuticals Inc, Eli Lilly and Company, EuroImmun, F. Hoffmann-La Roche Ltd and its affiliated company Genentech Inc, Fujirebio, GE Healthcare, IXICO Ltd, Janssen Alzheimer Immunotherapy Research and Development LLC, Johnson and Johnson Pharmaceutical Research and Development LLC, Lumosity, Lundbeck, Merck and Co Inc, Meso Scale Diagnostics LLC, NeuroRx Research, Neurotrack Technologies, Novartis Pharmaceuticals Corporation, Pfizer Inc, Piramal Imaging, Servier, Takeda Pharmaceutical Company, and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health. The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. The ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The members of the Alzheimer's Disease Genetics Consortium and the Alzheimer's Disease Neuroimaging Initiative are Erin Abner, PhD, University of Kentucky; Perrie Adams, PhD, University of Texas Southwestern Medical Center; Marilyn Albert, PhD, Johns Hopkins University; Roger Albin, MD, University of Michigan; Liana Apostolova, MD, Indiana University; Steven Arnold, MD, University of Pennsylvania Perelman School of Medicine; Sanjay Asthana, MD, University of Wisconsin; Craig Atwood, PhD, University of Wisconsin; Clinton Baldwin, PhD, Boston University; Robert Barber, PhD, University of North Texas Health Science Center; Lisa Barnes, PhD, Rush University Medical Center; Sandra Barral, PhD, Columbia University; Thomas Beach, MD, PhD, Banner Sun Health Research Institute; James Becker, PhD, University of Pittsburgh School of Medicine; Gary Beecham, PhD, University of Miami; Duane Beekly, BS. University of Washington; David Bennett, MD, Rush University Medical Center; Eileen Bigio, MD, Northwestern University Feinberg School of Medicine; Thomas Bird, MD, University of Washington; Deborah Blacker, MD, Harvard School of Public Health; Bradley Boeve, MD, Mayo Clinic; James Bowen, MD, Swedish Medical Center; Adam Boxer, MD, PhD, University of California San Francisco; James Burke, MD, PhD, Duke University; Jeffrey Burns, MD, MS, University of Kansas Medical Center; Joseph Buxbaum, PhD, Mount Sinai School of Medicine; Nigel Cairns, PhD FRCPath. Washington University; Laura Cantwell, MPH, University of Pennsylvania Perelman School of Medicine; Chuanhai Cao, PhD, University of South Florida; Chris Carlson, PhD, Fred Hutchinson Cancer Research Center; Cynthia Carlsson, MD, University of Wisconsin; Regina Carney, MD, University of Miami; Minerva Carrasquillo, PhD, Mayo Clinic; Helena Chui, MD, University of Southern California; Paul Crane, MD, MPH, University of Washington; David Cribbs, PhD, University of California Irvine; Elizabeth Crocco, MD, University of Miami; Carlos Cruchaga, PhD, Washington University School of Medicine; Philip De Jager, MD, PhD, Brigham and Women's Hospital and Harvard Medical School; Charles DeCarli, MD, University of California Davis; Malcolm Dick, PhD, University of California Irvine; Dennis Dickson, MD, Mayo Clinic; Rachelle Doody, MD, PhD, Baylor College of Medicine; Ranjan Duara, MD, Mount Sinai Medical Center; Nilufer Ertekin-Taner, MD, PhD, Mayo Clinic; Denis Evans, MD, Rush University Medical Center; Kelley Faber, MS, Indiana University; Thomas Fairchild, PhD, University of North Texas Health Science Center; Kenneth Fallon, MD, University of Alabama at Birmingham; David Fardo, PhD, University of Kentucky; Martin Farlow, MD, Indiana University; Lindsay Farrer, PhD, Boston University; Steven Ferris, PhD, New York University; Tatiana Foroud, PhD, Indiana University; Matthew Frosch, MD, PhD, Massachusetts General Hospital; Douglas Galasko, MD, University of California San Diego; Marla Gearing, PhD, Emory University; Daniel Geschwind, MD, PhD, University of California Los Angeles; Bernardino Ghetti, MD, Indiana University; John Gilbert, PhD, University of Miami; Alison Goate, D.Phil. Mount Sinai School of Medicine; Neill Graff-Radford, MD, Mayo Clinic; Robert Green, MD, MPH, Brigham and Women's Hospital and Harvard Medical School; John Growdon, MD, Massachusetts General Hospital/Harvard Medical School; Jonathan Haines, PhD, Case Western Reserve University; Hakon Hakonarson, MD, PhD, Children's Hospital of Philadelphia; Ronald Hamilton, MD, University of Pittsburgh; Kara Hamilton-Nelson, MPH, University of Miami; John Hardy, PhD, University College London; Lindy Harrell, MD, PhD, University of Alabama at Birmingham; Lawrence Honig, MD, PhD, Columbia University; Ryan Huebinger, PhD, University of Texas Southwestern Medical Center; Matthew Huentelman, PhD, Translational Genomics Research Institute; Christine Hulette, MD, Duke University; Bradley Hyman, MD, PhD, Massachusetts General Hospital/Harvard Medical School; Gail Jarvik, MD, PhD, University of Washington; Lee-Way Jin, MD, PhD, University of California Davis; Gyungah Jun, PhD, Boston University; M. Ilyas Kamboh, PhD, University of Pittsburgh; Anna Karydas, BA. University of California San Francisco; Mindy Katz, MPH, Albert

Einstein College of Medicine; John Kauwe, PhD, Brigham Young University; Jeffrey Kaye, MD, Oregon Health & Science University; C. Dirk Keene, MD, PhD, University of Washington; Ronald Kim, MD, University of California Irvine; Neil Kowall, MD, Boston University; Joel Kramer, PsyD. University of California San Francisco; Walter Kukull, PhD, University of Washington; Brian Kunkle, PHD MPH, University of Miami; Amanda Kuzma, MS, University of Pennsylvania Perelman School of Medicine; Frank LaFerla, PhD, University of California Irvine; James Lah, MD, PhD, Emory University; Eric Larson, MD, MPH, University of Washington; James Leverenz, MD, Cleveland Clinic; Allan Levey, MD, PhD, Emory University; Ge Li, MD, PhD, VA Puget Sound Health Care System/GRECC; Andrew Lieberman, MD, PhD, University of Michigan; Richard Lipton, MD, Albert Einstein College of Medicine; Oscar Lopez, MD, University of Pittsburgh Alzheimer's Disease Research Center; Kathryn Lunetta, PhD, Boston University; Constantine Lyketsos, MD, MHS. Johns Hopkins University; John Malamon, MSE. University of Pennsylvania Perelman School of Medicine; Daniel Marson, JD PhD, University of Alabama at Birmingham; Eden Martin, PhD, University of Miami; Frank Martiniuk, PhD, New York University; Deborah Mash, PhD, University of Miami; Eliezer Masliah, MD, University of California San Diego; Richard Mayeux, MD, Columbia University ; Wayne McCormick, MD, MPH, University of Washington; Susan McCurry, PhD, University of Washington; Andrew McDavid, BA. Fred Hutchinson Cancer Research Center; Stefan McDonough, PhD, Pfizer Worldwide Research and Development; Ann McKee, MD, Boston University; Marsel Mesulam, MD, Northwestern University Feinberg School of Medicine; Bruce Miller, MD, University of California San Francisco; Carol Miller, MD, University of Southern California; Joshua Miller, PhD, University of California Davis; Thomas Montine, MD, PhD, University of Washington; John Morris, MD, Washington University; Shubhabrata Mukherjee, PhD, University of Washington; Amanda Myers, PhD, University of Miami; Adam Naj, PhD, University of Pennsylvania Perelman School of Medicine; Sid O'Bryant, PhD, University of North Texas Health Science Center; John Olichney, MD, University of California Davis; Joseph Parisi, MD, Mayo Clinic; Henry Paulson, MDPhD, University of Michigan; Margaret Pericak-Vance, PhD, University of Miami; Elaine Peskind, MD, University of Washington School of Medicine; Ronald Petersen, MD, PhD, Mayo Clinic; Aimee Pierce, MD, University of California Irvine; Wayne Poon, PhD, University of California Irvine; Huntington Potter, PhD, University of Colorado School of Medicine; Liming Qu, MS, University of Pennsylvania Perelman School of Medicine; Joseph Quinn, MD, Oregon Health & Science University; Ashok Raj, MD, University of South Florida; Murray Raskind, MD, University of Washington School of Medicine; Eric Reiman, MD, Translational Genomics Research Institute; Barry Reisberg, MD, New York University; Joan Reisch, PhD, University of Texas Southwestern Medical Center; Christiane Reitz, MD, PhD, Columbia University; John Ringman, MD, University of Southern California; Erik Roberson, MD, PhD, University of Alabama at Birmingham; Ekaterina Rogaeva, PhD, University of Toronto; Howard Rosen, MD, University of California San Francisco; Roger Rosenberg, MD, University of Texas Southwestern; Donald Royall, MD, South Texas Veterans Health Administration Geriatric Research Education & Clinical Center (GRECC), UT Health Science Center at San Antonio; Mark Sager, MD, University of Wisconsin; Mary Sano, PhD, Mount Sinai School of Medicine; Andrew Saykin, PsyD. Indiana University; Gerard Schellenberg, PhD, University of Pennsylvania Perelman School of Medicine; Julie Schneider, MD, Rush University Medical Center; Lon Schneider, MD, University of Southern California; William Seeley, MD, University of California San Francisco; Amanda Smith, MD, University of South Florida; Joshua Sonnen, MD, University of Washington; Salvatore Spina, MD, Indiana University; Peter St George-Hyslop, MD, FRCP. University of Toronto; Robert Stern, PhD, Boston University; Russell Swerdlow, MD, University of Kansas Medical Center; Rudolph Tanzi, PhD, Massachusetts General Hospital/Harvard Medical School; John Trojanowski, MD, PhD, University of Pennsylvania Perelman School of Medicine; Juan Troncoso, MD, Johns Hopkins University; Debby Tsuang, MD, VA Puget Sound Health Care System/GRECC; Otto Valladares, MS, University of Pennsylvania Perelman School of Medicine; Vivianna Van Deerlin, MD, PhD, University of Pennsylvania Perelman School of Medicine; Linda Van Eldik, PhD, University of Kentucky; Badri Vardarajan, MS, Columbia University; Harry Vinters, MD, University of California Los Angeles; Jean Paul Vonsattel, MD, Columbia University; Li-San Wang, PhD, University of Pennsylvania Perelman School of Medicine; Sandra Weintraub, PhD, Northwestern University Feinberg School of Medicine; Kathleen Welsh-Bohmer, PhD, Duke University; Kirk Wilhelmsen, MD, PhD, University of North Carolina Chapel Hill; Jennifer Williamson, MS, Columbia University; Thomas Wingo, MD, Emory University; Randall Woltjer, MD, PhD, Oregon Health & Science University; Clinton Wright, MD, MS, University of Miami; Chuang-Kuo Wu, MD, PhD, Texas Tech University Health Science Center; Steven Younkin, MD, PhD, Mayo Clinic; Chang-En Yu, PhD, University of Washington; Lei Yu, PhD, Rush University Medical Center; and Yi Zhao, MS, University of Pennsylvania Perelman School of Medicine.

Additional Contributions: We thank the study participants and staff of the Rush Alzheimer's Disease Center and of the Kaiser Permanente (formerly Group Health)/University of Washington Adult Changes in Thought study.

REFERENCES

1. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261(5123):921-923.

2. Ridge PG, Hoyt KB, Boehme K, et al; Alzheimer's Disease Genetics Consortium (ADGC). Assessment of the genetic variance of late-onset Alzheimer's disease. *Neurobiol Aging*. 2016;41:200.e13-200.e20.

3. Farrer LA, Cupples LA, Haines JL, et al; APOE and Alzheimer Disease Meta Analysis Consortium. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. *JAMA*. 1997;278(16):1349-1356.

4. Neu SC, Pa J, Kukull W, et al. Apolipoprotein E genotype and sex risk factors for Alzheimer disease: a meta-analysis. *JAMA Neurol*. 2017;74(10):1178-1189.

5. Jagust WJ, Landau SM; Alzheimer's Disease Neuroimaging Initiative. Apolipoprotein E, not fibrillar β-amyloid, reduces cerebral glucose metabolism in normal aging. *J Neurosci*. 2012;32(50):18227-18233.

6. Ossenkoppele R, van der Flier WM, Zwan MD, et al. Differential effect of APOE genotype on amyloid load and glucose metabolism in AD dementia. *Neurology*. 2013;80(4):359-365.

7. Schilling S, DeStefano AL, Sachdev PS, et al. APOE genotype and MRI markers of cerebrovascular disease: systematic review and meta-analysis. *Neurology*. 2013;81(3):292-300.

8. Gottesman RF, Schneider AL, Zhou Y, et al. The ARIC-PET amyloid imaging study: brain amyloid differences by age, race, sex, and APOE. *Neurology*. 2016;87(5):473-480.

9. Reiman EM, Chen K, Liu X, et al. Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2009;106(16):6820-6825.

10. Shi Y, Yamada K, Liddelow SA, et al; Alzheimer's Disease Neuroimaging Initiative. ApoE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of tauopathy. *Nature*. 2017;549(7673):523-527.

11. Farfel JM, Yu L, De Jager PL, Schneider JA, Bennett DA. Association of APOE with tau-tangle pathology with and without β-amyloid. *Neurobiol Aging*. 2016;37:19-25.

12. Morris JC, Roe CM, Xiong C, et al. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Ann Neurol*. 2010;67(1):122-131.

13. Verghese PB, Castellano JM, Garai K, et al. ApoE influences amyloid-β (Aβ) clearance despite minimal apoE/Aβ association in physiological conditions. *Proc Natl Acad Sci U S A*. 2013;110(19):E1807-E1816.

14. Damoiseaux JS, Seeley WW, Zhou J, et al; Alzheimer's Disease Neuroimaging Initiative. Gender modulates the APOE ε4 effect in healthy older adults: convergent evidence from functional brain connectivity and spinal fluid tau levels. *J Neurosci*. 2012;32(24):8254-8262.

15. Jack CR Jr, Wiste HJ, Weigand SD, et al. Age, sex, and APOE ε4 effects on memory, brain structure, and β-amyloid across the adult life span. *JAMA Neurol*. 2015;72(5):511-519.

16. Jack CR Jr, Wiste HJ, Weigand SD, et al. Age-specific and sex-specific prevalence of cerebral β-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50-95 years: a cross-sectional study. *Lancet Neurol*. 2017;16(6):435-444.

17. Li G, Shofer JB, Petrie EC, et al. Cerebrospinal fluid biomarkers for Alzheimer's and vascular disease vary by age, gender, and APOE genotype in cognitively normal adults. *Alzheimers Res Ther*. 2017;9(1):48.

18. Corder EH, Ghebremedhin E, Taylor MG, Thal DR, Ohm TG, Braak H. The biphasic relationship between regional brain senile plaque and neurofibrillary tangle distributions: modification by age, sex, and APOE polymorphism. *Ann N Y Acad Sci*. 2004;1019(1):24-28.

19. Toledo JB, Zetterberg H, van Harten AC, et al; Alzheimer's Disease Neuroimaging Initiative. Alzheimer's disease cerebrospinal fluid biomarker

in cognitively normal subjects. *Brain*. 2015;138(pt 9):2701-2715.

20. Altmann A, Tian L, Henderson VW, Greicius MD; Alzheimer's Disease Neuroimaging Initiative Investigators. Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol*. 2014;75(4):563-573.

21. Sampedro F, Vilaplana E, de Leon MJ, et al; Alzheimer's Disease Neuroimaging Initiative. APOE-by-sex interactions on brain structure and metabolism in healthy elderly controls. *Oncotarget*. 2015;6(29):26663-26674.

22. Jefferson AL, Gifford KA, Acosta LMY, et al. The Vanderbilt Memory & Aging Project: study design and baseline cohort overview. *J Alzheimers Dis*. 2016;52(2):539-559.

23. Johnson SC, Koscik RL, Jonaitis EM, et al. The Wisconsin Registry for Alzheimer's Prevention: a review of findings and current directions. *Alzheimers Dement (Amst)*. 2017;10:130-142.

24. Albert M, Soldan A, Gottesman R, et al. Cognitive changes preceding clinical symptom onset of mild cognitive impairment and relationship to ApoE genotype. *Curr Alzheimer Res*. 2014;11(8):773-784.

25. Beecham GW, Hamilton K, Naj AC, et al; Alzheimer's Disease Genetics Consortium (ADGC). Genome-wide association meta-analysis of neuropathologic features of Alzheimer's disease and related dementias. *PLoS Genet*. 2014;10(9):e1004606.

26. Bennett DA, Schneider JA, Arvanitakis Z, Wilson RS. Overview and findings from the religious orders study. *Curr Alzheimer Res*. 2012;9(6):628-645.

27. Bennett DA, Schneider JA, Buchman AS, Barnes LL, Boyle PA, Wilson RS. Overview and findings from the rush Memory and Aging Project. *Curr Alzheimer Res*. 2012;9(6):646-663.

28. Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. *Arch Neurol*. 2002;59(11):1737-1746.

29. Naj AC, Jun G, Beecham GW, et al. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nat Genet*. 2011;43(5):436-441.

30. Jagust WJ, Landau SM, Shaw LM, et al; Alzheimer's Disease Neuroimaging Initiative. Relationships between biomarkers in aging and dementia. *Neurology*. 2009;73(15):1193-1199.

31. Moghekar A, Li S, Lu Y, et al; BIOCARD Research Team. CSF biomarker changes precede symptom onset of mild cognitive impairment. *Neurology*. 2013;81(20):1753-1758.

32. Bendlin BB, Carlsson CM, Johnson SC, et al. CSF T-Tau/Aβ42 predicts white matter microstructure in healthy adults at risk for Alzheimer's disease. *PLoS One*. 2012;7(6):e37720.

33. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol*. 1991;82(4):239-259.

34. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD): part II: standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology*. 1991;41(4):479-486.

35. Xu H, Gouras GK, Greenfield JP, et al. Estrogen reduces neuronal generation of Alzheimer β-amyloid peptides. *Nat Med*. 1998;4(4):447-451.

36. Green PS, Gridley KE, Simpkins JW. Estradiol protects against beta-amyloid (25-35)-induced toxicity in SK-N-SH human neuroblastoma cells. *Neurosci Lett*. 1996;218(3):165-168.

37. Zhao L, Yao J, Mao Z, Chen S, Wang Y, Brinton RD. 17β-Estradiol regulates insulin-degrading enzyme expression via an ERβ/PI3-K pathway in hippocampus: relevance to Alzheimer's prevention. *Neurobiol Aging*. 2011;32(11):1949-1963.

38. Rozovsky I, Hoving S, Anderson CP, O'Callaghan J, Finch CE. Equine estrogens induce apolipoprotein E and glial fibrillary acidic protein in mixed glial cultures. *Neurosci Lett*. 2002;323(3):191-194.

39. Alvarez-de-la-Rosa M, Silva I, Nilsen J, et al. Estradiol prevents neural tau hyperphosphorylation characteristic of Alzheimer's disease. *Ann N Y Acad Sci*. 2005;1052(1):210-224.

40. Wang C, Zhang F, Jiang S, et al. Estrogen receptor-α is localized to neurofibrillary tangles in Alzheimer's disease. *Sci Rep*. 2016;6:20352.

41. Srivastava RA, Srivastava N, Averna M, et al. Estrogen up-regulates apolipoprotein E (ApoE) gene expression by increasing ApoE mRNA in the translating pool via the estrogen receptor alpha-mediated pathway. *J Biol Chem*. 1997;272(52):33360-33366.

42. Dubal DB, Broestl L, Worden K. Sex and gonadal hormones in mouse models of Alzheimer's disease: what is relevant to the human condition? *Biol Sex Differ*. 2012;3(1):24-24.

43. Blennow K, Hampel H. CSF markers for incipient Alzheimer's disease. *Lancet Neurol*. 2003;2(10):605-613.

44. Koran MEI, Wagener M, Hohman TJ; Alzheimer's Neuroimaging Initiative. Sex differences in the association between AD biomarkers and cognitive decline. *Brain Imaging Behav*. 2017;11(1):205-213.

45. Fleisher A, Grundman M, Jack CR Jr, et al; Alzheimer's Disease Cooperative Study. Sex, apolipoprotein E ε 4 status, and hippocampal volume in mild cognitive impairment. *Arch Neurol*. 2005;62(6):953-957.

46. Liu C-C, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy [published correction appears in *Nat Rev Neurol*. 2013. doi: 10.1038/nmeurol.2013.32]. *Nat Rev Neurol*. 2013;9(2):106-118.

47. Ghebremedhin E, Schultz C, Thal DR, et al. Gender and age modify the association between APOE and AD-related neuropathology. *Neurology*. 2001;56(12):1696-1701.

48. Farrer LA, Cupples LA, Haines JL, et al; APOE and Alzheimer Disease Meta Analysis Consortium. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. *JAMA*. 1997;278(16):1349-1356.

49. Chêne G, Beiser A, Au R, et al. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *Alzheimers Dement*. 2015;11(3):310-320.

50. Cacciottolo M, Christensen A, Moser A, et al; Alzheimer's Disease Neuroimaging Initiative. The APOE4 allele shows opposite sex bias in microbleeds and Alzheimer's disease of humans and mice. *Neurobiol Aging*. 2016;37:47-57.