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Sex Differences in the Association of Global Amyloid and Regional Tau Deposition Measured By Positron Emission Tomography in Clinically Normal Older Adults

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IMPORTANCE Mounting evidence suggests that sex differences exist in the pathologic trajectory of Alzheimer disease. Previous literature shows elevated levels of cerebrospinal fluid tau in women compared with men as a function of apolipoprotein E (APOE) ε4 status and β-amyloid (Aβ). What remains unclear is the association of sex with regional tau deposition in clinically normal individuals.

OBJECTIVE To examine sex differences in the cross-sectional association between Aβ and regional tau deposition as measured with positron emission tomography (PET).

DESIGN, SETTING AND PARTICIPANTS This is a study of 2 cross-sectional, convenience-sampled cohorts of clinically normal individuals who received tau and Aβ PET scans. Data were collected between January 2016 and February 2018 from 193 clinically normal individuals from the Harvard Aging Brain Study (age range, 55-92 years; 118 women [61%]) who underwent carbon 11–labeled Pittsburgh Compound B and flortaucipir F^{18} PET and 103 clinically normal individuals from the Alzheimer's Disease Neuroimaging Initiative (age range, 63-94 years; 55 women [51%]) who underwent florbetapir and flortaucipir F 18 PET.

MAIN OUTCOMES AND MEASURES A main association of sex with regional tau in the entorhinal cortices, inferior temporal lobe, and a meta-region of interest, which was a composite of regions in the temporal lobe. Associations between sex and global Aβ as well as sex and APOE ε4 on these regions after controlling for age were also examined.

RESULTS The mean (SD) age of all individuals was 74.2 (7.6) years (81 APOE ε4 carriers [31%]; 89 individuals [30%] with high Aβ). There was no clear association of sex with regional tau that was replicated across studies. However, in both cohorts, clinically normal women exhibited higher entorhinal cortical tau than men (meta-analytic estimate: β [male] = −0.11 [0.05]; 95% CI, −0.21 to −0.02; P = .02), which was associated with individuals with higher Aβ burden. A sex by APOE ε4 interaction was not associated with regional tau (meta-analytic estimate: β [male, APOE ε4+] = −0.15 [0.09]; 95% CI, −0.32 to 0.01; P = .07).

CONCLUSIONS AND RELEVANCE Early tau deposition was elevated in women compared with men in individuals on the Alzheimer disease trajectory. These findings lend support to a growing body of literature that highlights a biological underpinning for sex differences in Alzheimer disease risk.

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Supplemental content

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Sex-specific risk on the rate of clinical progression in early Alzheimer disease (AD) remains to be fully elucidated,[1-4] although mounting evidence suggests that women are at heightened risk for exhibiting AD pathophysiology.[5-8] In clinically normal older adults[9,10] and individuals with mild cognitive impairment,[11] higher cerebrospinal fluid (CSF) tau levels have been observed in female apolipoprotein E (APOE) ε4 carriers compared with male carriers. In a 2018 meta-analysis of multiple independent cohorts with CSF data, Hohman and colleagues[10] found greater CSF total and phosphorylated tau in female APOE ε4 carriers than male carriers, with findings driven by abnormal levels of β-amyloid (Aβ). Sex differences in Aβ burden alone have not been reported in older adults,[11-13] supporting the notion that sex differences may be more likely to appear downstream after the onset of Aβ accumulation.[5,10] To our knowledge, studies have yet to fully explore this notion,[8] with little attention paid to elucidating sex differences in regional tau deposition in the context of Aβ burden and APOE ε4.

The primary aim of this study was to determine the extent to which sex differences exist in regional in vivo tau deposition in clinically normal older adults using positron emission tomography (PET) neuroimaging. Specifically, we examined the influence of sex to modify the well-characterized cross-sectional association between regional tau PET and global Aβ PET.[14-16] We also investigated the degree to which sex and APOE ε4 might interact to influence regional tau PET. We hypothesized that women would exhibit greater tau PET signal than men for a given level of global Aβ burden and that tau PET signal would be greater in female APOE ε4 carriers compared with male carriers.

Key Points

Questions Do sex differences exist in regional tauopathy, as measured with positron emission tomography, and is this largely driven by higher global amyloid burden?

Findings In this study of 2 cross-sectional cohorts of 296 clinically normal adults, women with higher amyloid burden showed greater entorhinal cortical tau signal compared with men with higher amyloid burden. Sex differences did not exist in amyloid load or apolipoprotein E ε4 frequency.

Meaning In conjunction with this finding, mounting evidence supports the notion that sex differences in the Alzheimer disease pathologic trajectory may well appear downstream of abnormal amyloid burden in the acceleration of tau deposition and brain atrophy.

Methods

Participants

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database[17] and the Harvard Aging Brain Study (HABS).[18] Initial inclusion criteria for recruitment for both HABS and ADNI have been published previously.[19,20] In HABS, participants were all considered clinically normal at the time of their first tau scan (n = 193; global clinical dementia rating score, 0; mean [SD] age, 74.3 (8.0) years; 118 women [62%]). For ADNI, we included 103 individuals who were classified as clinically normal (global clinical dementia rating score, 0; mean [SD] age, 75.6 (6.3) years; 55 women [53%]) at the time of their first tau scan. For HABS, the time between the first tau PET scan and the closest Aβ PET scan was a median (interquartile range) of 54 (14-135) days (maximum, 3.3 years). For ADNI, the interval was a median (interquartile range) of 8 (3-42) days (maximum, 4.8 years). Some participants had a duration delay of longer than a year between scans (HABS: n = 9; ADNI: n = 9 clinically normal individuals), and as such, we covaried for scan interval in our analyses. We also ran analyses without these aforementioned individuals, and the pattern of findings remained the same.

APOE Genotyping

A blood sample was collected in each study for direct genotyping of APOE (heterozygotes and homozygotes for the ε4 were collapsed into the 1 category with all ε4 haplotypes included). We conducted the procedures for this study under the ethical guidelines stipulated by the Partners Human Research Committee, which is the institutional review board for the Massachusetts General Hospital and Brigham and Women's Hospital. Written consent from all individuals was obtained in each cohort.

Aβ Positron Emission Tomography

The Harvard Aging Brain Study used the carbon 11-labeled Pittsburgh Compound B ([^{11}C]PiB) Aβ PET tracer, while ADNI used the florbetapir F 18 ([^{18}F]florbetapir) Aβ PET tracer. The PET acquisition parameters for each study have been published previously.[20-22] For both studies, we used non–partial volume corrected (PVC) amyloid PET data for all analyses, although we repeated our analyses with partial volume corrected Aβ PET data from HABS (for which these data were available).

In HABS, [^{11}C]PiB PET data were collected during a 4-hour dynamic acquisition of 69 volumes (12 × 15 seconds, 57 × 60 seconds). Positron emission tomography data underwent reconstruction and attenuation correction, evaluation for head motion, and coregistration to each individuals' magnetic resonance imaging using SPM12 (Wellcome Trust Centre for Neuroimaging). Structural magnetic resonance imaging scans were parcellated using FreeSurfer (version 5.3.0; http://surfer.nmr.mgh.harvard.edu), and summary measures were computed from a weighted average within a large aggregate cortical region of interest (ROI) consisting of frontal, lateral temporal and parietal, and retrosplenial cortices. The frontal, lateral temporal and parietal, and retrosplenial cortices regions have been used as a summary measure of global Aβ retention in previous publications.[23] Distribution volume ratio was computed using logan plotting, 40 to 60 minutes postinjection with a cerebellar gray reference region, for each participant.

In ADNI, florbetapir cortical summary standard uptake value ratios (SUVr) were downloaded from data previously processed by University of California Berkeley from the LONI data access point (http://adni.loni.usc.edu/). The Alzheimer's Disease Neuroimaging Initiative PET acquisition time was 50 to 70 minutes postinjection. Preprocessing pipelines have been published previously.[24,25] Tracer retention for a cortical summary ROI, containing lateral and medial frontal, anterior,

and posterior cingulate, lateral parietal, and lateral temporal regions, was referenced to the whole cerebellum to yield a global Aβ SUVr for each participant.[22] This composite ROI was slightly different than that used in HABS; however, our intention was to conduct analyses using Aβ composite ROIs that have traditionally been used within each cohort.

Tau Positron Emission Tomography

Both studies use the [^{18}F]flortaucipir tau PET tracer. The PET acquisition parameters for each study have been published previously.[14,26] [^{18}F]flortaucipir mean count images were created based on mean retention over 75 to 110 minutes (HABS) and 75 to 105 minutes (ADNI) postinjection. Preprocessing of tau PET data has been published previously.[14,26] Standard uptake value ratios were created by referencing to mean cerebellar gray matter retention[26] from each individual's FreeSurfer parcellations.[14,27] For both studies, PVC images were processed using the geometric transform matrix method.[28,29] We examined bilateral composites of the entorhinal cortex (EC), given it is among one of the first regions to develop tau pathology,[30] as well as bilateral inferior temporal cortex (IT), given it has been used as a surrogate marker of early AD-related tauopathy.[14,31] To examine a more stable ROI of the temporal lobe, we also calculated a meta-ROI including the following bilateral regions: EC, IT, amygdala, fusiform gyrus, and parahippocampal cortex. We also examined 2 extratemporal regions to determine the level of specificity of sex differences in the temporal lobe: the precuneus and superior parietal regions. These extratemporal regions were chosen owing to their salience in more advanced stages of the AD trajectory.[16,32] As sex differences exist in brain morphology,[33] we examined the association of FreeSurfer-derived whole-brain gray matter volume (adjusted for intracranial volume[34]) on sex differences in non-PVC tau retention. For analyses involving gray matter volume, we used non-PVC tau PET measures to reduce the issue of compounded noise as FreeSurfer is used to derive both geometric transform matrix method indices and volumes.

Statistical Analysis

All analyses were run with R (version 3.3.3; The R Foundation). Nonparametric Mann-Whitney and χ^2 tests were used to determine group differences between the studies (HABS vs ADNI) on demographics and biomarkers. Mann-Whitney *U* tests determined unadjusted sex differences between tau regions and global Aβ. A series of hierarchical linear regressions were conducted to examine the influence of sex on the association between tau and Aβ, after adjusting for age and delay between tau and Aβ scans (model 1). There were some missing data for APOE genotype (n = 34 for HABS; n = 7 for ADNI), and as such, we ran separate analyses including main associations of APOE (model 2). The following analyses were run in the HABS and ADNI cohorts separately:

1. Tau ROI ~ Aβ + Sex + Age
2. Tau ROI ~ Aβ + Sex + APOE + Age
3. Tau ROI ~ Aβ × Sex + Age
4. Tau ROI ~ APOE × Sex + Age

For the tau ROIs, we examined the EC, IT, the meta-ROI for tau, and 2 extratemporal regions (precuneus and superior parietal lobe). Models 3 and 4 are fully factorial.

Each model was compared against a prior model to determine goodness of fit using log likelihood ratio. We did not include sex × Aβ × APOE interactions as a stand-alone analysis in the current study owing to low statistical power; however, we included it as an exploratory meta-analysis estimate. We conducted post hoc analyses examining the influence of outliers using robust linear regression (using M estimation with Huber with the *rlm* package) on findings of interest. On models of interest, we probed the association of differing levels of Aβ burden on the percentage sex differences on tau retention. As extratemporal regions were used to test for specificity in the temporal regions, we refer to these as post hoc. We ran models of interest with non-PVC tau data for temporal tau regions, including an additional covariate of whole-brain gray matter volume, and included these in eTable 1 in the Supplement.

For models of interest, we conducted exploratory linear mixed models of interactions of sex and regional tau on cognitive decline after adjusting for age and education, including random intercept and slopes (eTable 2 in the Supplement). To measure cognition, we used the Preclinical Alzheimer Cognitive Composite,[35] which has been applied across these cohorts in previous publications.[35,36] The baseline cognitive time point was considered within 18 months of the tau scan; for HABS this resulted in up to 5 follow-up time points and for ADNI, up to 3 follow-up time points.

A final meta-analysis estimate was calculated for sex, sex × Aβ, sex × APOE, and sex × Aβ × APOE on EC tau in clinically normal older adults from both HABS and ADNI using the Metafor package, version 2.0 (R Project for Statistical Computing). In brief, all standardized β weights, along with their SEs, for each of the aforementioned estimates were run in the *rma* function to fit a meta-analytic fixed-effect model with a predefined weighted estimation (inverse-variance weights).

Results

Cohort and Sex Differences in Demographics

Clinically normal individuals in HABS performed significantly better on logical memory (delayed recall) than their ADNI counterparts ($t = -5.56$, $P < .001$) but did not differ by age, sex, Aβ$^+$ status, or APOE ε4 status. Women exhibited higher scores on logical memory delayed recall in the HABS clinically normal group (**Table 1**); however, no sex differences were found in demographics in the ADNI clinically normal group.

Main Association Between Sex With Tau, Aβ, and APOE ε4

In the HABS clinically normal group, using a simple group comparison without adjusting for age, no sex differences existed in any temporal tau regions or in global Aβ distribution volume ratio (eFigure in the Supplement). However, in the ADNI clinically normal group, women exhibited higher median EC tau SUVr than men by 5.8% (M-W = 1699, $P = .01$). Adjusting for age yielded no changes to the above findings, except that clinically normal women in ADNI now showed slightly elevated IT tau SUVr compared with clinically normal men in ADNI (robust *F* test = 4.33, $P = .04$).

Table 1. Demographic Comparison by Sex[a]

Variable	Mean (SD) [Range]					
	HABS (n = 193)			ADNI (n = 103)		
	Women (n = 118)	Men (n = 74)	*P* Value	Women (n = 55)	Men (n = 48)	*P* Value
Age, y	73.4 (8.3)	75.6 (7.2)	.08	75.1 (6.3)	76.0 (6.9)	.58
Education, y	15.9 (2.7)	16.2 (3.3)	.32	16.1 (2.5)	17.0 (2.2)	.08
White, No. (%)	93 (83)	64 (86)	.99	53 (98)	46 (95)	.96
APOE ε4$^+$, No. (%)	37 (31)	22 (30)	.99	21 (38)	14 (30)	.57
MMSE score	29.3 (1.0)	29.2 (1.0)	.21	29.1 (1.2)	29 (1.3)	.67
Logic memory (delayed recall)	16.8 (3.4)	15.2 (3.6)	.002	13.9 (3.7)	13.4 (3.7)	.65
Aβ DVR/SUVr	1.18 (0.2) [0.99-1.86]	1.18 (0.2) [0.95-1.90]	.09	1.16 (0.2) [0.91-1.71]	1.09 (0.1) [0.91-1.50]	.13
Aβ$^+$ status, No. (%)	28 (24)	23 (31)	.39	21 (38)	16 (33)	.76
EC tau SUVr PVC	1.31 (0.3) [0.77-2.51]	1.29 (0.2) [0.79-2.03]	.95	1.58 (0.4) [0.83-3.07]	1.38 (0.3) [0.78-2.01]	.01
IT tau SUVr PVC	1.43 (0.2) [1.02-2.18]	1.43 (0.2) [1.13-2.04]	.72	1.57 (0.3) [1.20-3.15]	1.46 (0.2) [1.20-1.94]	.13
Precuneus tau SUVr PVC	1.32 (0.2) [0.89-1.84]	1.33 (0.1) [0.93-1.62]	.40	1.31 (0.2) [0.98-2.03]	1.18 (0.2) [0.79-1.70]	.03
Superior parietal tau SUVr PVC	1.24 (0.2) [0.85-1.86]	1.15 (0.2) [0.70-1.55]	<.001	1.23 (0.2) [0.86-2.00]	1.10 (0.2) [0.78-1.47]	.004

Abbreviations: Aβ, β-amyloid; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, apolipoprotein E; DVR, distribution volume ratio; EC, entorhinal cortex; HABS, Harvard Aging Brain Study; IT, inferior temporal cortex; MMSE, Mini-Mental State Examination; PVC, partial volume corrected; SUVr, standard uptake value ratios.

[a] Group comparisons using nonparametric Wilcoxon test.

Table 2. Standardized Regression Coefficients of Sex Differences on Regional Partial Volume–Corrected Tau[a]

Variable[b]	EC Tau			IT Tau			Meta-ROI		
	β (95% CI)	R^2	*P* Value	β (95% CI)	R^2	*P* Value	β (95% CI)	R^2	*P* Value
Clinically Normal HABS									
Sex + Aβ + age (model 1)									
Male sex	−0.08 (−0.19 to 0.04)	0.31	.22	−0.04 (−0.16 to 0.08)	0.29	.52	−0.03 (−0.14 to 0.08)	0.40	.57
Sex + Aβ + APOE + age (model 2)									
Male sex	−0.08 (−0.21 to 0.05)	0.29	.25	−0.02 (−0.15 to 0.12)	0.27	.80	−0.05 (−0.17 to 0.08)	0.36	.49
Sex × Aβ (model 3)									
Male sex × Aβ	−0.17 (−0.32 to −0.01)	0.33	.04	−0.09 (−0.24 to 0.07)	0.30	.30	−0.13 (−0.27 to 0.02)	0.41	.09
Sex × APOE (model 4)									
Male sex × APOE (ε4+)	−0.09 (−0.30 to 0.12)	0.18	.41	−0.07 (−0.28 to 0.14)	0.17	.51	−0.08 (−0.28 to 0.13)	0.22	.49
Clinically Normal ADNI									
Sex + Aβ + age (model 1)									
Male sex	−0.19 (−0.36 to −0.02)	0.30	.03	−0.12 (−0.29 to 0.06)	0.26	.19	−0.18 (−0.16 to −0.01)	0.40	.03
Sex + Aβ + APOE + age (model 2)									
Male sex	−0.16 (−0.33 to 0.02)	0.31	.09	−0.12 (−0.30 to 0.07)	0.26	.21	−0.15 (−0.32 to 0.01)	0.40	.07
Sex × Aβ (model 3)									
Male sex × Aβ	−0.23 (−0.42 to −0.04)	0.34	.02	−0.15 (−0.35 to 0.05)	0.28	.15	−0.20 (−0.38 to −0.02)	0.43	.03
Sex × APOE (model 4)									
Male sex × APOE (ε4+)	−0.26 (−0.54 to 0.03)	0.17	.08	−0.16 (−0.46 to 0.13)	0.09	.28	−0.30 (−0.58 to −0.02)	0.19	.04

Abbreviations: Aβ, β-amyloid; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, apolipoprotein E; EC, entorhinal cortex; HABS, Harvard Aging Brain Study; IT, inferior temporal cortex; meta-ROI, includes the following regions: entorhinal, inferior temporal, fusiform gyrus, amygdala, and parahippocampus.

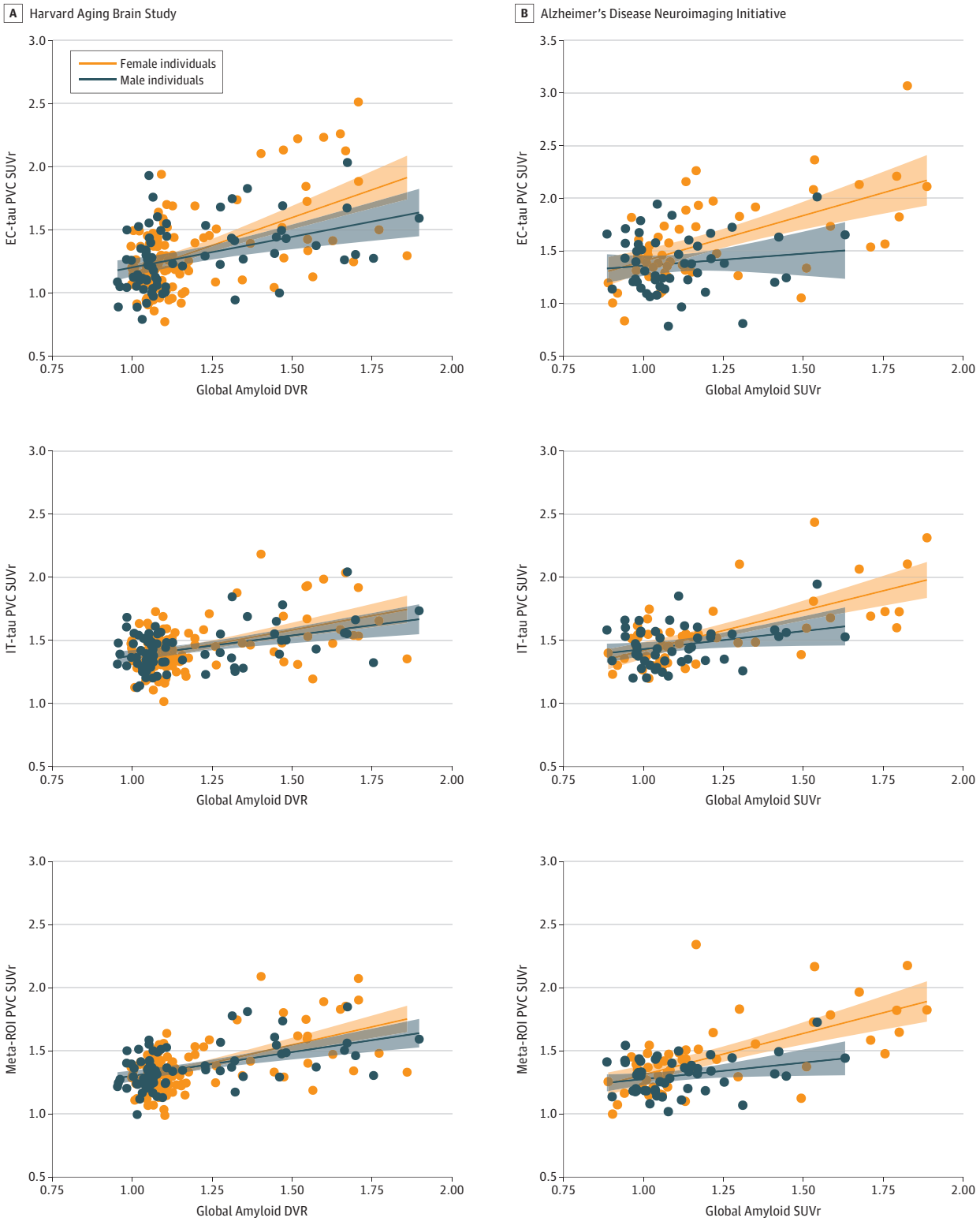
[a] Aβ, age, and duration between positron emission tomography scans are continuous variables.

[b] All models are adjusted for age and include main effects. Model estimates for models 3 and 4 found in eTable 3 in the Supplement.

Interactive Association Between Sex and Aβ With Tau

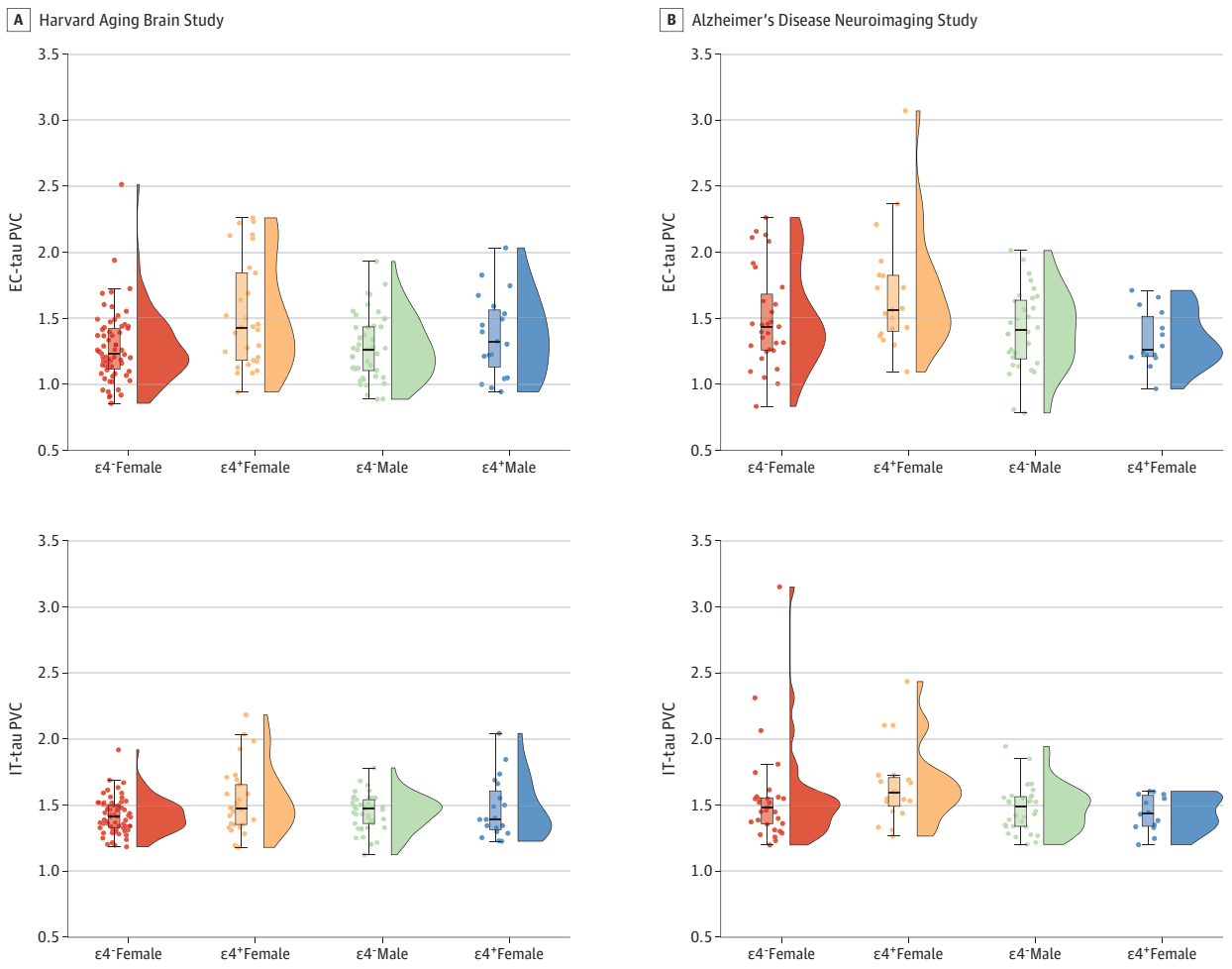
In the HABS clinically normal group, women exhibited higher EC tau SUVr than men in individuals with higher Aβ burden (β = −0.17; 95% CI, −0.32 to −0.01; *P* = .04; **Table 2** and **Figure 1**). This was a significantly better-fitting model than the main effects-only model (model 1 vs model 3 log likelihood ratio: 4.42, *P* = .04). The finding became attenuated using robust regression analysis (robust *F* for sex × Aβ = 4.64, *P* = .08). There was no sex-Aβ interaction on either IT tau or the meta-ROI.

Figure 1. Sex Differences in the Association Between Regional Temporal Tau and Global β-Amyloid in Clinically Normal Older Adults



DVR indicates distribution volume ratio; EC, entorhinal cortex; PVC, partial volume corrected; ROI, region of interest; SUVr, standard uptake value ratio.

Figure 2. Sex-Apolipoprotein E (APOE) Differences in Regional Tau in Clinically Normal Older Adults



EC indicates entorhinal cortex; IT, inferior temporal cortex; PVC, partial volume corrected.

In the ADNI clinically normal group, women also showed higher EC tau compared with men (β = −0.23; 95% CI, −0.42 to −0.04) in individuals with higher Aβ burden (Figure 1). This model fit significantly better than the main effects-only model (model 1 vs model 3 log likelihood ratio: $F = 5.57$, $P = .02$) and remained significant with robust linear regression (robust $F = 5.55$, $P = .02$). When removing the outlying women with higher levels of amyloid than men (n = 7), the sex differences remained (β = −0.29; 95% CI, −0.55 to −0.02; $P = .04$).

In conclusion, clinically normal women from both the HABS and ADNI studies showed higher EC tau retention than in clinically normal men with higher Aβ burden (full models in eTable 3 in the Supplement). Analyses involving non-PVC tau PET (with and without gray matter used as a covariate) can be found in eTable 1 in the Supplement.

Interactive Association Between Sex and APOE With Tau

For the HABS clinically normal group, sex and APOE did not interact to influence tau retention (model 4; **Figure 2**). For the ADNI clinically normal group, a sex × APOE ε4 interaction term was found with the tau meta-ROI (β = −0.30; 95% CI, −0.58 to −0.02; $P = .04$; model 4), whereby the association between APOE ε4 and tau retention was stronger among women compared with men. This model fit significantly better than a main effects-only model ($F = 4.37$, $P = .04$).

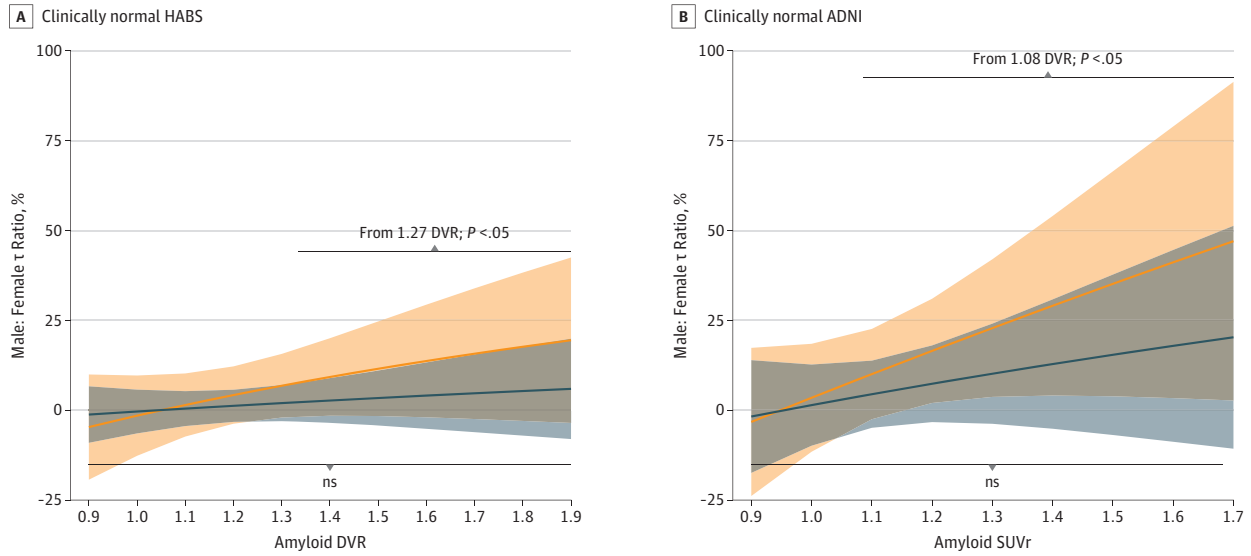
Specificity of Sex Differences in the Temporal Region

No sex differences were evident in the precuneus ROI in either cohort (eTable 4 in the Supplement). However, both clinically normal HABS and ADNI women showed elevated signal in the superior parietal ROI compared with men, after adjusting for age (β = −0.29; 95% CI, −0.42 to −0.15; $P < .001$ for HABS and β = −0.23; 95% CI, −0.40 to −0.06; $P = .01$ for ADNI). Neither cohort showed significant interactions of sex × Aβ or sex × APOE on either extratemporal ROI.

Meta-analytic Estimate of Sex Difference on EC Tau

Fitting a fixed-effects *rma* model to the standardized coefficients and SEs from the EC tau models in both clinically normal cohorts, we found that the main effect of sex on EC tau SUVr was significant: β (male) = −0.11 (0.05); 95% CI, −0.21 to −0.02; $P = .02$. The interactive effect of sex and APOE on EC tau SUVr was not sig-

Figure 3. Exemplification of the Magnitude of the Sex × Aβ Differences in Regional Tau in Clinically Normal Adults Represented by the Predicted Women:Male Ratio of Standard Uptake Value Ratio (SUVR) at a Given Level of β-Amyloid



The y-axis represents the predicted ratio of tau–positron emission tomography (PET) SUVr between women and men given a level of β-amyloid burden. Orange indicates the percentage woman:male ratio for EC tau SUVR, and blue indicates the percentage woman:male ratio for IT tau SUVR. Error bands represent an uncertainty parameter, which was calculated from the following estimates from the model: ([the upper 95% CI bound for men − the lower 95% CI bound for women] / the regional tau PET SUVR for men) × 100. *P* values represent a floodlight analysis of the point at which the association between β-amyloid and tau PET diverge between the sexes. ADNI, indicates Alzheimer's Disease Neuroimaging Initiative; DVR, distribution volume ratio; HABS, Harvard Aging Brain Study; ns, not significant.

nificant, β (male, ε4$^+$) = −0.15 (0.09); 95% CI, −0.32 to 0.01; *P* = .07, while the interaction between sex and Aβ on EC tau SUVr was significant: β (male, Aβ$^+$) = −0.19 (0.06) [95% CI, −0.32 to −0.07], *P* = .002. An exploratory examination of a 3-way interaction between sex, APOE, and Aβ was not significant: β (male, ε4$^+$, Aβ$^+$) = 0.01 (0.09); 95% CI, −0.16 to 0.18; *P* = .91.

Exemplification of Sex Differences

To observe a sex difference of 10% tau signal in the EC in clinically normal individuals, global Aβ was estimated at approximately 1.40 [11^C]PiB distribution volume ratio in HABS (published cutpoint = 1.2 distribution volume ratio[34]) and 1.10 florbetapir SUVr in ADNI (published cut point = 1.11[22]; **Figure 3** and eTable 5 in the Supplement).

Discussion

Clinically normal women exhibited higher EC tau than men in individuals with higher Aβ burden across both cohorts. We did not find a significant influence of gray matter volume on our results. Further, this association may carry some level of specificity, as other extratemporal regions did not exhibit this interactive Aβ-by-sex effect on tau signal. However, this interaction was dependent on PVC for the NCs from both cohorts, suggesting that partial volume adjustment facilitates detection of this association at lower levels of tau.

Minimal,[6] if any,[11,12,36] sex differences have been found cross sectionally in levels of global Aβ burden in clinically normal older adults, although some evidence suggests sex differences in Aβ burden may be related to menopausal stage[6] and parental family history.[37] In the current study, we found a trend toward slightly higher median Aβ values in women, similar to a 2018 study.[38] As such, subtle association with sex on Aβ may be apparent at the earliest stages of disease. It is possible that a sex-modifying effect on the association between Aβ and tau reflects a secondary pathway driven by sex-specific lifestyle determinants, such as cardiovascular disease or inflammation.[39] For instance, heightened inflammatory responses have been reported in women,[8] which is an important consideration given that AD may be influenced to some extent by immune system function. In addition, men show disproportionate mortality rates due to cardiovascular disease in midlife, arguably leaving older male survivors to exhibit reduced cardiovascular disease risk factors for AD[40]; however, older women could maintain persistent cardiovascular disease risk and thus be exposed to greater vascular and AD comorbidity. The influence of sex steroid hormones also cannot be discounted as a possible mechanism,[41] although we were unable to measure these association in these predominantly older cohorts.

By contrast, sex-APOE interactions were unclear, with only clinically normal ADNI female APOE ε4 carriers showing elevated signal in the tau meta-ROI. Epidemiologic studies show sex differences in clinical risk are largely discernable within the context of APOE ε4,[11,42,43] particularly between the ages of 65 to 75 years compared with APOE ε4 clinically normal male carriers.[44] Female APOE ε4 carriers with abnormal levels of CSF Aβ also exhibit higher CSF tau than male carriers.[10] It is possible that our comparatively lower statistical power may have hampered the abil-

ity to detect APOE associations[44]; however, given that APOE ε4 is highly associated with Aβ,[45] previous studies may simply reflect unaccounted for Aβ effects.

Animal models of AD have often reported sex differences in Aβ and tau deposition. Transgenic mouse models that overexpress human Aβ show greater rates of Aβ40 and Aβ42 burden in Tg2576[46] and double-mutant APPswe × PS1.M146V (TASTPM) older female mice[47] compared with male mice. Double-mutant mice that overexpress both hyperphosphorylated mutant tau (P301L) and Aβ precursor protein (APP; TAPP mice) show a marked female-biased density of neurofibrillary tangles in limbic areas compared with male mice.[48] Finally, cellular models of AD tauopathy, using hyperphosphorylated tau-overexpressing P301L cells, show that treatment with progesterone and estrogen significantly recovers cellular bioenergetic function (ie, mitochondria),[49] suggesting a potential mechanism underlying female susceptibility to tauopathy in AD that may be driven by depleted progesterone/estrogen during menopause.[50] Together, these animal and cellular models of AD support a female-specific vulnerability to AD pathophysiology.

An unresolved question related to these data is that of survival bias.[8] Clinically normal men, particularly those who carry APOE ε4,[51] may struggle to maintain clinical health in the presence of elevated Aβ and tau burden (perhaps due to vascular contributions) and thus may exhibit poorer resilience to increasing pathological burden. Clinically normal men in the ADNI group, for instance, showed lower dynamic range for Aβ and lower IT tau retention compared with women. We did not have statistical power to robustly assess this issue, and so the association of survival will need to be explored with larger cohorts. Further, extricating the sex biological component from the epiphenomenon surrounding gender construct (eg, different education/occupational attainment, lifestyle) will need to be explored to determine the association of these factors.

Strengths and Limitations

A strength of this study is the replication of our findings across 2 independent studies of aging with Aβ and tau PET. However, the magnitude of association was notably higher in the ADNI clinically normal group; since the ADNI clinically normal group were older than the HABS clinically normal cohort, exhibited lower memory performance, and had greater dynamic range in tau SUVrs, it is possible that the ADNI clinically normal group were further along the preclinical trajectory than the HABS clinically normal group. This is highlighted by the 10% sex difference in EC tau; although the ADNI clinically normal group hit this difference within the Aβ cut-off, the HABS clinically normal cohort exhibited this difference far above their established cutoff. This may also be a function of other factors such as different dynamic range of the amyloid PET radiotracers, methodologic differences in PET processing pipelines for [^{18}F]flortaucipir, and potential unexplained and idiosyncratic components of the cohort. However, these cohorts are convenience samples and involve recruitment and sampling biases that may result in a lack of generalizability of findings. In addition, it is possible that sex-specific partial volume effects may be inherent in these data, although we found no association of gray matter volume on our findings. In an exploratory analysis, we examined whether the interaction of sex and EC tau influenced cognitive decline. Entorhinal cortex tau was chosen owing to the sex effects that were seen in the previous models. We did not find a significant interactive sex × EC tau association with cognitive decline (eTable 2 in the Supplement). Owing to issues of power and limited follow-up neuropsychological observations post–tau scan in both cohorts, these preliminary null findings should be approached with caution. Our future work will explore these associations in more depth once we have statistical power to examine interactive associations in the context of longitudinal cognition. Finally, we predominantly focused on temporal ROIs, although we did find some preliminary evidence of main effects of sex on an extratemporal region of the brain. As such, future studies, should examine whole-brain patterns of sex differences in tau signal across larger cohorts.

Conclusions

In conclusion, clinically normal women exhibited higher regional tau compared with men, predominantly in those with higher Aβ burden, with this difference apparent in the EC. These findings were stronger in the ADNI clinically normal cohort in comparison with the HABS clinically normal group, and it is possible that this is because they represent a more clinically advanced group. As such, early tau deposition may be accelerated in women compared with men, with our findings lending support to a growing body of literature that exposes a biological underpinning for sex differences in AD risk.

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