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# Associations between baseline amyloid, sex, and APOE on subsequent tau accumulation in cerebrospinal fluid

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ABSTRACT

We investigated the effect of baseline Aβ, sex, and *APOE* on longitudinal tau accumulation in cerebrospinal fluid (CSF) in clinically normal older adults. Two hundred thirty-nine participants (aged 56–89 years, clinical dementia rating = 0) underwent serial CSF collection for $A\beta_{1-42}$, total-tau (t-tau) and phospho-$tau_{181P}$ (p-tau). We used preprocessed data from fully automated Roche Elecsys immunoassays. A series of linear regressions were used to examine cross-sectional effects of $A\beta_{1-42}$, sex, and *APOEε4* on baseline CSF tau and linear mixed models for longitudinal changes in CSF tau. Cross-sectionally, CSF t-tau and p-tau were associated with abnormal $A\beta_{1-42}$ and *APOEε4* but not with sex. Longitudinally, low baseline CSF $A\beta_{1-42}$ levels, but not *APOEε4* or sex, predicted faster p-tau accumulation. The relationship between baseline CSF $A\beta_{1-42}$ and tau accumulation was strongest in *APOEε4* carriers, and particularly female carriers, relative to other groups. The current findings support an association between baseline CSF $A\beta_{1-42}$ and changes in CSF tau. Elevated risk in females, apparent only in carriers, reinforces findings of sex-related vulnerability in those with genetic predisposition for Alzheimer's disease.



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

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Since the mid-1990s, amyloid-β (Aβ) and tau, the hallmark pathological proteins of Alzheimer's disease (AD), can be detected and quantified in the cerebrospinal fluid (CSF) (Blennow et al., 1995; Nitsch et al., 1995), including in normal older adults (Petrie et al., 2009). Given the close association between tau and cognition (Nelson et al., 2012), identifying biological factors associated with the accumulation of tau pathology is critical to our understanding of the disease. Lack of standardization across centers and poor test-retest reliability, however, have made longitudinal CSF studies difficult to conduct until recently. Using conventional assays, no relationships have been observed between baseline CSF Aβ and changes in tau (Donohue. et al., 2017), even though Aβ pathology is an important factor promoting tau pathology(Jack et al., 2013). With the advent of more sophisticated immunoassays for measuring changes in CSF Aβ and tau, such as the Roche Elecsys in the ADNI cohort (Bittner et al., 2016; Schindler et al., 2018), investigating potential risk factors for tau accumulation is now possible in the preclinical, clinically normal stage of the disease.

The female sex and carriage of apolipoprotein ε4 (*APOE*ε4) have both been implicated in the early pathophysiology of AD. Sex-specific elevated risk for AD biomarkers in *APOE*ε4 carriers is increasingly evidenced in cross-sectional studies of CSF markers across the diagnostic spectrum from the ADNI sample (Altmann et al., 2014; Damoiseaux et al., 2012), as well as in meta-analyses (Hohman et al., 2018). In patients with mild cognitive impairment (MCI) from ADNI, female *APOE*ε4 carriers exhibit a more AD-like elevated pattern of CSF tau levels relative to males (Altmann et al., 2014). Clinically normal female *APOE*ε4 carriers may also exhibit elevated cross-sectional CSF t-tau relative to males (Damoiseaux et al., 2012; Hohman et al., 2018); however, this finding has not been proven as robust in more recent studies (Altmann et al., 2014; Hohman et al., 2018). By contrast, human studies do not report consistent evidence of sex by *APOE* effects on Aβ burden across a range of cohorts (Altmann et al., 2014; Buckley et al., 2018; Hohman et al., 2018; Morris et al., 2010), suggesting that an emergence of sex-specific biological risk may appear downstream of Aβ (Fisher et al., 2018). Furthermore, although mounting evidence exists of sex-*APOE* effects at the cross-section, studies have yet to examine the modifying association of sex and *APOE* on longitudinal CSF changes.

The aim of the present study was to examine the effect of baseline Aβ, sex, and *APOE* on longitudinal changes in CSF tau in clinically normal older adults. The primary hypothesis was abnormal CSF Aβ would lead to greater CSF tau accumulation. We hypothesized that this relationship would be exacerbated in *APOE*ε4 carriers, and that clinically normal female *APOE*ε4 carriers would show greater longitudinal changes in CSF tau in comparison with males.

## 1. Methods

### 1.1. Participants

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). From this publicly available data set, 239 who were diagnosed as clinically normal participants at baseline (52% female, age = 74 (5.9) years [56–89 years]) were selected based on their availability of serial CSF collection. In this study, participants had a median of 2 visits of CSF collection and a range of 2–7 visits. To be classified as clinically normal, participants were required to score 0 on the clinical dementia rating scale global score, greater than 24 on the mini-mental state examination, less than 6 on the geriatric depression scale (short form) and perform within validated education-adjusted norms on logical memory II delayed recall. To be included in this study, participants were required to possess at least 2 annual CSF collections: 139 only completed 2 visits in all, 62 completed 3 visits, 12 completed 4 visits, 12 completed 5 visits, 4 completed 6 visits, and 10 completed 7 visits. Baseline demographics can be found in Table 1. A blood sample for assessment of *APOE* genotype was also obtained for the purposes of grouping individuals as *APOE*ε4 carriers and noncarriers (five individuals were *APOE*ε4 homozygotes). Written informed consent was obtained from all individuals participating in the ADNI study. 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.

### 1.2. Cerebrospinal fluid

Data for cerebrospinal fluid analyses were accessed from previously processed samples that were available through the ADNI website (http://loni.adni.usc.edu/). Lumbar punctures were performed as previously described in the ADNI procedures manual (http://www.adni-info.org/). CSF samples were frozen on dry-ice soon after collection (~1 hour) and shipped to the UPenn Medical Center ADNI Biomarker Core laboratory. Aliquots of 0.5 mL were prepared from these and stored in polypropylene tubes at −80 °C.

For the present study, preprocessed LONI data using the fully automated Roche Elecsys immunoassays (Bittner et al., 2016; Shaw et al., 2016) for $A\beta_{1-42}$, total-tau (t-tau), and phospho-$tau_{181P}$ (p-tau) were used for analyses (http://loni.adni.usc.edu/). Unthawed aliquots of ADNIGO/2 CSF samples were analyzed by the electrochemiluminescence immunoassays (ECLIA) for the 3 analytes on a fully automated Elecsys cobas e 601 instrument (software v05.02) and a single lot of reagents for each biomarker. These measures were gathered via a Roche Study Protocol at the UPenn/ADNI

**Table 1**
Baseline demographics and CSF biomarkers

| Demographics and CSF biomarkers | Overall (n = 239) | Females (n = 125) | | Males (n = 114) | | Uncorrected group comparison *p* value |
|---|---|---|---|---|---|---|
| | | APOEε4- (n = 98) | APOEε4+ (n = 27) | APOEε4- (n = 83) | APOEε4+ (n = 31) | |
| | Mean (*SD*) | | | | | |
| Age (years) | 74.3 (5.9) | 74.3 (5.6) | 72.9 (6.1) | 74.8 (5.5) | 73.9 (7.4) | 0.54 |
| Education (years) | 16.4 | 15.8 (2.5) | 16.2 (2.9) | 17.1 (2.5) | 16.5 (2.8) | 0.18 |
| Race (% white) | 90 | 89 | 93 | 93 | 87 | 0.71 |
| CSF $A\beta_{1-42}$ | 1331.8 (651.4) | 1434.7 (652.6) | 999.2 (606.2)[b] | 1418.4 (587.5) | 1064.2 (706.7)[b] | <0.001 |
| CSF t-tau | 239.8 (90.9) | 234.2 (96.5) | 283.4 (99.8)[b] | 221.9 (73.3) | 267.4 (93.1)[b] | <0.001 |
| CSF p-tau | 22.0 (9.4) | 21.0 (9.2) | 27.8 (11.6)[b] | 20.1 (7.8) | 25.3 (9.8)[b] | <0.001 |
| Aβ (% positive[a]) | 41 | 32 | 67 | 34 | 65 | <0.001 |

Key: CSF, cerebrospinal fluid; t-tau, total-tau; p-tau, phospho-tau.
[a] Based on published cutoff: positive = <1100 pg/mL (Hansson et al., 2018).
[b] significant difference between APOEε4+ and APOEε4−.

Biomarker Laboratory. Quantification of these measures was performed using 36 runs, with each sample running a single time for each of the 3 CSF analytes. For each run, quality control results were required to adhere to within stated limits to meet acceptance criteria for validation. Although each of the three CSF analytes were treated as continuous measures in analyses (in picograms per milliliter [pg/mL]), a cutoff for CSF $A\beta_{1-42}$ of 1100pg/mL was also used that best demarcated PET-positive and PET-negative groups from a previous publication (Bittner et al., 2016; Hansson et al., 2018).

### 1.3. Analyses

We used R (version 3.3.3) software to conduct a series of linear regressions and linear mixed models ascertaining the relationship between sex, *APOE*ε4, and CSF $A\beta_{1-42}$ on CSF t-tau and p-tau. Linear regression models were constructed to ascertain the effects of sex, *APOE*ε4, and baseline CSF $A\beta_{1-42}$ on CSF t-tau and p-tau at baseline after adjusting for the effect of age. Linear mixed effects models examined the influence of sex, *APOE*ε4, and baseline CSF $A\beta_{1-42}$ over time on longitudinal CSF t-tau and p-tau. Fixed effects of time were considered as both a main effect and in interaction with other predictors. In these models, random effects of intercept and slope were modeled using maximum likelihood estimation, while covarying for age at baseline. The following fully factorial linear mixed-effects models were examined:

Model 1: CSF tau[a] ~ Baseline CSF $A\beta_{1-42}$ OR sex OR *APOE*ε4 * time + age * time.

Model 2: CSF tau[a] ~ Baseline CSF $A\beta_{1-42}$ * sex * time + age * time.

Model 3: CSF tau[a] ~ Baseline CSF $A\beta_{1-42}$ * *APOE*ε4 * time + age * time.

Model 4: CSF tau[a] ~ Baseline CSF $A\beta_{1-42}$ *sex * *APOE*ε4 * time + age * time.

[a]tau = CSF t-tau or CSF p-tau.

We report all longitudinal analyses but also adjust for 12 multiple comparisons in our longitudinal analyses, using a Sidak-corrected $\alpha = 0.004$. As baseline analyses have been previously reported in the literature, and as such were not of direct interest, we did not include these comparisons in our significance adjustment. We ran post hoc analyses constraining CSF $A\beta_{1-42}$ to the technical limits of 200–1700 (i.e., 58 data points sat above the 1700 range, with none below, and so were constrained to 1700 but not removed from analyses) to confirm findings were not driven by outliers.

## 2. Results

### 2.1. Demographics

Subject demographics can be found in Table 1. There was no difference in the frequency of *APOE*ε4 status between males and females ($\chi^2 = 0.73$, $p = 0.39$). *APOE*ε4 carriers exhibited abnormal baseline CSF $A\beta_{1-42}$ and CSF tau. There was no significant difference by sex and *APOE* status with regard to length of time in the study ($F = 0.24$, $p = 0.65$). There were no differences in progression rates to MCI or dementia by sex (hazard ratio [HR] = 1.10 [95% CI: 0.53–2.29], $p = 0.79$), *APOE*ε4 status (HR = 1.93 [95% CI: 0.82–4.54], $p = 0.79$), or the interaction between these factors (HR = 1.92 [95% CI: 0.38–9.81], $p = 0.43$), after adjusting for age or CSF $A\beta_{1-42}$, t-tau, or p-tau slopes. In all, 32 individuals progressed to MCI or dementia over the course of the present study, with 15% female *APOE*ε4 carriers, 10% female noncarriers, 13% male carriers, and 17% male noncarriers progressing over approximately 4.43 years (SD = 3.1). The $R^2$ between p-tau and t-tau was 0.95, and as such, observed identical results with both outcomes for the cross-sectional analyses below. By contrast, the $R^2$ between t-tau and p-tau slopes was 0.74, and as such, their trajectories were highly, but not perfectly, correlated.

### 2.2. Baseline CSF t-tau and p-tau

Fig. 1 represents violin plots of sex, *APOE*, and CSF $A\beta_{1-42}$ on CSF t-tau and p-tau. After adjusting for age, both *APOE* and CSF $A\beta_{1-42}$ were significantly associated with greater CSF t-tau ($\beta_{APOE} = 0.23$, $p < 0.001$; $\beta_{A\beta} = 0.20$, $p = 0.002$), while *APOE* alone was associated with greater p-tau ($\beta_{APOE} = 0.28$, $p < 0.001$; $\beta_{A\beta} = 0.06$, $p = 0.35$).

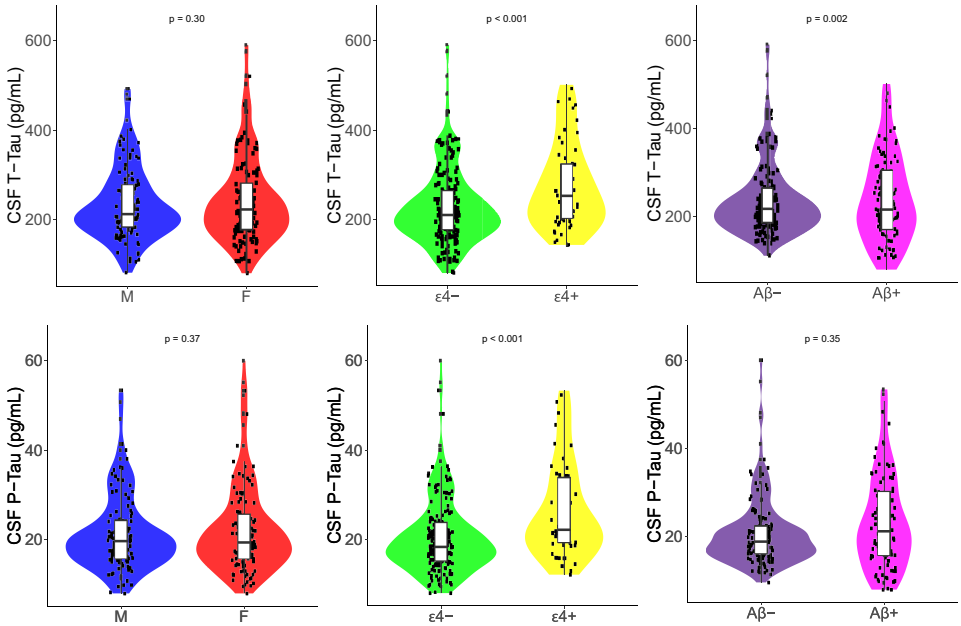


**Fig. 1.** Baseline CSF t-tau and p-tau by (A) sex (B) *APOE*ε4 status, and (C) CSF $A\beta_{1-42}$ status. The x-axis represents CSF t-tau or p-tau pg/mL at baseline. Each violin plot represents the density of the data at each level of pg/mL, with a boxplot overlaid to indicate the median level for each group.

**Table 2**
Unstandardized model estimates in association with longitudinal CSF t-tau and p-tau

| Variable | CSF t-tau | | | | | CSF p-tau | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Estimate | Std.Error | DF | *t* value | *p* value | Estimate | Std.Error | DF | *t* value | *p* value |
| Model 1A: Baseline CSF Aβ*Time | | | | | | | | | | |
| CSF Aβ | 0.02 | 0.01 | 236 | 2.97 | 0.003 | 0.001 | 0.001 | 236 | 0.84 | 0.40 |
| CSF Aβ:Time | −0.001 | 0.11 | 423 | −0.93 | 0.35 | −0.0002 | 0.0001 | 423 | −2.50 | 0.01 |
| Model 1B: Sex*Time | | | | | | | | | | |
| Sex (F) | 12.27 | 11.63 | 236 | 1.06 | 0.29 | 1.06 | 1.21 | 236 | 0.88 | 0.38 |
| Sex (F):Time | 0.19 | 1.29 | 423 | 0.15 | 0.88 | 0.02 | 0.14 | 423 | 0.17 | 0.87 |
| Model 1C: *APOE**Time | | | | | | | | | | |
| *APOEε4+* | 50.73 | 13.22 | 236 | 3.84 | <0.001 | 6.22 | 1.36 | 236 | 4.58 | <0.001 |
| *APOEε4+*:Time | −1.74 | 1.54 | 423 | −1.13 | 0.26 | 0.07 | 0.17 | 423 | 0.40 | 0.67 |
| Model 2: Baseline CSF Aβ*Sex*Time | | | | | | | | | | |
| CSF Aβ:Sex (F):Time | 0.001 | 0.002 | 421 | 0.53 | 0.59 | 0.0002 | 0.0002 | 421 | 1.15 | 0.25 |
| Model 3: Baseline CSF Aβ*_APOE_*Time | | | | | | | | | | |
| CSFAβ:*APOEε4+*:Time | −0.005 | 0.003 | 421 | −2.12 | 0.03 | 0.001 | 0.0002 | 421 | −2.50 | 0.01 |
| Model 4: Baseline CSF Aβ*Sex*_APOE_*Time | | | | | | | | | | |
| CSFAβ:Sex(F):*APOEε4+*:Time | −0.01 | 0.005 | 417 | −1.99 | 0.04 | −0.001 | 0.001 | 417 | −1.77 | 0.08 |
| Post hoc Model in FEMALES: Baseline CSF Aβ*_APOE_*Time | | | | | | | | | | |
| CSFAβ:*APOEε4+*:Time | −0.01 | 0.004 | 213 | −2.52 | 0.01 | | | | | |
| Post hoc Model in MALES: Baseline CSF Aβ*_APOE_*Time | | | | | | | | | | |
| CSFAβ:*APOEε4+*:Time | −0.003 | 0.003 | 203 | −1.06 | 0.29 | | | | | |

Sex had no association with baseline CSF t-tau ($\beta = 0.07$, $p = 0.30$) or CSF p-tau ($\beta = 0.06$, $p = 0.37$) after adjusting for covariates. There was no sex-*APOE* interaction on baseline CSF tau ($\beta_{t\text{-}tau} = 0.03$, $p = 0.83$; $\beta_{p\text{-}tau} = 0.10$, $p = 0.50$) and no sex-CSF $A\beta_{1-42}$ interaction on baseline CSF tau ($\beta_{t\text{-}tau} = < -0.001$, $p = 0.49$; $\beta_{p\text{-}tau} < -0.001$, $p = 0.39$); however, CSF $A\beta_{1-42}$-*APOE* was associated with CSF tau ($\beta_{t\text{-}tau} < -0.001$, $p = 0.03$; $\beta_{p\text{-}tau} < -0.001$, $p = 0.03$). A borderline three-way interaction between sex, *APOE,* and CSF $A\beta_{1-42}$ was found with CSF t-tau ($\beta < -0.001$, $p = 0.05$) but was subthreshold for p-tau ($\beta < -0.001$, $p = 0.07$).

### 2.3. Longitudinal CSF t-tau and p-tau

Model estimates can be found in Table 2 (with full models in Appendix A). After adjusting for age, baseline CSF $A\beta_{1-42}$ was trend-associated with increasing CSF p-tau levels ($t_{t\text{-}tau} = -0.93$, $p = 0.35$; $t_{p\text{-}tau} = -2.50$, $p = 0.01$); however, this did not survive multiple comparison. This effect appeared after the first year of follow-up ($p_{<1\ year} = 0.94$; $p_{>1\ year}$−0.01–0.002); to determine this significance, we subset data in the analyses according to follow-up year. Neither sex nor *APOE* genotype was associated with increasing CSF tau over time. No interactions between sex and CSF $A\beta_{1-42}$ were found on longitudinal CSF tau ($t_{t\text{-}tau} = 0.53$; $p = 0.59$; $t_{p\text{-}tau} = 1.15$; $p = 0.25$). An interaction between *APOE* and CSF $A\beta_{1-42}$ exhibited a trend-level association with changing CSF t-tau and p-tau ($t_{t\text{-}tau} = -2.12$; $p = 0.03$; $t_{p\text{-}tau} = -2.50$; $p = 0.01$; see Fig. 2) that did not survive multiple comparison. A post hoc analysis revealed that lower baseline CSF $A\beta_{1-42}$ was associated with increasing CSF t-tau and p-tau in *APOEε4* carriers ($t_{t\text{-}tau} = -1.93$, $p = 0.05$; $t_{p\text{-}tau} = -2.36$, $p = 0.02$), but not in noncarriers ($t_{t\text{-}tau} = -0.03$, $p = 0.97$; $t_{p\text{-}tau} = -0.92$, $p = 0.36$). When constraining CSF $A\beta_{1-42}$ to the technical limits of 200–1700 pg/mL (not removing these data points from the model), the interaction was not significant ($t_{t\text{-}tau} = -1.04$, $p = 0.30$; $t_{p\text{-}tau} = -1.77$, $p = 0.08$).

A three-way interaction between sex, *APOEε4* status, and CSF $A\beta_{1-42}$ was found only in association with rates of accumulation of CSF t-tau ($t = -1.95$, $p_{t\text{-}tau} = 0.04$; $t = -1.73$, $p_{p\text{-}tau} = 0.08$; see Fig. 3). After adjusting for multiple comparisons, however, this relationship was not considered significant. In addition, we found that one female *APOEε4* carrier outlier exhibited a strong influence on this relationship ($p_{t\text{-}tau} = 0.40$), and as such, this finding needs to be interpreted with caution. A post hoc analysis revealed a significant interaction between baseline CSF $A\beta_{1-42}$ and *APOEε4* status on CSF t-tau change in females ($t = -2.52$, $p = 0.01$) but not in males ($t = -1.11$, $p = 0.29$). That is, in the female group, *APOEε4* carriers showed greater CSF t-tau change in those with abnormal CSF $A\beta_{1-42}$ in comparison with noncarriers. When constraining CSF $A\beta_{1-42}$ to the technical limits of 200–1700 pg/mL, the above three-way interaction was not significant ($t = -1.81$, $p_{t\text{-}tau} = 0.07$; $t = -1.84$, $p_{p\text{-}tau} = 0.07$).

## 3. Discussion

We present preliminary findings suggesting a trend toward greater CSF tau accumulation in clinically normal *APOEε4* carriers with abnormal CSF $A\beta_{1-42}$ than noncarriers. In addition, these data provide preliminary evidence of a trend this greater tau accumulation occurring in female carriers. Because of the trend-level associations reported in our results, however, replication is necessary in other longitudinal cohorts. Accumulating evidence supports an important role of the interaction between Aβ and tau in the earliest stages of AD pathophysiology. This Aβ-tau interaction has been shown to have greater impact than either pathology alone on glucose metabolism (Hanseeuw et al., 2017), resting-state functional connectivity (Schultz et al., 2017), retrospective (Schöll et al.,

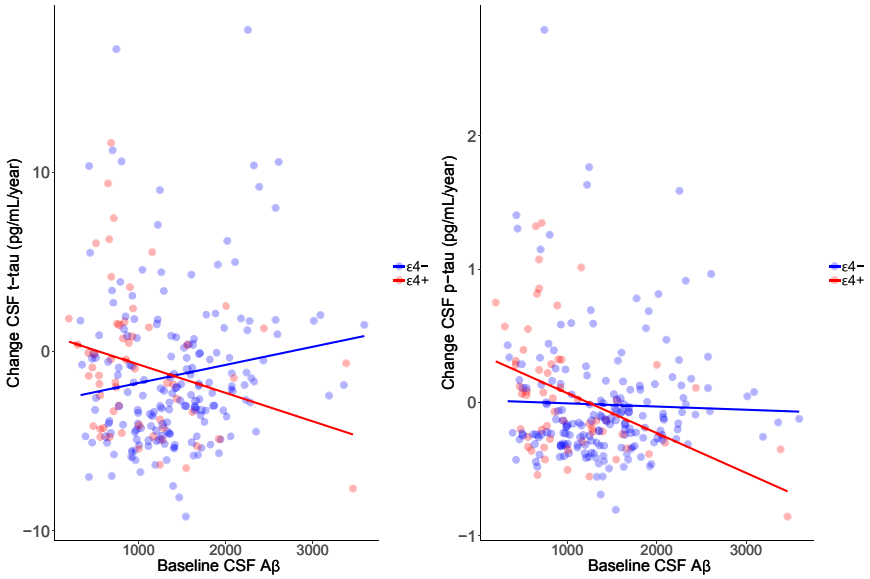


**Fig. 2.** Longitudinal CSF t-tau and p-tau slopes by baseline CSF $A\beta_{1-42}$ as stratified by *APOEε*4 status. The y-axis represents slopes of CSF tau change in pg/mL per year (extracted from linear mixed models), whereas the x-axis represents baseline CSF $A\beta_{1-42}$. The colors represent red = *APOEε*4 carriers and blue = *APOEε*4 noncarriers.(For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2016) or prospective cognitive decline (Sperling et al., 2018), and clinical progression (Desikan et al., 2012; Hansson et al., 2006). In this longitudinal CSF data set, we observed a significant association between baseline CSF $A\beta_{1-42}$ and the rate of CSF p-tau accumulation using the Roche Elecsys immunoassay, indicating that both pathologies interact in clinically normal older adults. Baseline CSF $A\beta_{1-42}$ did not predict t-tau change as some *APOEε*4 noncarriers with normal Aβ had an increase in t-tau but not p-tau (see Fig. 2) supporting the notion that t-tau changes may be less specific to AD physiopathology. Both analytes are proximal to clinical progression of the disease (Mattsson et al., 2009) and tau-PET topographies (Brier et al., 2016), however, and are traditionally highly correlated together (Mattsson et al., 2009), although their slopes do not correlate as well as their baseline values. Among *APOEε*4 carriers, we found baseline CSF $A\beta_{1-42}$ was associated with both t-tau and p-tau changes. By contrast, previous reports using overlapping data with the xMAP immunoassay have not reliably revealed an association between baseline CSF Aβ and longitudinal CSF p-tau (Donohue et al., 2017) underscoring the use of the more advanced assay to interrogate CSF tau accumulation.

This study is the first to describe the interactive effect of *APOE* genotype and CSF $A\beta_{1-42}$ on longitudinal measures of CSF t-tau and p-tau in a CN cohort. Previous cross-sectional findings of clinically normal older adults did not find a relationship between *APOE* and CSF tau (Morris et al., 2010). Indeed, *APOE* has been more closely associated with Aβ than tau at the cross-section (Morris et al., 2010) and has also been associated with faster Aβ accumulation in CN older adults with subthreshold levels of baseline Aβ (Lim et al., 2017). Similar to our findings, an earlier study in ADNI using the xMAP immunoassay did not report a main effect of *APOE* on longitudinal changes in CSF tau (Toledo et al., 2013). Our findings suggest that *APOEε*4 carriers do exhibit greater tau accumulation, but only in those with abnormal Aβ, and this effect was subtle. Mouse models support Aβ-associated neuritic degeneration exacerbated by the presence of the apolipoprotein E protein (i.e., in apoE+ mice) (Holtzman et al., 2000). Although interactive effects of *APOE* and baseline Aβ on changes in tau have not yet been reported, effects on downstream cognitive decline have been repeatedly shown (Lim et al., 2015; Mormino et al., 2014), highlighting the deleterious effect of *APOE* on pathological processes in AD. Effects of *APOE* and baseline Aβ on neurodegeneration are less robust (Jack et al., 2015; Villemagne et al., 2013), suggesting that *APOE* genotype may express only subtle effects on downstream pathology. Because of issues of power, we did not explore dose-response effects based on heterozygotic or homozygotic genotype; it is possible that stronger effects exist in homozygotes, which may be masked by the rarity of this variant.

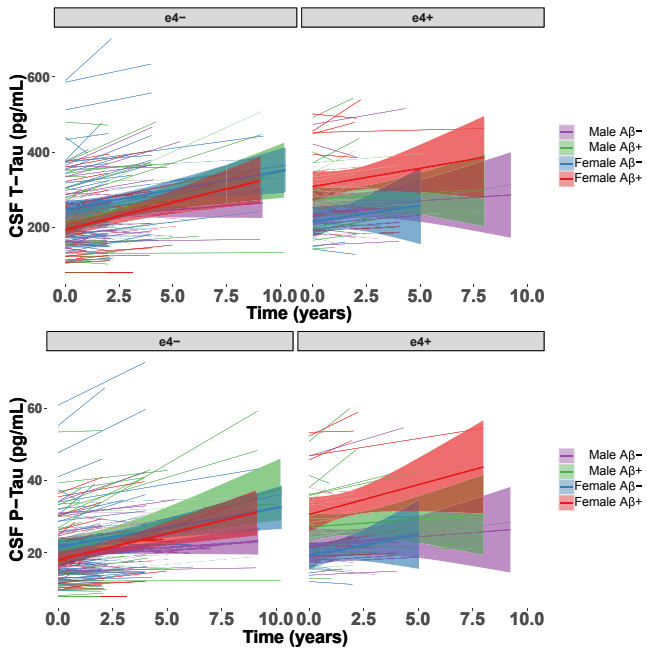


**Fig. 3.** Longitudinal CSF t-tau and p-tau accumulation by sex, *APOE*, and baseline CSF $A\beta_{1-42}$ (depicted here as a dichotomous variable). The y-axis represents CSF tau pg/mL, whereas the x-axis represents time in the study (in years). The colors represent purple = male Aβ−, green = male Aβ+, blue = female Aβ-, red = female Aβ+.(For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Although cross-sectional differences in CSF tauopathy predominantly exist in cognitively impaired female *APOEε4* carriers, regardless of Aβ (Altmann et al., 2014; Hohman et al., 2018), our findings, suggest that in clinically normal individuals, changes in CSF tau can be detected in clinically normal female *APOEε4* carriers when CSF $A\beta_{1-42}$ levels at baseline are abnormally low. This finding must be interpreted with caution as it did not survive multiple comparison adjustment and was influenced, to some degree, by outliers. Nevertheless consistent with our finding, Hohman et al recently observed that CN female *APOEε4* carriers with low CSF $A\beta_{1-42}$ had higher tau levels at the cross-section in a meta-analysis of several independent cohorts (Hohman et al., 2018). It is very possible that the early appearance of Aβ in preclinical stages of the disease instigate downstream tauopathological events (Sperling et al., 2014), which may represent the crucial epicenter for emerging sex differences in AD risk. Taken together, our findings and those of others support the notion of an interaction between sex and *APOE* to play a disease modifying role on the Aβ-tau relationship. The present study, however, extends beyond cross-sectional evidence and provides preliminary longitudinal evidence of sex-*APOE* effects on CSF tau changes in preclinical AD.

In transgenic mouse models, deposition of both Aβ and tauopathy are greater in females. In a mouse model that expresses both mutant tau (P301 L) and Aβ precursor protein (APP), females show greater and earlier neurofibrillary deposition than males (Lewis et al., 2001). This same study also reported this female bias exists to a greater extent in the double-mutation than solely in models of mutant tau alone. The authors posited this arose as a function of sex differences in initial levels of Aβ accumulation (supported by findings of sex differences in the Tg2576 mouse model that exhibits only mutant APP (Callahan et al., 2001)). Human studies have not replicated sex differences in Aβ burden with either CSF (Altmann et al., 2014) or PET imaging (Mielke et al., 2012; Morris et al., 2010); however, a recent study suggests clinically normal females with familial history of AD dementia may exhibit greater Aβ accumulation than males with familial history proximal to estimated parental year of onset (Villeneuve et al., 2018). Furthermore, recent studies also suggest that clinically normal females display faster cognitive decline (Buckley et al., 2018) and hippocampal atrophy (Koran et al., 2017) than males despite similarly abnormal levels of Aβ, implying that female susceptibility to tauopathy and neurodegeneration may occur after the onset of Aβ abnormality. Further investigations are needed, however, to fully elucidate the temporal pattern of sex-related differences along the AD pathophysiologic trajectory.

The present study has several limitations. A major drawback involves the trend-level results that we report in this study; although these findings allude to a promising relationship between sex, *APOE,* and Aβ to influence CSF tau, it is imperative to replicate these data in other out-of-sample cohorts. These data also involve a convenience subsample of participants from the ADNI study who opted into serial CSF collection, and as such, are not representative of the wider population. In addition, the ADNI population includes large highly educated, less racially diverse, and higher-socioeconomic individuals, which also limits the generalizability of these findings. It will be important for future studies to examine other covariates, beyond age, that might influence sex and *APOE* relationships on CSF $A\beta_{1-42}$ and longitudinal tau. Our analyses also included CSF $A\beta_{1-42}$ data that were extrapolated beyond the technical limits of the 200–1700 pg/mL measuring range of the Elecsys assay. To account for this, we also carried out *post hoc* analyses within these ranges and found the same pattern of results; however, these findings require replication in an independent sample. Furthermore, the issue of multiple comparisons and outlier influences, along with a large majority of sex difference findings in this area arising from ADNI, underscores the need for validation in another sample.

Further, postmortem research has found that for a given level of clinical impairment at death, females exhibit greater expression of both neuritic plaques and neurofibrillary tangles (Barnes et al., 2005). Here, the authors implicated *APOEε4* as the mechanistic pathway for female vulnerability. The biological mechanism explaining the greater impact of *APOEε4* on females remains unclear; however, animal models have implicated the role of sex hormones (Pfankuch et al., 2005). Indeed, the menopausal phase cannot be discounted as a watershed moment in the critical loss of protection for females along the AD pathophysiological pathway, which may be exacerbated by *APOEε4* (Hasanpour et al., 2018).

## 4. Conclusions

We provide evidence that clinically normal *APOEε4* carriers with abnormal baseline CSF $A\beta_{1-42}$ exhibit accelerated rates of longitudinal CSF t-tau and p-tau change in comparison with noncarriers with similar levels of CSF $A\beta_{1-42}$. Specifically, preliminary findings suggest that female *APOEε4* carriers demonstrated a stronger Aβ-tau relation than males *APOEε4* carriers. Mounting evidence implicates female-*APOEε4* vulnerability to tau across the diagnostic spectrum. Although recent work supports the notion of sex-*APOE* effects on CSF tau at the cross-section across multiple independent cohorts (Hohman et al., 2018), our findings reveal the potential early emergence of sex-*APOE* differences in longitudinal tau in preclinical AD, mirroring findings in transgenic mouse models of AD.

## Disclosure

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2019.02.019.

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