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Original Research

Is late-life vulnerability to cardiovascular disease risk associated with longitudinal tau accumulation in older adults with mild cognitive impairment?

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ABSTRACT

Background: Older females have higher Alzheimer's Disease (AD) risk and tau burden, especially in early disease stages, compared to males. Overlapping cardiovascular disease (CVD) and dementia risk factors, like the apolipoprotein (APOE)-ε4 allele, show mixed sex-specific results. We previously found that late-life CVD risk related more strongly to tau at a single timepoint in cognitively normal, older female APOE-ε4 carriers than in males.

Objectives: Do composite and component CVD risk factors explain sex differences in tau accumulation in older adults with mild cognitive impairment (MCI) and underlying amyloid-beta (Aβ) pathology?

Design: Longitudinal analysis in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort.

Setting: ADNI is a multi-site longitudinal study across the United States and Canada.

Participants: $n = 52$ older adults (aged 60–90), designated as both Aβ-positive and MCI.

Measurements: CVD risk was measured by body mass index (BMI) and FRS, which includes age, systolic blood pressure (BP), high-density lipoprotein (HDL), total cholesterol, hypertension treatment, smoking, and diabetes. Regional standardized uptake value ratios (SUVRs) were extracted at each tau-PET timepoint. Composite SUVRs for Braak34 and Braak56 were calculated. Statistical models examined the separate and interactive effects of sex and APOE-ε4 on tau accumulation, and moderating effects of FRS, its components, or BMI, on tau accumulation.

Results: Females accumulated more tau than males in bilateral Braak34 and right Braak56, while APOE-ε4 carriers trended toward more tau accumulation in left Braak56. FRS and its components did not relate to tau accumulation, nor influence sex effects, although they attenuated APOE-ε4 effects. In left Braak56, higher baseline BMI in males showed a trend toward greater tau accumulation.

Conclusions: In MCI and Aβ-positive older adults, females accumulated more tau than males, and late-life vascular risk did not explain this relationship. Higher BMI related to more tau accumulation in males only, suggesting sex-specific vulnerability to BMI on brain health. Although replication in larger and more representative cohorts is needed, these findings corroborate accelerated tau progression in older females, independent of CVD risk, and suggest that vascular health has limited influence on tau progression once AD pathology is established in the brain.

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1. Introduction

omen are affected by Alzheimer's disease (AD) at a higher rate than men [1,2], only partly explained by their greater longevity [3,4], and studies suggest that women have higher levels of pathological tau [5–9], one of the hallmark AD pathologies, in the brain. This sex difference in pathology has been demonstrated in cognitively normal older adults and across the AD diagnostic continnuum [6,7], but particularly in the mild cognitive impairment (MCI) stage, females demonstrate greater tau burden [8] and faster rates of tau accumulation over time [9] compared to men. Furthermore, females tend to show higher vulnerability to AD risk associated with the apolipoprotein $\varepsilon 4$ (APOE-$\varepsilon 4$) allele, such that female carriers exhibit more rapid cognitive decline [10], greater pathological tau burden [11], and higher AD incidence rates [12], compared to male carriers.

It has been established that cardiovascular disease (CVD) risk factors such as mid-life hypertension, smoking, and obesity are associated with higher risk for dementia in later-life [13,14]. Furthermore, animal and human studies have demonstrated that CVD risk factors promote AD-related neuropathology and overlap with well-established AD risk factors [15], including the APOE-$\varepsilon 4$ genotype. At a molecular level, the APOE genotype dictates the properties and functions of the resulting protein isoform, such that the APOE-$\varepsilon 2$, APOE-$\varepsilon 3$, and APOE-$\varepsilon 4$ isoforms differentially interact with various lipoprotein receptors [16], in turn influencing the level of plasma metabolites such as cholesterol. This association has been explored as a potential mechanism by which the APOE-$\varepsilon 4$ genotype heightens plasma high density lipoprotein (HDL) cholesterol levels. Although the APOE-$\varepsilon 4$ allele is the strongest genetic risk factor for sporadic AD, there are conflicting results as to whether APOE-$\varepsilon 4$-associated elevated HDL, especially in later-life, increases AD risk [17,18].

More specific links between vascular risk factors and the AD pathologies of amyloid-beta (Aβ) and pathological tau have also been explored. When coupled with Aβ, the Framingham Risk Score (FRS), a composite measure of vascular disease risk, has been associated with higher tau burden in the inferior temporal cortex of cognitively normal older adults [19]. Furthermore, longitudinal studies in cognitively normal older adult cohorts demonstrated that higher FRS was associated with increases in brain and cerebrospinal fluid (CSF) tau accumulation [20]. Despite evidence of overall vascular risk relating to greater tau pathology in later life, it is unclear whether certain components are working synergistically to promote pathology or whether a specific component of cardiovascular risk may be driving these effects. For example, Vemuri et al. [21] found that hyperlipidemia had a greater effect on entorhinal cortex tau compared to hypertension or diabetes, whereas Glodzik et al. [22] found decreases in mean arterial pressure related to increased pathological tau in CSF in hypertensive participants only. There are also conflicting results on how the associations between vascular risk factors and AD-related outcomes differ by sex; while Hayden et al. [23] and Gilsanz et al. [24] found that obesity and mid-life hypertension increased risk for incident dementia in females only, others found that hypertension and obesity are associated with increased risk of incident AD specifically in males [25,26].

In our previous cross-sectional study examining the relationship between CVD risk and early cortical tau deposition among older adults of the Alzheimer's Disease Neuroimaging Initiative (ADNI), we found that associations were stronger for female APOE-$\varepsilon 4$ carriers than male carriers [27]. The current study investigates whether vulnerability to vascular disease risk factors might explain the higher longitudinal tau accumulation in females with MCI and existing Aϵ pathology, compared to males. Our objective was to understand whether body mass index (BMI) and specific components of the FRS account for sex differences in tau accumulation in the Braak34 and Braak56 regions, where tau typically spreads during the MCI stage of AD. Based on our prior findings, we expected to find greater tau accumulation in females, driven by APOE-$\varepsilon 4$ genotype, and we hypothesized that this difference might be accounted for by BMI and other specific or compound vascular risk factors.

2. Methods

2.1. Participants

Data were downloaded from the ADNI database, which is publicly accessible at https://adni.loni.usc.edu. ADNI is a multi-site longitudinal study dedicated to characterizing the AD trajectory using neuroimaging and biological methods. In order to enrich our sample for participants who were likely to accumulate tau, we restricted our sample to those who were MCI (ADNI diagnostic criteria described in Weiner et al. [28]) and Aβ-positive based on Aβ-PET (Florbetapir-AV45) at baseline, given previous findings where associations between CVD factors and tau pathology were specific to Aβ-positive cohorts. Baseline Aβ values were used to determine amyloid status, with the threshold for Aβ-positive being a standardized uptake value ratio (SUVR) greater than 1.44 in regions including the frontal, temporal, parietal, and cingulate cortices [29]. Among ADNI participants who were MCI and Aβ-positive at baseline, we included participants who had T1-weighed MRI data and two tau (Flortaucipir-AV1451) PET scans obtained between nine to thirty months apart. Additionally, we only included participants who had complete clinical and medical history data required for the FRS calculations, vitals for baseline blood pressure (BP), and height and weight for BMI calculations. Supplemental Figure 1 shows the flowchart for inclusion of participants in the final analytical sample of $n = 52$.

2.2. Image Acquisition and Processing

In ADNI, T1-weighted images were acquired at multiple study sites and underwent quality control and intensity normalization, further described on the ADNI website (https://adni.loni.usc.edu/data-samples/adni-data/neuroimaging/mri/). T1-weighted scans were further processed using Freesufer v6.0 (https://surfer.nmr.mgh.harvard.edu), which included a subcortical segmentation and cortical parcellation (Desikan–Killainy atlas) to obtain volume measures for each region of interest (ROI). Tau-PET scans were acquired 75-105 minutes post injection of 10.0 mCi ± 10 % of AV-1451 and downloaded as raw data files from ADNI. Our tau-PET processing pipeline was modeled after "Flortaucipir (AV-1451) processing methods" [30], which calculates a regional SUVR by coregistering the PET scan to the T1-weighted image, and then dividing ligand signal in each Freesurfer-derived ROI by the signal in the reference region, the cerebellar grey matter, as recommended for longitudinal tau-PET processing [31]. Braak regions were calculated using a previously defined approach in Landau & Jagust [30] from regional partial volume corrected (PVC) tau SUVRs to calculate volume weighted averages for Braak34 and Braak56. Braak12 was not investigated due to known off-target binding of AV-1451 in the choroid plexus [32]. Supplemental Figure 1 illustrates criteria for participant inclusion/exclusion for image processing, with participants who underwent image processing ($n = 116$) being removed throughout the pipeline for improper image format ($n = 9$), lack of scanner smoothing information ($n = 12$), and outliers for time between tau-PET scans ($n = 15$).

2.3. FRS and BMI Calculation

The FRS, which is a sex-specific composite measure of CVD risk was calculated following the method outlined in D'Agostino et al. [33]. Using each participant's age, systolic BP, HDL and total cholesterol, hypertension treatment status, smoking status, and diabetic status, points are differentially allotted for males and females to generate an FRS value, where higher scores indicate more risk for developing CVD. For FRS calculation, age and sex were determined from subject demographics at baseline, which is available through ADNI "Subject Characteristics". The systolic BP component of the FRS, as well as the height and

Table 1
Characteristics of the Sample by Sex.

	Female (n = 21)	Male (n = 31)	Overall (n = 52)	p-value	es[a]
Age					
Mean (SD)	74.0 (7.66)	75.2 (6.46)	74.7 (6.92)	0.547	0.171
Median [Min, Max]	75.0 [60.0, 89.0]	75.0 [65.0, 90.0]	75.0 [60.0, 90.0]		
Years of Education					
Mean (SD)	15.0 (2.65)	16.9 (2.59)	16.1 (2.75)	**0.014**	**0.716**
Median [Min, Max]	15.0 [12.0, 20.0]	17.0 [12.0, 20.0]	16.0 [12.0, 20.0]		
APOE-ε4					
n (%)	12 (57%)	14 (45%)	26 (50%)	0.572	0.078
HDL					
Mean (SD)	64.5 (14.9)	53.8 (10.7)	58.1 (13.5)	**0.004**	**0.855**
Median [Min, Max]	62.9 [41.6, 97.7]	50.5 [39.9, 76.5]	54.9 [39.9, 97.7]		
Smoking status					
n (%)	3 (14%)	3 (10%)	6 (11%)	0.946	0.009
Systolic BP					
Mean (SD)	128 (13.5)	129 (15.9)	129 (14.9)	0.900	0.036
Median [Min, Max]	128 [103, 155]	128 [100, 168]	128 [100, 168]		
Total Cholesterol					
Mean (SD)	227 (41.9)	183 (33.4)	201 (42.5)	**< 0.001**	**1.173**
Median [Min, Max]	225 [160, 321]	189 [124, 248]	196 [124, 321]		
BMI					
Mean (SD)	30.1 (7.34)	27.9 (3.67)	28.8 (5.49)	0.169	0.394
Median [Min, Max]	27.4 [20.2, 47.9]	27.5 [21.5, 34.5]	27.4 [20.2, 47.9]		
FRS					
Mean (SD)	14.9 (3.83)	17.5 (3.77)	16.4 (3.97)	**0.020**	**0.68**
Median [Min, Max]	16.0 [7.00, 21.0]	17.0 [10.0, 25.0]	16.0 [7.00, 25.0]		

Abbreviations: APOE-ε4 = Apolipoprotein E ε4 allele; HDL = high density lipoprotein cholesterol; BP = Blood Pressure; BMI = Body Mass Index (kg/ m^2); FRS = Framingham Risk Score; [a]es=effet size (Cohen' s d for continuous variables and Cramer 's V for categorical variables); Bold font text indicates a statistically significnt group diffe ence.

weight used for BMI [53] calculation, was downloaded from ADNI "Vital Signs [ADNI1, GO, 2, 3]" file within Physical/Neurological Exams, where measurements closest in time to the baseline PET scans were used. BMI was calculated as weight in kilograms / (height in meters)2. HDL and total cholesterol were obtained from the file "ADMC Nightingale Platform NMR Analysis of Lipoproteins and Metabolites Longitudinal [ADNI1, GO, 2]" within Biospecimen Results in ADNI. For FRS, total cholesterol and HDL were converted to mmol/L by multiplying by 38.67, then rounded to the nearest whole number. Diabetic status was found in the "Recent Medical History Details Log [ADNI1, GO, 2]" file in the Medical History section of ADNI, and smoking status was self-reported in "Medical History [ADNI1, GO, 2]".

2.4. Statistical approach

Multiple regression analyses using PVC tau-PET data were used to assess change in tau levels over time. We used the covariate adjustment approach where baseline tau SUVR was included as a covariate in the model; a preferred alternative to difference score analysis to analyze two-wave longitudinal data [34]. Specifically we used a hierarchal regression (ANCOVA-type approach) to regress tau SUVRs at the second timepoint (dependent variable) for each Braak region onto baseline tau values and demographic predictors, or independent variables, including sex, age, and APOE-ε4 status (model 1). Subsequent models introduced FRS (model 2) or component cardiovascular predictors (model 3). Cardiovascular predictors included BMI as well as the individual components of the FRS: HDL, smoking status, systolic BP, and total cholesterol (variance inflation factor [VIF] values for these predictors were all less than 2). Diabetic status was not considered as a cardiovascular risk component due to the inconsistencies in self-reported medical history, insulin-dependency, and serum insulin values, in determining status. Finally, we examined whether APOE-ε4, FRS, or BMI interact with sex to predict tau accumulation. Model comparisons were based on the significance of specific predictors and the difference in the total variance explained (ΔR2). Significance was determined using a two-tailed test, with $p < 0.05$. All analyses were conducted using R (version 4.3.1) and the base stats package. All models controlled for the time interval between scans. Model residuals for the first hierarchical model were examined for normality using the Lilliefors test and were found to satisfy the normality assumption. Change scores (tau at second time point minus baseline tau) were calculated for the purposes of plotting results. A supplemental analysis using non-PVC data is included and reported in Supplemental Table 1.

3. Results

3.1. Participants

See Table 1 for sample characteristics stratified by sex. The final sample of 52 Aβ positive subjects with MCI included 21 females and 31 males. There were no significant differences between the average age (female vs. male $M = 74.0 \pm 7.7$ yearsvs. 75.2 ± 6.5 years), systolic BP (female vs. male $M = 128$ vs. 129), BMI (female vs. male $M = 30.1$ vs. 27.9), nor in the percentage of APOE-ε4 carriers (female vs. male 57 % vs. 45 %) between the male and female participants (all ps < 0.05). Female participants had significantly higher plasma HDL (female vs. male $M = 64.5$ vs. 53.8) and total cholesterol (female vs. male $M = 227$ vs. 183) levels than males ($ps < 0.01$); Males were significantly more

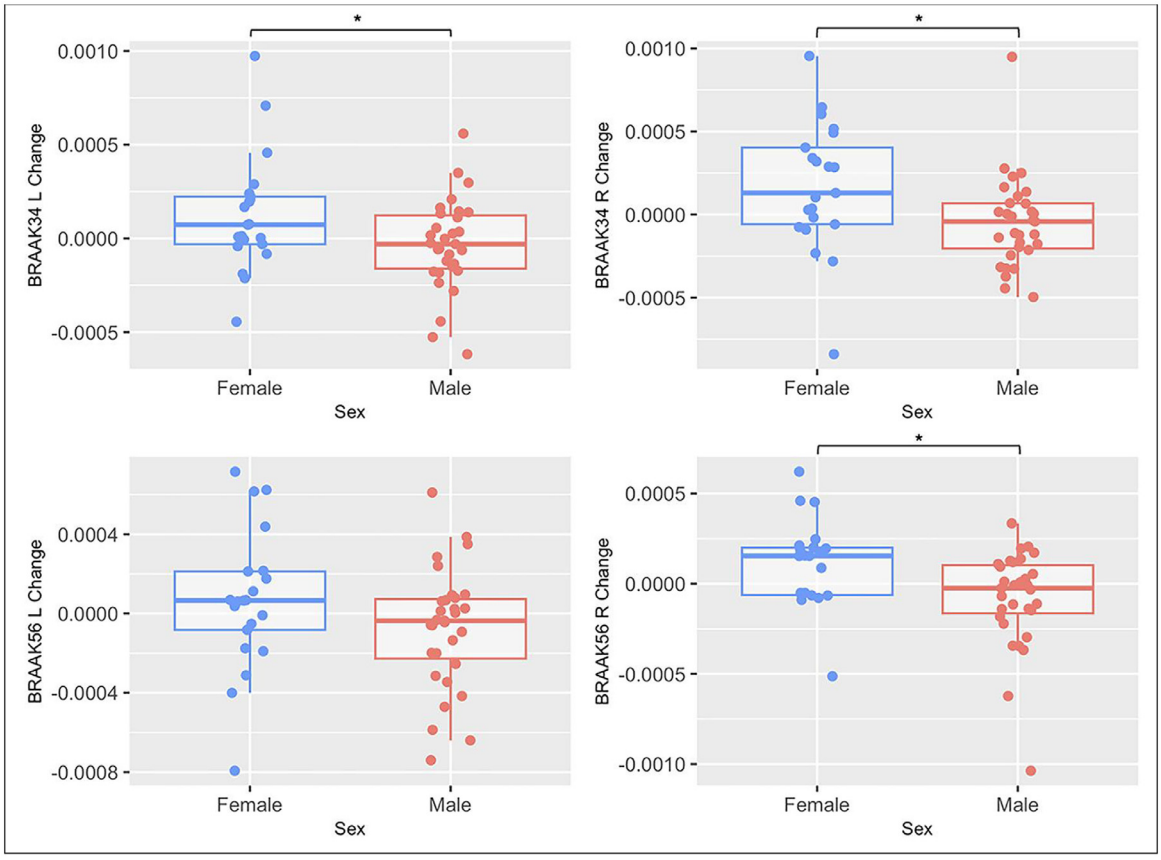


Fig. 1. Change in Tau Standardized Uptake Value Ratio in Braak34 and Braak 56 Left (L) and Right (R) by sex.

educated (female vs. male M = 15.0 vs. 16.9; p = .01), and had higher composite FRS scores (female vs. male M = 14.9 vs. 17.5; p = 0.02).

3.2. Demographic predictors of tau accumulation in Braak regions

Fig. 1 demonstrates patterns of tau accumulation in Braak34 and Braak56 in females and males. There was a significant effect of sex on tau accumulation in Braak34 bilaterally (right: β = 0.218, p = .029; left: β = 0.213, p = .016) with females accumulating more tau over time relative to men. Females also showed significantly greater tau accumulation in right hemisphere Braak56 (β = 0.192, p = 0.016), but not left hemisphere Braak56 (β = 0.154, p = .131). There was no effect of APOE-ε4 on tau accumulation in Braak34 bilaterally (right: β = 0.116, p = .254; left: β = 0.126, p = 0.138), and in right Braak56 (β = 0.069, p = 0.368), but there was a trending main effect of APOE-ε4 on tau accumulation in left Braak56 such that carriers accumulated more tau over time than non-carriers (β = 0.163, p = 0.093). Table 2 presents complete model parameter estimates using PVC data. Analyses were repeated with non-PVC data (Supplemental Table 1), and remained substantively unchanged.

3.3. FRS as a predictor of tau accumulation in Braak regions

FRS did not predict tau accumulation in bilateral Braak34 (right: β = -0.009, p = .50; left: β = -0.009, p = 0.421) nor in Braak56 (right: β = -0.003, p = 0.816; left: β = -0.016, p = 0.229). FRS attenuated the trending main effect of APOE-ε4 in left Braak56 (β = 0.138, p = 0.161). Controlling for composite FRS had a minor impact on the main effects of sex on tau accumulation. Specifically, right Braak34 moved slightly over the non-significant threshold (p = 0.054), both left Braak34 (p = 0.023) and right Braak56 (p = 0.025) remained significant, and left Braak56 remained non-significant (p = 0.221). Table 2 contains complete model parameter estimates using PVC data. Analyses did not substantively change when repeated with non-PVC data (Supplemental Table 1).

3.4. Component cardiovascular predictors of tau accumulation in Braak regions

For the component cardiovascular predictors, HDL, smoking status, systolic BP, total cholesterol, and BMI were all not related to tau accumulation (Table 2, all ps> .05). The cardiovascular components attenuated the trending main effect of APOE-ε4 in left Braak56 (β = 0.147, p = 0.130). In addition, the cardiovascular components did not change the pattern of the observed sex effects in left Braak34 (β = 0.203, p = 0.046), nor in bilateral Braak56 (right: β = 0.267, p = 0.009; left: β = 0.194, p = 0.103); however, the significant main effect of sex dropped to trending in right Braak34 (β = 0.225, p = 0.066). When using non-PVC data (Supplemental Table 1), main effects of sex and APOE-ε4 were not substantively affected by component cardiovascular factors.

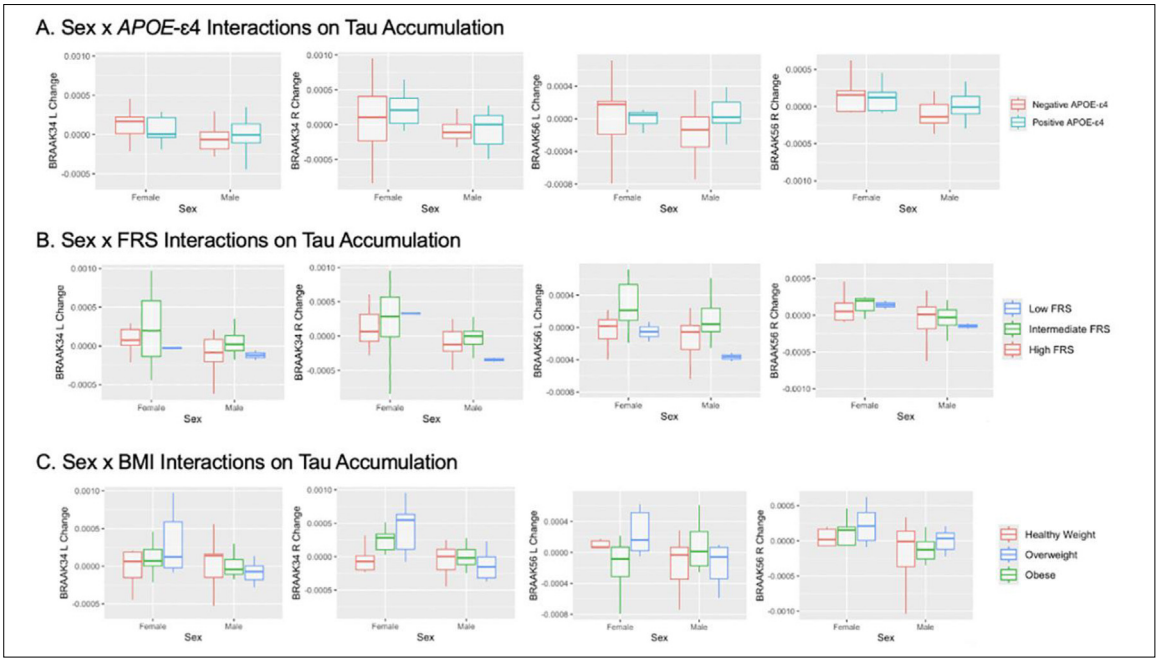
3.5. Interaction effects between Sex and APOE-ε4, FRS, and BMI

Fig. 2A-C shows the relationships between tau accumulation and sex by APOE-ε4, FRS, and BMI respectively. Table 3 reports parameter estimates for each moderator (interaction term). FRS and APOE-ε4 showed non-significant interactions with sex when predicting tau accumulation in both Braak34 and Braak56 bilaterally (all ps> .10), and visual inspection of Figure 3A does not reveal an apparent pattern in sex differences between APOE-ε4 carriers and non-carriers regarding change in tau. Similarly, sex and FRS showed non-significant interactions when predicting tau accumulation in both Braak34 and Braak56 bilaterally

Table 2
. Results of Hierarchical Regression Analyses using PVC data.

Region	Predictor	Beta	p-value	Predictor	Beta	p-value	Predictor	Beta	p-value
Braak34 Right	Intercept	5.058	< 0.001	Intercept	5.054	< 0.001	Intercept	4.824	< 0.001
Braak34 Right	Braak34 Right T1	0.994	< 0.001	Braak34 Right T1	0.989	< 0.001	Braak34 Right T1	0.995	< 0.001
Braak34 Right	Age	0.003	0.778	Age	0.005	0.632	Age	0.006	0.561
Braak34 Right	TD	0.073	0.494	TD	0.083	0.442	TD	0.087	0.445
Braak34 Right	APOE-ε4	0.116	0.254	APOE-ε4	0.103	0.321	APOE-ε4	0.118	0.268
Braak34 Right	Female	0.218	0.029	FRS	-0.009	0.500	HDL	-0.004	0.397
Braak34 Right				Female	0.200	0.054	Smoker	-0.251	0.121
Braak34 Right							Sys. Blood Press.	-0.001	0.792
Braak34 Right							Total Cholesterol	0.001	0.578
Braak34 Right							BMI	0.007	0.486
Braak34 Right							Female	0.225	0.066
Braak34 Left	Intercept	4.365	< 0.001	Intercept	4.318	< 0.001	Intercept	4.452	< 0.001
Braak34 Left	Braak34 Left T1	0.961	< 0.001	Braak34 Left T1	0.953	< 0.001	Braak34 Left T1	0.974	< 0.001
Braak34 Left	Age	0.010	0.153	Age	0.013	0.105	Age	0.012	0.133
Braak34 Left	TD	0.127	0.148	TD	0.14	0.120	TD	0.137	0.136
Braak34 Left	APOE-ε4	0.126	0.138	APOE-ε4	0.118	0.169	APOE-ε4	0.118	0.172
Braak34 Left	Female	0.213	0.016	FRS	-0.009	0.421	HDL	-0.006	0.159
Braak34 Left				Female	0.203	0.023	Smoker	-0.227	0.081
Braak34 Left							Sys. Blood Press.	-0.002	0.479
Braak34 Left							Total Cholesterol	0.001	0.246
Braak34 Left							BMI	0.004	0.559
Braak34 Left							Female	0.203	0.046
Braak56 Right	Intercept	3.682	< 0.001	Intercept	3.694	< 0.001	Intercept	3.661	< 0.001
Braak56 Right	Braak56 Right T1	1.005	< 0.001	Braak56 Right T1	1.006	< 0.001	Braak56 Right T1	0.972	< 0.001
Braak56 Right	Age	0.004	0.503	Age	0.004	0.484	Age	0.006	0.380
Braak56 Right	TD	0.005	0.956	TD	0.007	0.936	TD	0.034	0.714
Braak56 Right	APOE-ε4	0.069	0.368	APOE-ε4	0.065	0.419	APOE-ε4	0.108	0.200
Braak56 Right	Female	0.192	0.016	FRS	-0.003	0.816	HDL	-0.001	0.786
Braak56 Right				Female	0.187	0.025	Smoker	0.02	0.877
Braak56 Right							Sys. Blood Press.	0.001	0.740
Braak56 Right							Total Cholesterol	-0.002	0.218
Braak56 Right							BMI	0.003	0.738
Braak56 Right							Female	0.267	0.009
Braak56 Left	Intercept	3.114	< 0.001	Intercept	3.139	< 0.001	Intercept	2.626	0.003
Braak56 Left	Braak56 Left T1	0.971	< 0.001	Braak56 Left T1	0.963	< 0.001	Braak56 Left T1	0.951	< 0.001
Braak56 Left	Age	0.009	0.258	Age	0.012	0.148	Age	0.012	0.141
Braak56 Left	TD	0.042	0.692	TD	0.061	0.566	TD	0.072	0.498
Braak56 Left	APOE-ε4	0.163	0.093	APOE-ε4	0.138	0.161	APOE-ε4	0.147	0.130
Braak56 Left	Female	0.154	0.131	FRS	-0.016	0.229	HDL	0.007	0.096
Braak56 Left				Female	0.127	0.221	Smoker	-0.205	0.170
Braak56 Left							Sys. Blood Press.	0.001	0.772
Braak56 Left							Total Cholesterol	-0.002	0.104
Braak56 Left							BMI	0.007	0.436
Braak56 Left							Female	0.194	0.103

Abbreviations: PVC = Partial Volume Corrected; T1 = baseline; APOE-ε4 = Apolipoprotein E ε4 allele; TD = Time between scans; FRS = Framingham Risk Score; BMI = Body Mass Index. Tau values rescaled by 1,000 to avoid small decimal estimates.



A. Negative = APOE-ε4 non-carrier; Positive = APOE-ε4 carrier; B. FRS categories were adapted from D'Agostino et al (2008), which provided sex-specific scores for risk of incident CVD (cardiovascular disease, including coronary death, myocardial infarction, stroke, and heart failure). In females, low risk is a FRS of 12 or lower, intermediate is a score of 13 to 17, and high risk is 18 or more. In men, low risk is a FRS of 10 or lower, intermediate is 11 to 14, and high risk is 15 or more; C. BMI categories were adapted from the US Centers for Disease Control and Prevention53, where BMI of 25 and below is healthy weight, BMI between 25.1 and 29 is overweight, and BMI 29.1 and over is obese. These categorizations were only used to visually depict interaction data in figures and analyses were done with continuous variables. For significance, please refer to Table 2

Fig. 2. Interaction effects on Change in Tau Standardized Uptake Value Ratio values in Braak34 and Braak 56 Left (L) and Right (R) between Sex and APOE-ε4, Framingham Risk Score (FRS), and BMI.

Table 3
Results of Change in Tau Moderator Analyses using PVC data.

Region	Moderator	Beta	p-value
Braak34 Right	APOE-ε4	0.05	0.800
Braak34 Left	APOE-ε4	-0.111	0.495
Braak56 Right	APOE-ε4	-0.137	0.390
Braak56 Left	APOE-ε4	-0.136	0.493
Braak34 Right	FRS	-0.009	0.728
Braak34 Left	FRS	-0.011	0.597
Braak56 Right	FRS	0.002	0.916
Braak56 Left	FRS	-0.008	0.765
Braak34 Right	BMI	0.014	0.490
Braak34 Left	BMI	0.021	0.215
Braak56 Right	BMI	-0.005	0.749
Braak56 Left	BMI	-0.037	0.062

Abbreviations: PVC = Partial Volume Corrected; APOE-ε4 = Apolipoprotein E ε4 allele; FRS = Framingham Risk Score; BMI = Body Mass Index. Moderators were treated as interaction terms with sex: Positive betas imply that the effect of the moderator effect is higher in women, negative betas imply that the effect of the moderator effect is higher in men

(all ps> .10). Results indicated that sex and BMI had a trending interaction effect in left Braak56 (β= -0.037, p =0.062), such that relative to females, males with higher BMI showed greater accumulation of tau (Figure 3C). Supplementary Table 2 reports the parameter estimates for the same moderators using non-PVC data, which shows the same pattern of results, but a heightened effect of BMI such that males show a marginally significant or trending relationship between higher BMI and greater tau accumulation in left Braak56 (β = -0.746, p = 0.05) in right Braak34 (β = -0.614, p = 0.09).

4. Discussion

Consistent with hypotheses, our longitudinal study showed that, among older Aβ positive adults with MCI, females show significantly greater tau accumulation in bilateral Braak34 and right Braak56 compared to males. Contrary to our hypotheses, neither the FRS, its individual cardiovascular risk components, nor BMI seemed to attenuate the main effect of sex on tau accumulation in this sample. Although FRS and its components did not have an effect on tau accumulation, interestingly, we observed a trending interaction between sex and BMI in Braak56 left, where higher BMI predicted more tau accumulation for males, but not females. Lastly, although we expected sex differences to be greater among APOE-ε4 carriers, we found no significant interactions between sex and APOE-ε4 or between sex and FRS on tau accumulation. However, a trending relationship between APOE-ε4 carriership and greater tau accumulation was attenuated by the FRS and its individual cardiovascular risk components.

We previously found a cross-sectional relationship between higher FRS score and greater tau in cognitively normal females, but not male, APOE-ε4 carriers in regions relating to early tau accumulation in the entorhinal cortex and inferor temporal lobe [27]. The current findings suggest that this relationship does not apply to tau accumulation across an interval of nine to thirty months in regions of later-stage tau deposition in MCI participants. We can only speculate as to why we did not observe an independent effect of vascular risk factors on tau accumulation in females or males. These effects may have been specific to APOE-ε4 carriers, and we may have been underpowered to examine the sex by APOE-ε4 interactions considering the small sample sizes of APOE-ε4 carriers in each sex (n = 12 females, n = 14 males). Second, the null effect may have been due to the brain regions and cohort we used in our analysis. In our present study, we focused on Braak34 and Braak56 regions, which are associated with later stage tau deposition. In alignment with our previous cross-sectional findings, Rabin et al. [19] also demonstrated that Aβ and vascular risk are synergistically associated with more tau in the inferior temporal lobe of cognitively normal older adults. Although Yau et al. [35] extended these findings to demonstrate that elevated vascular risk and Aβ predict greater longitudinal tau accumulation, which is contrary to our present findings, there are several

differences between our study design, as their study examined inferior temporal regions in cognitively normal older adults and had a longer follow-up interval. In our present analysis, we selected MCI individuals with pre-existing AD-pathlogy, to explore the relationships between CVD and tau accumulation in partipants on the AD continuum, whereas the aforementioned studies focused on cognitively normal older adults. The difference in findings between cognitively normal and MCI individuals was further exemplified by a recent study that demonstrated that vascular factors interact with Aβ to predict tau accumulation in cognitively normal individuals, but not cognitively impaired older adults [36], which confirms our findings and may inform at what timepoint along the AD continuum we may see effects of vascular risk factors on tau accumulation. Another reason we may not have seen an effect of cardiovascular risk factors on tau accumulation may be due to our assessment of CVD risk later in life. Previous work has demonstrated that mid-life hypertension increases dementia risk in females [25] and that higher overall vascular risk in mid-life, but not in late-life, is associated with elevated Aβ pathology [37]. These findings suggest that cardiovascular risk in mid-life, as opposed to late-life, may be more predictive of neuropathology in older adulthood. The current results are supportive of a null association of late-life cardiovascular risk factors on tau pathology and also suggest that later-life CVD factors do not impact sex differences in tau accumulation in later stage AD-related brain regions in MCI older adults.

While we did not observe effects of CVD risk factors on tau accumulation, we did see a male-specific relationship between higher BMI and greater tau accumulation. Similar to other mid-life cardiovascular risk factors, prior research links mid-life obesity to elevated dementia risk [38,39]; however late-life obesity has been associated with lower dementia risk [40,41]. Furthermore, research has shown that this protective effect of late-life BMI may be specific to women, where higher BMI is linked to lower tau and Aβ in female, but not male, cognitively normal adults [42]. One biological pathway to explain why higher BMI is protective against AD pathology in females may be via estrogen-adipose mechanisms. Previous research has established bidirectional relationships between estrogen and adipose tissue, where adipose tissue has been shown to produce peripheral estrogen [43], estrogen receptors regulate adipose tissue differentiation [44], and higher serum estrogen levels relate to higher fat mass in older females [45]. Females also tend to have more subcutaneous adipose tissue compared to males [46], a specific pattern of adiposity which tends to be associated with lower metabolic risk [47] despite contributing to weight gain and in turn, higher BMI. These pathways between adiposity and estrogen may explain the positive effect of BMI in older women, as estrogen is known to have neuroprotective effects [48]. Therefore, the specificity of the relationship of higher BMI to greater tau accumulation in males may contribute to the emerging understanding of sex differences in the impact of late-life BMI on AD neuropathology.

There are several study limitations to consider regarding our study. Mid-life cardiovascular risk assessment is not available for ADNI participants, which as previously described, may be more predictive of tau accumulation than late-life CVD risk profiles. In addition, ADNI participants are largely white and relatively healthy, MCI or AD diagnoses, which limits the generalizability of our results to the broader population. This is especially important when examining factors relating to CVD [49], as rates of hypertension [50], obesity [51], and diabetes [52] vary among different racial and socioeconomic groups. In addition, the time between PET scans was relatively brief, and a longer window may be necessary to accurately capture tau accumulation patterns. Lastly, our sample size was realtively low, as participants were selected to bias for an observed effect of tau accumulation (MCI, Aβ positive), which may have limited our analytic power when performing statistical models. This relatively small size may limit the generalizability of our findings and increases the risk undetected true effects. A power analysis for the general linear model framework and Cohen's f2 statistic suggested that we were powered to detect medium sized effects in the current study ($f2 = 0.16$) for the main effect of sex. It is possible that small effects went undetected in the current study.

In conclusion, our results confirm that older Aβ positive females with MCI accumulate more tau in Braak34 and Braak 56 than males. Our results suggest that except for BMI in males, late-life vascular risk factors do not contribute to greater tau accumulation, nor do they account for the aforementioned sex effect. Our finding of a male-specific relationship between higher late-life BMI and greater tau accumulation contributes to our growing understanding of sex disparities in the influence of BMI on tau. Given our null association between most late-life CVD factors and tau accumulation, these findings may underscore the clinical relevance of modifying health habits relating to hypertension, cholesterol, and smoking in mid-life stages. Future studies are necessary to explore associations between cardiovascular risk and AD pathologies in other ethnoracial groups, and may examine the importance of mid-life medical history.

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Declaration of competing interest

MAD has no conflicts of interest to report. JMD has no conflicts of interests to report. MLT has no conflicts of interest to report. QS has no conflicts of interest to report. AAT has no conflicts of interest to report. KAR has no conflicts of interest to report. EES has no conflicts of interest to report. SJB has no conflicts of interest to report.

Ethical Standards

All participants provided written informed consent for ADNI. Data collection procedures were approved by institutional review boards at each of the ADNI sites.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jarlif.2025.100001.

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