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Sex-Related Differences in the Relationship Between β-Amyloid and Cognitive Trajectories in Older Adults

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Abstract

Objective: We aimed to test the hypothesis that elevated neocortical β-amyloid (Aβ), a hallmark feature of Alzheimer's disease (AD), predicts sex-specific cognitive trajectories in clinically normal older adults, with females showing greater risk of decline than males.

Method: Florbetapir Aβ positron emission tomography (PET) was acquired in 149 clinically normal older adults (52% female, mean age = 74). Participants underwent cognitive testing at baseline and during annual follow-up visits over a timespan of up to 5.14 years. Mixed-effects regression models evaluated whether relations between baseline neocortical Standardized Uptake Value Ratio (SUVR) and composite scores of episodic memory, executive functioning, and processing speed were moderated by sex (male/female) and apolipoprotein E (*APOE*) status (ε4 carrier/non-carrier).

Results: Higher baseline SUVR was associated with longitudinal decline in episodic memory in females ($b = -1.32$, $p < .001$) but not males ($b = -0.30$, $p = .28$). Female *APOE* ε4 carriers with elevated SUVR showed particularly precipitous declines in episodic memory ($b = -4.33$, $p < .001$) whereas other cognitive domains were spared. SUVR did not predict changes in executive functioning or processing speed, regardless of sex (ps >.63), though there was a main effect of SUVR on processing speed ($b = 2.50$, $p = .003$).

Conclusions: Clinically normal females with elevated Aβ are more vulnerable to episodic memory decline than males. Understanding sex-related differences in AD, particularly in preclinical stages, is crucial for guiding precision medicine approaches to early detection and intervention.

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Keywords

aging; Alzheimer's disease; cognition; memory; positron emission tomography

Alzheimer's disease (AD) is the most common cause of dementia among older adults and is currently the sixth leading cause of death within the United States (Alzheimer's Association, 2019). Clinically, AD is a neurodegenerative condition that is typified by slowly progressive declines in episodic memory though patients can present with deficits in other aspects of cognition, such as language, executive functioning, or visuospatial skills (McKhann et al., 2011). A definitive diagnosis is made on postmortem examination by evaluating for β-amyloid (Aβ) plaques and neurofibrillary tau deposits in brain tissue (Montine et al., 2012). It is the presence of these two abnormal proteins—Aβ and tau—that defines AD as a unique neuropathologic entity. Recent advancements in cerebrospinal fluid (CSF) assays, positron emission tomography (PET), and other biomarker techniques have greatly improved our ability to diagnose and track disease progression by measuring Aβ and tau levels *in vivo* (Jack et al., 2018). CSF and PET biomarker studies have indicated that AD pathologic changes, particularly the accumulation of Aβ, accrue years or even decades prior to the emergence of frank cognitive or functional impairments (Bateman et al., 2012; Fagan et al., 2014; Sperling et al., 2011; Villemagne et al., 2013).

Accumulating evidence suggests that females may be more vulnerable to AD than males (Nebel et al., 2018). For example, at age 45, the probability of developing AD dementia at some point across the lifespan is 1 in 5 for women versus 1 in 10 for men (Chêne et al., 2015). Within the United States, there are approximately 3.5 million women living with dementia due to AD compared to 2.1 million men (Alzheimer's Association, 2019). AD dementia may also follow a more aggressive course in females as evidenced by disproportionate rates of hippocampal atrophy (Ardekani et al., 2016) and faster clinical symptom progression (Tschanz et al., 2011). Genetic risk factors for AD, such as the apolipoprotein E (*APOE*) ε4 allele, appear to confer higher risk for pathologic tau aggregation and dementia onset in females relative to males (Farrer et al., 1997; Hohman et al., 2018; Neu et al., 2017).

Although the bulk of the available literature favors a female vulnerability to AD, there are notable inconsistencies and nuances in the literature. For example, one systematic review found that while incidence and prevalence of AD dementia were consistently higher in females compared to males, this difference was not statistically significant (Fiest et al., 2016). In a similar vein, Beydoun et al. (2012) observed *APOE* ε4 status to be a sex-*neutral* risk factor for dementia onset (though female ε4 carriers were at increased risk for declines in episodic memory relative to males). In contrast to other reports, Armstrong et al. (2019) found Aβ positivity on PET to be associated with longitudinal declines in medial temporal lobe volumes in cognitively normal *males* but not females. Given that females tend to live longer than males on average and age is the single greatest risk factor for AD, it has even been questioned whether sexual dimorphism in AD is an artifact of differences in life expectancies (Hebert et al., 2001, 2013).

Taken together, these discrepancies in the literature highlight the need for additional research to better understand and clarify the possibility of sexual dimorphism in AD manifestations. In particular, sex-difference studies are needed in sub- or pre- clinical disease states—when AD pathophysiology begins to accumulate but cognition remains unimpaired—to improve early detection, diagnosis, and intervention efforts (Nebel et al., 2018). Although several reports have indicated that elevated cortical Aβ in cognitively normal older adults predicts future cognitive decline (for a systematic review and meta-analysis, see: Baker et al., 2017), sex is often controlled for as a "nuisance" variable or is not considered at all.

Recent findings support the possibility that sex-related differences in vulnerability to AD pathophysiology may emerge in preclinical stages, well prior to the onset of cognitive impairment or dementia. Perhaps most notably, clinically normal older females with elevated Aβ were found to show greater cortical tau deposition on PET than males (Buckley et al., 2019). Considering that tau aggregation correlates with neuronal loss and appears to drive clinical symptoms in AD (Arriagada et al., 1992), one might expect females in early stages of AD to be at increased risk for cognitive decline. To the authors' knowledge, however, only one study has directly tested this hypothesis by evaluating whether the relationship between preclinical AD pathologic changes and cognitive functioning varies by sex. This seminal work, conducted by Buckley et al. (2018), demonstrated that clinically normal older females with elevated Aβ on PET showed significantly greater rates of longitudinal cognitive decline than male counterparts. Yet the primary outcome of interest was a *global* cognitive composite score and the extent to which sex-specific trajectories are observed to varying degrees across different cognitive domains remains unclear. In addition, Buckley et al. (2018) defined "clinically normal" using the Mini-Mental State Examination (total score > 23) and the Clinical Dementia Rating (CDR; global score = 0), both of which are weighted heavily toward memory loss and may be inappropriate for ruling out atypical presentations of AD dementia or other non-amnestic neurological disorders (Borroni et al., 2010; Knopman et al., 2008). A separate study by Koran et al. (2017) observed females with low Aβ−42 in CSF (indicative of higher brain Aβ−42 levels) to show increased rates of longitudinal decline on tests of verbal memory and executive functioning compared to males, though their sample included individuals with mild cognitive impairment and dementia in addition to clinically normal older adults.

A more complete understanding of sex-related differences in cognition, particularly during sub- or pre-clinical disease states, is critical for understanding the natural course of AD and informing early detection and intervention efforts (Mielke et al., 2014). The present study aimed to extend the limited research base on this topic in three main ways. *First*, we more comprehensively evaluated the relation between Aβ PET deposition in clinically normal older adults and sexual dimorphism in cognitive trajectories by capturing performance in multiple cognitive domains, rather than focusing on global cognition as has been done previously. We specifically assessed episodic memory, executive functioning, and processing speed given the sensitivity of these cognitive functions to brain aging and early AD changes (Buckner, 2004; Han et al., 2017; Ho & Nation, 2018; Salthouse, 1996). *Second*, interactions of sex and Aβ with *APOE* ε4 status were examined within each cognitive domain based on prior work suggesting that female ε4 carriers may be at increased risk for AD pathophysiological changes and brain atrophy compared to males (Farrer et al., 1997;

Hohman et al., 2018; Koran et al., 2017). *Third*, we sought to replicate and extend Buckley et al.'s (2018) findings in an independent cohort of older adults who were determined to be clinically normal by consensus conference with a board-certified neuropsychologist and neurologist, in addition to the CDR. Although more time consuming and laborious, the use of consensus conference diagnosis was implemented to increase confidence in clinical normality while ruling out atypical (non-amnestic) presentations of AD dementia, frontotemporal dementia, and other neurological disorders impacting functions such as behavior or language that are less emphasized on the CDR (Borroni et al., 2010; Knopman et al., 2008).

Based on the majority of the available literature, we hypothesized that elevated neocortical Aβ burden on PET in clinically normal older adults would be more strongly associated with cognitive decline in females relative to males. This effect was expected to be present in each of the cognitive domains assessed: episodic memory, executive functioning, and processing speed. In addition, we hypothesized that *APOE* status would further moderate the relation between Aβ and cognition, such that female ε4 allele carriers with increased Aβ would show particularly precipitous decline.

Method

Study Sample

The study sample was comprised of 149 community-dwelling older adults (age range: 52–91 years) enrolled in the Hillblom Aging Network at the University of California, San Francisco (UCSF) Memory and Aging Center. Participants were recruited from the Bay Area starting in 2000, using flyers, newspaper advertisements, and community outreach events. In addition, a minority of the cohort was recruited via "snowball" sampling techniques (Sadler et al., 2010), whereby current participants helped to identify other persons (e.g., friends or neighbors) who may be eligible and interested in participating. Typically, this recruitment strategy involved prospective study participants initiating contact with our research team after current participants had provided them with our contact information. Alternatively, current participants provided the research team with prospective participants' contact information and we initiated contact.

All participants underwent comprehensive neurobehavioral evaluations and met the following inclusionary criteria at baseline: 1) clinically normal based on consensus conference with a neurologist and board-certified neuropsychologist; 2) no history of neurological disorder known to impact cognition (e.g., epilepsy, stroke); and 3) functionally intact as defined by an informant-obtained CDR global score of 0 (Morris, 1993). More specifically, the determination of clinically normal by consensus conference involved ruling out the presence of mild cognitive impairment, dementia, or any other neurological condition resulting in cognitive, behavioral, motor, or functional decline (e.g., Parkinson's disease), according to widely used diagnostic criteria (e.g., Albert et al., 2011; Armstrong et al., 2013; Gorno-Tempini et al., 2011; Höglinger et al., 2017; McKeith et al., 2017; McKhann et al., 2011; Postuma et al., 2015; Rascovsky et al., 2011). Three main sources of information were considered by the neurologist and neuropsychologist during the diagnostic conference. First, participants underwent a thorough evaluation with the neurologist that

involved a comprehensive neurological examination, clinical interview, and review of systems. Second, neuroimaging (structural MRI) was reviewed to screen out gross brain pathology with potential to negatively impact cognition (e.g., tumor). Third, participants completed a battery of neuropsychological tests to objectively assess major domains of cognitive function, including attention, executive functioning, memory, language, and visuospatial skills. Strict psychometric cutoffs to identify cognitive impairment were not employed given that rigid normative thresholds may not be universally appropriate for individuals of varying demographic backgrounds and premorbid abilities (Petersen, 2004). Instead, cognitive impairment was defined by the presence of subjective cognitive decline, as reported by the participant or informant, together with objective performance on neuropsychological testing that was below expectation given the participant's age and level of premorbid functioning (Albert et al., 2011). In making the determination of clinically normal, emphasis was placed on ruling out any declines in the participant's ability to perform everyday tasks due to cognitive changes. The neurologist and neuropsychologist were blinded to the cognitive composite measures that served as our primary outcomes of interest (described below) during the diagnostic process.

Cognitive testing was performed at baseline and at each follow-up visit occurring approximately 15–18 months apart, spanning across a timeframe of up to 5.14 years. The study protocol received institutional ethics approval from the UCSF Committee on Human Research and written informed consent was obtained from every participant.

Cognitive Outcome Measures

Cognitive performance was quantified using sample-based z-score composites of episodic memory, executive functioning, and processing speed, as described and published previously (Lindbergh et al., 2019; Staffaroni et al., 2018). We elected to use cognitive composite scores based on prior work showing enhanced validity and reliability in aging populations relative to individual test scores, particularly when evaluating relationships with AD biomarkers (Jonaitis et al., 2019). The episodic memory composite was derived from Benson Figure Recall (Kramer et al., 2003), which is a measure of visual memory, and the California Verbal Learning Test, second edition (CVLT-II; immediate recall, delayed free recall, and recognition discriminability) (Delis et al., 2000). The composite measure of executive functioning included Stroop interference, modified Trail Making Test, phonemic fluency (number of D-words per minute), digit span backward, and design fluency (Condition 1, Delis–Kaplan Executive Function System) (Delis et al., 2001). As elaborated in greater detail elsewhere (Kerchner et al., 2012), the processing speed composite was derived from six tests of visually-based processing speed (Length Judgment, Visual Search, Distance Judgment, Abstract Matching 1, Abstract Matching 2, and Shape Judgment) that are normalized using a healthy young adult reference group (the seventh test, Mental Rotation, was discontinued in the Hillblom cohort). All processing speed tests are presented on a computer with the examiner instructing the participant to enter their responses as quickly and accurately as possible via binary (yes/no or left/right) keypress. Each test begins with up to 10 practice trials; if accuracy is below 70%, participants are required to complete additional rounds of practice trials to ensure task comprehension. Briefly, Length Judgment involves rapidly determining which of two parallel vertical lines is the longest (left/right).

Visual Search requires participants to indicate (yes/no) whether a target stimulus (green circle) is present amongst an array of distractor stimuli (blue circles and green squares). In the Distance Judgment task, participants are asked to judge which of two colored circles (left/right) is closer to a white circle located at the center of the display. Abstract Matching 1 involves determining which of two different arrays of shapes (left/right) is most similar to a target array, with the shape arrays varying along three dimensions (shape, number, and color). Abstract Matching 2 is very similar to Abstract Matching 1, except that the shape arrays vary along four dimensions (shape, number, color, and orientation) instead of three dimensions. For the Shape Judgment task, participants are required to judge which of two different shapes (left/right) presented on the bottom portion of the screen is most similar to a target shape presented on the top portion of the screen.

For both the episodic memory and executive functioning composites, higher scores indicate better performance. On the processing speed composite, lower scores reflect better performance (faster response times).

APOE Genotyping

Standard procedures were employed to extract genomic DNA from peripheral blood (Gentra PureGene Blood Kit, Qiagen) and TaqMan or Sequenom were used to perform the genotyping. More specifically, *APOE* genotyping (rs429358 and rs7412) was achieved using the TaqMan Allelic Discrimination Assay, which was conducted on an ABI 7900HT Fast Real-Time PCR system (Applied Biosystems) based on the manufacturer's guidelines. SpectroAquire and MassARRAY Typer Software (Sequenom) were used for interpretation, and the data were reviewed and analyzed using Typer analyzer (v3.4.0.18).

Neuroimaging Acquisition and Analysis

Aβ PET—Aβ PET was acquired using Florbetapir (^{18}F-AV45) on a GE Discovery STE/VCT PET-CT scanner within an average of 0.33 years (SD = 0.28 years) from the baseline neuropsychological assessment. A low-dose CT scan was acquired for attenuation correction and PET data were reconstructed using an iterative algorithm (4 iterations, 20 subsets).

Data pre-processing followed ADNI procedures (http://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/). Briefly, four 5-min frames were acquired starting 50 minutes after the injection of ~10 mCi of Florbetapir. Frames were smoothed to a final resolution of 8 mm full width at half maximum (FWHM) isotropic, realigned, averaged, and coregistered to corresponding T1-weighted magnetization prepared rapid gradient echo (MPRAGE) MRI scans. The MRI scans were acquired within an average of 0.29 years (SD = 0.4 years) from the PET scans on either a 3T Siemens Tim Trio or a 3T Siemens Prisma Fit scanner. Both MRI scanners had very similar acquisition parameters (1 mm isotropic resolution; repetition time = 2.3 ms; inversion time = 900 ms; flip angle = 9°), with slightly different echo times (Trio: 2.98 ms; Prisma: 2.9 ms). MRI data were parcellated using FreeSurfer 5.3 to derive a whole cerebellum mask that was used as a reference region (Landau et al., 2013) to compute Standardized Uptake Value Ratio (SUVR) images. Freesurfer segmentation of the cortical mantle was used to define a cortical composite region encompassing frontal, cingulate,

parietal, and lateral temporal areas (Landau et al., 2013) from which an average SUVR value was extracted as a measure of neocortical Aβ burden. Aβ was modeled continuously as SUVR values in the present analyses given literature showing a dose-response relationship between Aβ burden and rates of cognitive decline in aging adults (Farrell et al., 2017).

Medial Temporal Lobe Volumes—Medial temporal lobe volumes were calculated using the T1-weighted images from the 3T Siemens Tim Trio and 3T Siemens Prisma Fit MRI scans, described above. Magnetic field bias was corrected using the N3 algorithm (Sled et al., 1998). Tissue segmentation was performed using the unified segmentation procedure in SPM12 (Friston et al., 2011). Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) was implemented to create a study-specific template and to allow warping of individual T1-weighted images (Ashburner, 2007). Images were normalized and modulated in the study-specific template using nonlinear and rigid-body registration. For smoothing, an 8-mm FWHM Gaussian kernel was employed. To permit registration with a brain parcellation atlas, both linear and nonlinear transformations between DARTEL's space and ICBM (International Consortium for Brain Mapping) space were performed (Mazziotta et al., 1995). The standard parcellation atlas (Desikan et al., 2006) was transformed into ICBM space and all gray matter within bilateral hippocampal, entorhinal, and parahippocampal cortices were added together to create a measure of medial temporal lobe volume in MNI space (Squire et al., 2004).

Statistical Analyses

Cross-Sectional—The cross-sectional baseline relationship between Aβ and cognition was evaluated using multiple regression models to control for age and education. Aβ SUVR values were entered into the models as a continuous independent variable. Episodic memory, executive functioning, and processing speed composite scores served as the dependent variables. The potential moderating role of sex was evaluated using the PROCESS macro (Version 3.1) (Hayes, 2018) with the interaction between Aβ and sex (Aβ × sex) as the independent parameter of interest and sex dummy coded (male/female). The possibility of a three-way interaction with *APOE* (*APOE* × Aβ × sex) was similarly investigated by entering *APOE* ε4 status as a dummy coded dichotomous moderator (ε4 carrier/non-carrier).

Longitudinal—Longitudinal changes in cognition were evaluated using linear mixed-effects regression models allowing for random intercepts and slopes. Random intercept only models were employed in the rare instances in which models failed to converge. Time (in years) from baseline was modeled as a continuous independent variable and all analyses were adjusted for baseline age and educational attainment. To evaluate the independent and synergistic effects of sex (male/female), Aβ (SUVR), and *APOE* status (ε4 carrier/non-carrier) on cognitive trajectories, models were tested with the following two-, three-, and four-way interaction terms: sex × time, Aβ × time, Aβ × sex × time, *APOE* × time, *APOE* × sex × time, and *APOE* × Aβ × sex × time. Follow-up analyses were run replacing cognition with medial temporal lobe volumes as the dependent variable of interest to investigate whether observed effects might be explained by changes in underlying brain structure. Medial temporal lobe volumes were adjusted for total intracranial volume in all analyses to control for differences in head size.

In addition to testing for linear relationships, we also probed for the possibility of curvilinear (quadratic) effects in all of our primary analyses. However, inclusion of a quadratic term did not significantly improve the fit of any of our mixed-effects models. Accordingly, only linear results are reported below.

Statistical significance was defined by a conventional α-level of $p < .05$, two-tailed. A correction for multiple comparisons was not applied to any of our analyses.

Results

Of the 149 participants with Aβ PET at baseline, all had data available for the executive functioning and processing speed composites. However, 1 participant was missing data for both the episodic memory composite and educational attainment (a demographic covariate). Accordingly, the final sample size was 148 for cross-sectional and longitudinal models evaluating the effects of sex, Aβ, and time (aging) on cognition. This included the cross-sectional analyses of the effect of Aβ × sex on cognitive composite scores and the longitudinal mixed-effects regression analyses of the effects of sex × time, Aβ × time, and Aβ × sex × time on cognitive composite trajectories ("Models A").

APOE genotyping was unavailable for 11 of the 149 participants with Aβ PET scans. Accordingly, the sample size was slightly reduced (N = 138) for cross-sectional and longitudinal models evaluating the effects of *APOE* status (ε4 carrier/non-carrier) on cognition. This included the cross-sectional analyses of the effects of sex × Aβ × *APOE* on cognitive composite scores and the longitudinal mixed-effects regression models evaluating the effects of *APOE* × time, *APOE* × sex × time, and *APOE* × Aβ × sex × time on cognitive composite trajectories ("Models B").

A more detailed breakdown of the sample sizes for each of our primary longitudinal analyses is provided in Table 1. Because the Hillblom Aging Network is an active longitudinal study with ongoing recruitment and enrollment, participants had varying numbers of study visits, depending upon the length of time that a given participant had been enrolled in the study. The total number of study visits for participants who met inclusionary criteria ranged from 1 to a maximum of 6 (mean = 2.54 visits). Cognitive outcome data of interest were collected for up to a maximum of 4 visits over a timeframe of up to 5.14 years from baseline (see Table 1).

Baseline (Cross-Sectional)

Baseline descriptive statistics are provided in Table 2. Carriers of the *APOE* ε4 allele (N = 30) showed significantly greater Aβ levels (SUVR) compared to non-carriers [$t(136) = -3.73$, $p < .001$], consistent with prior findings (Morris et al., 2010). Aβ was not significantly related to age ($r = .034$, $p = .68$) or education ($r = .045$, $p = .59$) in bivariate correlational analyses. As indicated in Table 2, males and females did not significantly differ with respect to Aβ, age, or *APOE* ε4 status (ps > .54), though males tended to have somewhat higher educational attainment [$t(146) = 2.25$, $p = .026$]. There were no significant sex differences on the composite measures of processing speed, executive functioning, or episodic memory, though the latter was in the direction of a female advantage [$t(146) =$

−1.54, p = .126]. Upon decomposing the episodic memory composite into visual memory (Benson Figure recall) and verbal memory (CVLT-II delayed free recall), females displayed similar visual memory performance compared to males [t(146) = 1.40, p = .163] but significantly better verbal memory performance [t(146) = −2.03, p = .044]. This pattern is consistent with prior literature documenting an episodic memory advantage for females relative to males, particularly in the verbal domain (Kramer et al., 1988).

Greater neocortical Aβ burden was cross-sectionally associated with slower processing speed (b = 2.52, p = .001, N = 148), as represented in Figure 1. By contrast, there was not a significant relationship between Aβ and the episodic memory (b = −0.103, p = .84, N = 148) or executive functioning (b = −0.39, p = .25, N = 148) composite scores.

Sex did not moderate the cross-sectional relationships between Aβ and processing speed (b = −0.01, p = .99, N = 148), episodic memory (b = 0.75, p = .45, N = 148), or executive functioning (b = −0.02, p = .98, N = 148). There were no significant three-way interactions between sex, Aβ, and *APOE* status (sex × Aβ × *APOE*) in predicting processing speed (b = 6.65, p = .08, N = 138), episodic memory (b = −1.77, p = .49, N = 138), or executive functioning (b = −1.81, p = .29, N = 138).

Longitudinal

A summary of the results reported below from the longitudinal mixed-effects regression models for all primary terms of interest and covariates is provided in Table 3. Longitudinal episodic memory trajectories for individual participants are plotted in Figure 2. Longitudinal plots of executive functioning trajectories and processing speed trajectories for individual participants are available in online supplemental materials (see Figures S1 and S2, respectively).

Effects of Aging and Sex on Cognitive Trajectories—Adjusting for baseline age and education, episodic memory (b = −0.05, z = −2.00, p = .046) and processing speed (b = 0.12, z = 2.69, p = .007) both declined over time. Executive functioning did not significantly change over time in this sample (b = −0.004, z = −0.18, p = .86).

Sex did not significantly interact with time (sex × time) in predicting episodic memory trajectories (b = 0.03, z = 0.54, p = .59), indicating that males and females evidenced similar rates of decline over time. The main effect of sex did not reach statistical significance in this model but was trending in the direction of females showing better episodic memory performance than males (b = 0.22, z = 1.69, p = .09). Sex did not significantly interact with time in predicting processing speed (b = 0.01, z = 0.06, p = .95) or executive functioning (b = 0.01, z = 0.16, p = .88) trajectories.

Effects of Aβ and Sex on Cognitive Trajectories—Baseline Aβ significantly interacted with time (Aβ × time) in predicting episodic memory trajectories, demonstrating that clinically normal participants with greater neocortical Aβ burden showed more precipitous declines in episodic memory performance over time (b = −0.64, z = −2.94, p = .003; see Figure 3). By contrast, Aβ did not significantly interact with time in predicting changes in executive functioning (b = 0.14, z = 0.78, p = .44) or processing speed (b = 0.47,

z = 1.29, p = .20). However, there was a significant main effect of baseline Aβ on processing speed (b = 2.50, z = 2.99, p = .003); individuals with greater neocortical Aβ burden were slower, consistent with the cross-sectional findings reported above.

There was a significant three-way interaction between Aβ, sex, and time (Aβ × sex × time) in predicting changes in episodic memory (b = −1.02, z = −2.21, p = .027), indicating that the effect of Aβ on memory decline was greater in females than in males (see Figure 4). More specifically, there was a large effect of Aβ on memory decline in females (b = −1.32, z = −3.70, p < .001, N = 77) whereas Aβ was not significantly associated with episodic memory trajectories in males (b = −0.30, z = −1.09, p = .28, N = 71). A sensitivity analysis with the sample restricted to only participants who were Aβ-positive (N = 31) using established thresholds for Florbetapir (SUVR > 1.11; Landau et al., 2016) revealed a similar interaction between Aβ and sex on episodic memory trajectories (b = −4.32, z = −2.46, p = .014); specifically, Aβ-positive females continued to show significant memory decline (p = .004) and males did not (p = .11).

Post-hoc analyses with the episodic memory composite decomposed into verbal memory (CVLT-II delayed free recall) and visual memory (Benson Figure recall) suggested that greater Aβ burden was associated with declines in both verbal (b = −1.63, z = −2.91, p = .004) and visual (b = −0.94, z = −2.48, p = .013) memory performance in females. By contrast, Aβ did not significantly interact with time in predicting either visual (b = 0.22, z = 0.68, p = .49) or verbal (b = −0.69, z = −1.75, p = .08) memory trajectories in males, though the latter was at trend level.

Aβ, sex, and time (Aβ × sex × time) did not significantly interact in predicting changes in executive functioning (b = 0.13, z = 0.35, p = .73; see Figure 5) or processing speed (b = −0.37, z = −0.49, p = .63; see Figure 6).

Effects of Aβ, Sex, and APOE Status on Cognitive Trajectories—*APOE* status (ε4 carrier/non-carrier) significantly interacted with time (*APOE* × time) in predicting episodic memory trajectories (b = −0.13, z = −2.08, p = .038) with carriers of the ε4 allele showing more precipitous episodic memory decline than non-carriers. This effect remained significant after controlling for baseline Aβ levels (b = −0.13, z = −2.09, p = .037). *APOE* status did not significantly interact with time in predicting changes in processing speed (b = −0.10, z = −0.90, p = .37) or executive functioning (b = 0.02, z = 0.33, p = .74).

There were no significant three-way interactions between *APOE* status, sex, and time (*APOE* × sex × time) in predicting episodic memory (b = −0.19, z = −1.53, p = .127), processing speed (b = 0.11, z = 0.51, p = .61), or executive functioning (b = 0.18, z = 1.88, p = .06) trajectories, though the latter was at trend level with male ε4 carriers showing relatively greater declines in executive functions over time than females.

The relationship between baseline Aβ levels and declines in episodic memory performance over time (Aβ × time) remained significant upon controlling for *APOE* status (b = −0.68, z = −3.05, p = .002). In addition, the three-way interaction between Aβ, sex, and time (Aβ × sex

× time) in predicting changes in episodic memory remained significant after adjusting for *APOE* status (b = −1.01, z = −2.18, p = .029).

As shown in Figure 7, there was a significant four-way interaction between *APOE* status, Aβ, sex, and time (*APOE* × Aβ × sex × time) in predicting episodic memory trajectories (b = −2.62, z = −2.49, p = .013). More specifically, female carriers of the ε4 allele (N = 17) with elevated baseline Aβ showed particularly precipitous declines in episodic memory (b = −4.33, z = −4.24, p < .001) though elevated Aβ in female non-carriers (N = 57) was also associated with significant decline (b = −0.82, z = −2.29, p = .022). By contrast, *APOE* status did not interact with baseline Aβ levels in predicting episodic memory trajectories in males (b = 0.81, z = 1.19, p = .24, N = 64).

APOE status, Aβ, sex, and time (*APOE* × Aβ × sex × time) did not significantly interact in predicting executive functioning (b = −0.21, z = −0.23, p = .82) or processing speed (b = −0.87, z = −0.49, p = .62) trajectories.

Medial Temporal Lobe Volumes and Episodic Memory Trajectories—Follow-up analyses of the effects of sex and Aβ on brain structural trajectories were conducted in 147 participants with data available for medial temporal lobe volumes and all demographic covariates of interest (age, sex, and education). *APOE* data were unavailable for 10 of these participants, resulting in a sample size of 137 for analyses of the effect of ε4 carrier status on medial temporal lobe changes. Longitudinal medial temporal lobe data were available for a timespan of up to 4.25 years from baseline with an average follow-up length of 2.61 years (average number of follow-up visits = 2.09, SD = 0.29).

Sex did not significantly interact with baseline Aβ levels (Aβ × sex × time) in predicting changes in medial temporal lobe volumes (b = −0.04, z = −0.19, p = .85). There was also not a significant four-way interaction between *APOE* status, Aβ, sex, and time (*APOE* × Aβ × sex × time) in predicting medial temporal lobe volume trajectories (b = −0.51, z = −1.01, p = .31).

The three-way interaction between Aβ, sex, and time (Aβ × sex × time) in predicting episodic memory trajectories remained significant upon inclusion of medial temporal lobe volumes in the model as a covariate (b = −1.02, z = −2.01, p = .045). The four-way interaction between *APOE* status, Aβ, sex, and time (*APOE* × Aβ × sex × time) in predicting episodic memory trajectories also remained significant after controlling for medial temporal lobe volumes (b = −2.40, z = −2.18, p = .029).

Discussion

We found that clinically normal females with elevated baseline levels of cortical Aβ, a hallmark feature of AD, showed significantly greater declines in episodic memory over time compared to males. This effect was further moderated by *APOE* status, such that female ε4 allele carriers with increased Aβ were particularly at risk for decrements in episodic memory. By contrast, Aβ was not significantly associated with episodic memory decline in males, regardless of *APOE* status, though the relationship was in the expected direction. Taken together, these findings support the possibility that sex-related differences in the

clinical manifestation of AD biology emerge in the earliest disease stages, well prior to the onset of dementia and perhaps even among individuals who will never evidence frankly observable AD symptoms. In addition, the present results are inconsistent with views that sex-related differences in AD can be fully explained by longer average life expectancies in females and instead suggest an inherent sex-specific vulnerability to AD pathophysiology with subclinical cognitive changes occurring even among females with subclinical Aβ levels.

Contrary to expectation, sex did not interact with Aβ or *APOE* status to predict longitudinal change in executive functioning or processing speed. This extends prior work by Buckley et al. (2018), which focused on cognition globally, and suggests specificity of sex-related differences in cognitive trajectories to episodic memory, at least in subclinical disease stages. A "cognitive reserve" model was recently proposed whereby the lifelong female superiority in verbal memory, which is well documented in the literature (Kramer et al., 1988), helps to buffer decline until a critical threshold of disease burden is reached, beyond which more precipitous loss is observed (Sundermann et al., 2016). If the reserve model is correct, the present findings suggest that the critical threshold occurs in relatively early stages along the AD continuum, given that even clinically normal females may begin to show more precipitous rates of verbal memory decline over time. Consistent with the reserve hypothesis, females in our sample demonstrated significantly better *verbal* memory performance than males at baseline and post-hoc analyses hinted at a somewhat larger effect of Aβ on longitudinal declines in verbal relative to visual memory. In addition, although the main effect of sex on the overall episodic memory composite (which incorporates visual as well as verbal memory) did not reach statistical significance, there was a notable trend ($p = .09$) toward females showing better performance on average compared to males (see Figure 4, Panels A versus B).

It is further notable that females with low levels of Aβ at baseline appeared to show considerable resilience to age-associated declines in episodic memory performance, even improving over time possibly due to practice effects (see Figure 4, Panel A). By contrast, males with low Aβ did not show similar improvements but did evidence relative stability in episodic memory performance over time (see Figure 4, Panel B). Accordingly, low Aβ levels (e.g., $\leq 16^{th}$ percentile or SUVR ≤ 0.957 in our sample) may be a prognostic marker for positive memory trajectories in aging females in particular. It should also be acknowledged that the presence of these "memory-resilient" females with low Aβ in our sample likely increased the magnitude of the observed Aβ × sex × time interactions (by enhancing the contrast with memory-declining females who had higher Aβ levels). That said, a sensitivity analysis revealed that our observed interactions between Aβ and sex on episodic memory trajectories persisted even when restricting the sample to only participants who were Aβ-positive. This suggests a frank vulnerability to memory decline in females with elevated Aβ that was not driven by the memory-resilient trajectories observed in female counterparts with low Aβ.

It is noteworthy that we did not detect a sex-specific Aβ effect when examined cross-sectionally at baseline. This underscores the importance of capturing *longitudinal rates* of episodic memory decline to understand how AD biology unfolds across sexes and when

attempting to identify females at highest risk for AD, as cross-sectional assessments may contribute to under detection.

The mechanism(s) responsible for the observed sex-related differences in episodic memory trajectories remain to be elucidated. We evaluated changes in medial temporal lobe volumes as a possible mediator, given the known role of this brain system in supporting episodic memory performance and its involvement in early stages of AD (Pettigrew et al., 2017). However, sex did not interact with Aβ in predicting medial temporal lobe volumetric changes and our primary findings remained significant upon controlling for medial temporal lobe volumes. It is possible that more sensitive indicators of early medial temporal lobe dysfunction that precede frank structural neurodegeneration, such as pathologic tau deposition (Leuzy et al., 2019) or functional connectivity alterations (Sheline & Raichle, 2013), may help to explain the observed sex differences. More generally, as reviewed in detail elsewhere (Mielke et al., 2014; Nebel et al., 2018), there are a host of biological (e.g., hormonal, immunological, and cardiovascular) and sociocultural (e.g., educational and occupational disparities) factors that may help to explain why females are disproportionately at risk for AD-related changes. It will be important to explore these factors, as well as their interactions, in future research.

Another important finding of the present study was that information processing speed appears to be cross-sectionally sensitive to Aβ levels in clinically normal older adults, regardless of sex. Interestingly, baseline Aβ did not predict longitudinal declines in processing speed, as was the case with episodic memory. This raises the possibility that cognitive slowing may be among the first cognitive changes associated with AD biology, potentially preceding episodic memory dysfunction, but remains relatively static over time or at least does not outpace rates of decline seen in typical aging. More broadly, the observation that Aβ relates to some aspects of cognition cross-sectionally (processing speed) and other aspects of cognition longitudinally (episodic memory) highlights the importance of conducting both types of analyses, as different patterns of results may emerge in different cognitive domains (Baker et al., 2017).

There are limitations to the present study that should be considered. The study sample was homogenous in terms of race (majority White) and socioeconomic status (average education greater than 16 years), which hinders generalization to populations characterized by greater diversity. For example, differences in racial and ethnic background have been shown to influence the risk for AD conferred by the *APOE* ε4 allele (Tang et al., 1996) and may also influence sex-specific cognitive trajectories. Moreover, the use of snowball sampling for recruiting some of our participants may have systematically biased portions of the sample such that it was not fully representative of the larger target population (Magnani et al., 2005). As examples, snowball recruitment can lead to an overrepresentation of individuals who are agreeable, possess larger social networks, and share similar characteristics with one another (Sadler et al., 2010). In addition, snowball sampling has been criticized for contributing to “saturation” effects, whereby more recently recruited participants fail to provide new information that meaningfully differs from previously recruited peers (Magnani et al., 2005; Sadler et al., 2010).

Our sample size was relatively small, particularly for drawing definitive conclusions from analyses stratified by both sex and *APOE* status. For example, there were only 17 female *APOE* ε4 allele carriers (16 of which were ε4 heterozygous) and 13 male *APOE* ε4 carriers (12 of which were ε4 heterozygous). Due to the limited cell sizes in our models, we may have been statistically underpowered to detect all of our effects of interest, especially when evaluating for interactions among multiple predictor variables. Accordingly, there was an exploratory element to our analyses and our findings should be interpreted with some caution. We also did not correct for multiple comparisons due to sample size limitations and associated power constraints, which raises concern about the possibility of Type I error. For all of these reasons, it will be important for future studies to replicate our findings in samples that are larger and that are followed for longer spans of time. For example, it is possible that statistically significant effects of Aβ and *APOE* status on episodic memory trajectories would emerge in males if drawn from larger cohorts with more lengthy follow-up periods, particularly considering that some of the male-specific effects we observed were trending in the expected direction (e.g., Aβ × time interaction on verbal memory changes). It would also be informative to evaluate whether sex-specific cognitive trajectories are influenced by number of copies of the *APOE* ε4 allele (heterozygous versus homozygous), in addition to the coarser measure of *APOE* ε4 status (carrier versus non-carrier) that we used. Sample size constraints prevented us from testing this directly, particularly due to the small number of participants who were *APOE* ε4 homozygous (1 female and 1 male), which reflects a limitation of the present study.

Given that random assignment is not possible for a biologically determined characteristic like sex, the present results may have been influenced by pre-existing group differences that were not of primary interest to our hypotheses. For instance, males and females differed slightly in educational attainment (17.75 versus 17.00 years, respectively), though all of our results held upon statistically controlling for education.

Despite these limitations, the present study expands the literature on sex-related differences in the earliest stages of AD, suggesting an episodic memory vulnerability in females that emerges well prior to the onset of dementia and in fact is detectable even among clinically normal adults with subclinical Aβ levels who may never evidence an AD dementia syndrome. Although sex is often treated as a “nuisance” variable that must be controlled for in statistical analyses, our findings highlight the importance of evaluating for meaningful differences between males and females across the spectrum of AD research endeavors, from basic science studies to human clinical trials. A better understanding of factors such as sex that influence risk and progression of AD is crucial for shedding light onto the biology of the disease and facilitating a precision medicine approach to early detection and intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question:

This study evaluated whether older males and females are differentially susceptible to cognitive decline in very early, pre-symptomatic stages of the Alzheimer's disease (AD) continuum.

Findings:

Our results indicated that clinically normal females with elevated β-amyloid (a protein associated with AD that accumulates in the brain) show significantly greater rates of memory decline over time compared to males, especially when they carry the *APOE* ε4 allele (a genetic risk factor for AD).

Importance:

These findings suggest that females are particularly vulnerable to memory changes in early stages of AD and may help to improve early diagnosis and intervention efforts.

Next Steps:

Future work should investigate biological (e.g., hormonal, immunological, and cardiovascular), sociocultural (e.g., educational and occupational disparities), and other factors that may help to explain why females are disproportionately at risk for early AD-related cognitive changes.

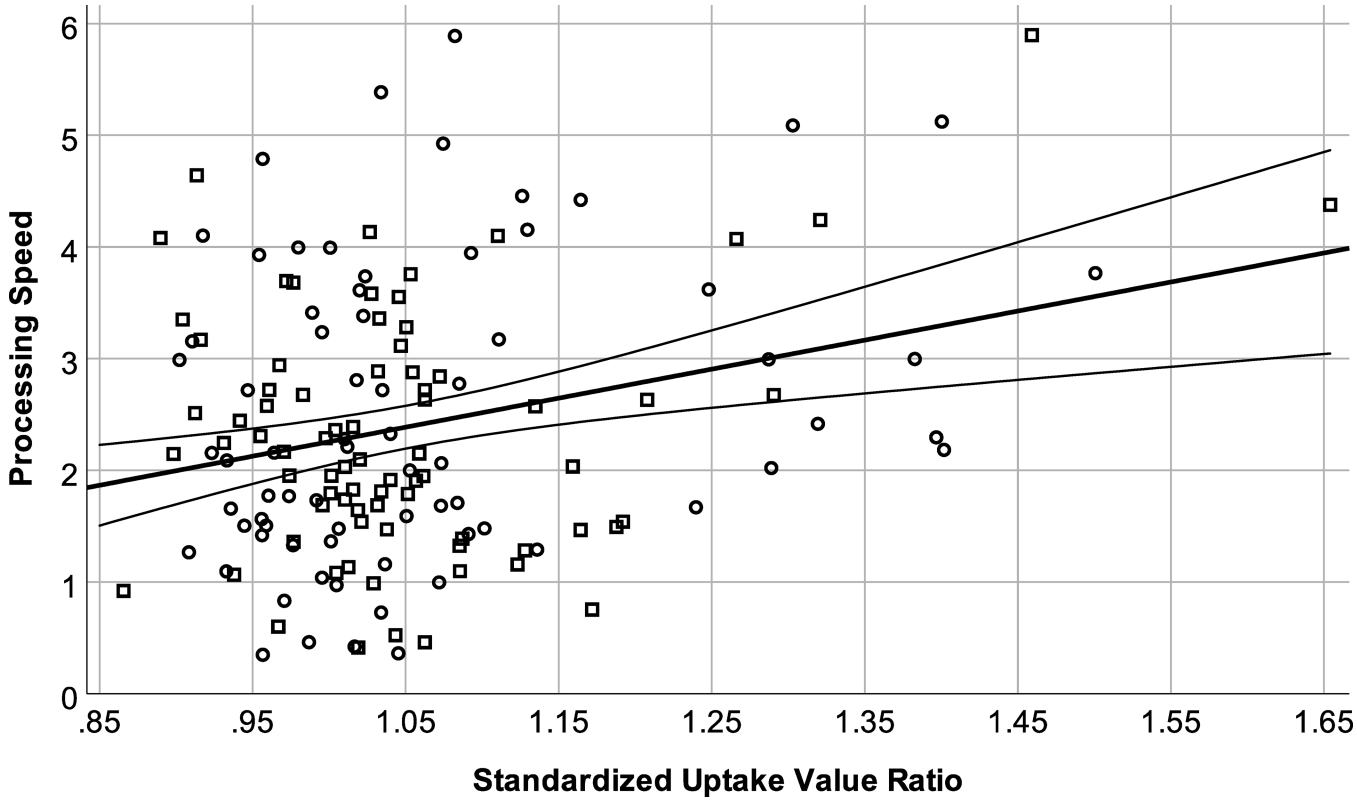

Figure 1. Cross-Sectional Relationship Between β-Amyloid and Processing Speed

Note. Greater neocortical Aβ burden (Florbetapir Standardized Uptake Value Ratio) was cross-sectionally associated with cognitive slowing in clinically normal older adults at baseline. This effect was not moderated by sex (squares = females; circles = males). Processing speed is depicted in z-score units relative to a healthy young adult comparison group with 95% confidence intervals around the regression line. Higher scores correspond to worse performance (slower response times).

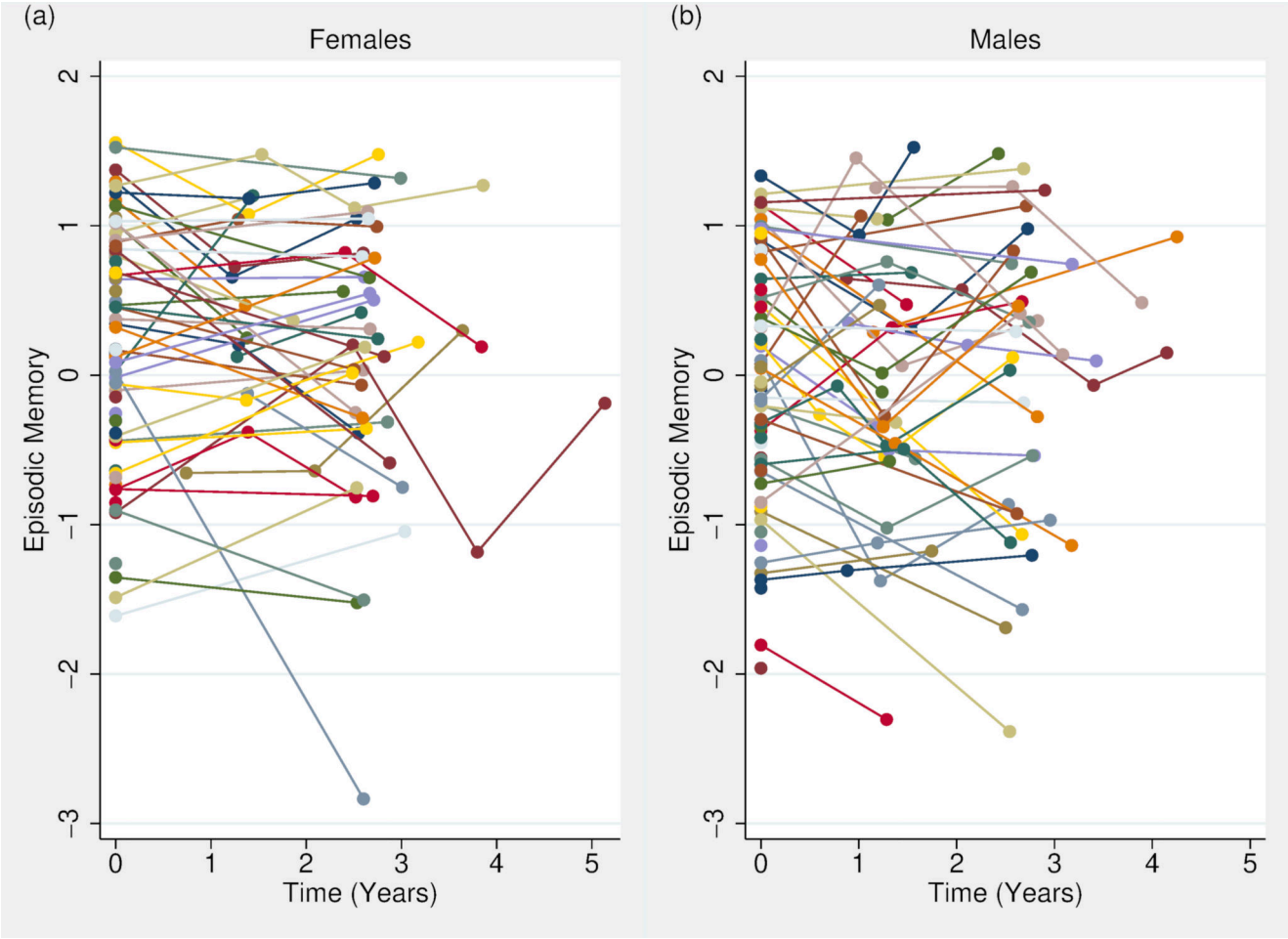

Figure 2. Longitudinal Episodic Memory Trajectories by Sex

Note. Longitudinal episodic memory trajectories for individual participants are plotted for females (Panel A) and males (Panel B). Episodic memory is depicted on the y-axis as a sample-based z-score composite measure with higher scores corresponding to better performance. Time is plotted continuously on the x-axis as years from baseline.

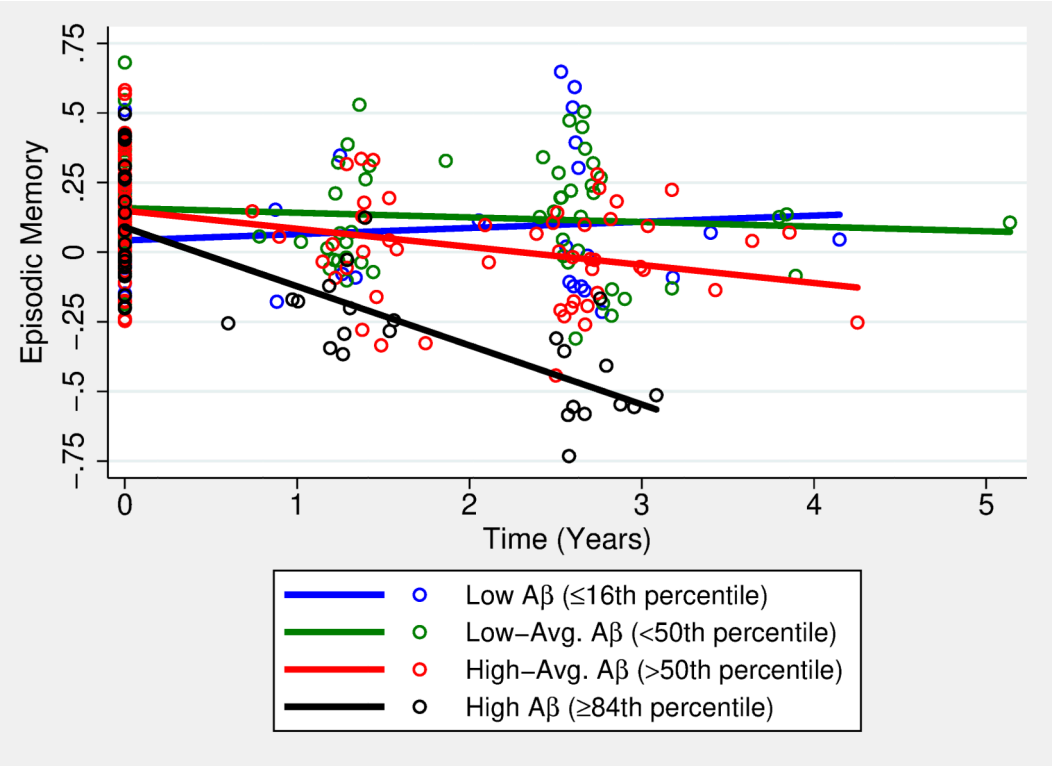

Figure 3. Relationship Between β-Amyloid and Episodic Memory Trajectories

Note. Greater neocortical Aβ burden (Florbetapir Standardized Uptake Value Ratio) at baseline was associated with more precipitous declines in episodic memory performance over time. To help visualize the interaction (Aβ × time), demographically-adjusted predicted values from the mixed-effects regression model are plotted for individuals with "low" levels of Aβ (≤16th percentile), "low-average" levels of Aβ (>16th percentile to the 50th percentile), "high-average" levels of Aβ (>50th percentile to the 84th percentile), and "high" levels of Aβ (≥84th percentile). The 16th, 50th, and 84th percentiles from this sample (N = 148) correspond to baseline SUVR values of 0.957, 1.027, and 1.136, respectively. Fitted lines are plotted for each of the four subgroups (low Aβ, low-average Aβ, high-average Aβ, and high Aβ), though it should be kept in mind that Aβ was treated as a continuous variable in our model; the categorical delineation of the sample into subgroups is presented here solely for visualization purposes. Time is plotted continuously on the x-axis as years from baseline while episodic memory is plotted on the y-axis as a sample-based z-score composite.

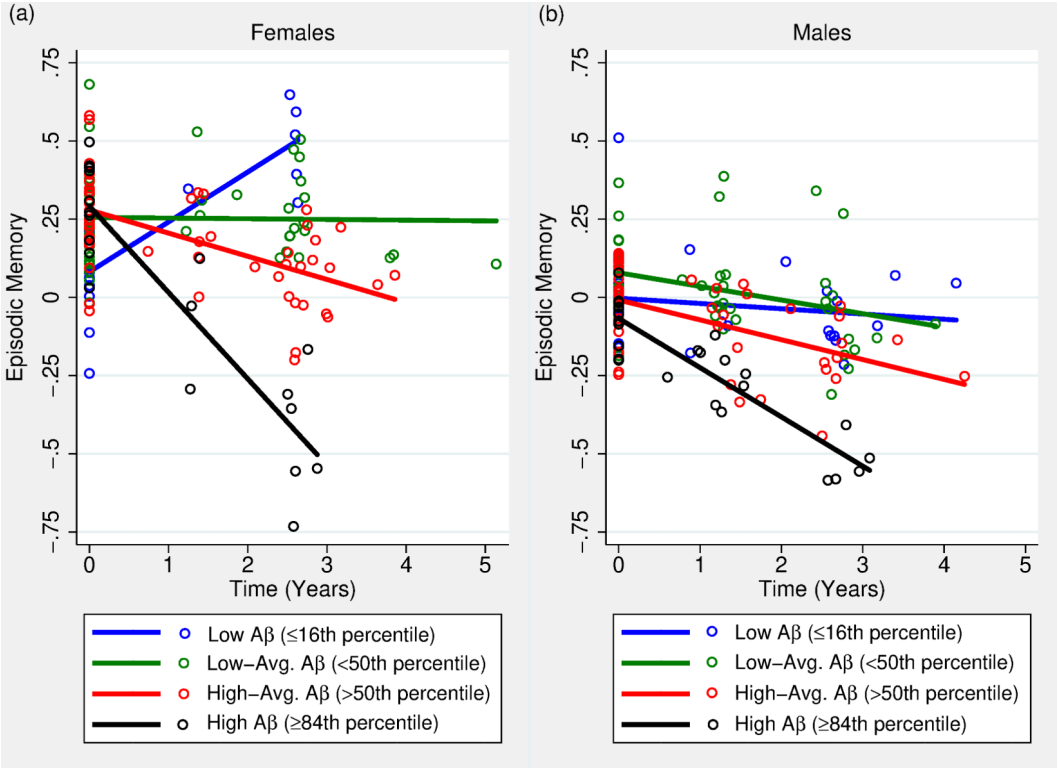

Figure 4. Relationship Between β-Amyloid and Episodic Memory Trajectories by Sex

Note. Greater neocortical Aβ burden (Florbetapir Standardized Uptake Value Ratio) at baseline was more strongly associated with episodic memory trajectories in females (Panel A) relative to males (Panel B). To help visualize the interaction (Aβ × sex × time), demographically-adjusted predicted values from the mixed-effects regression model are plotted for individuals with "low" levels of Aβ (≤16th percentile), "low-average" levels of Aβ (>16th percentile to the 50th percentile), "high-average" levels of Aβ (>50th percentile to the 84th percentile), and "high" levels of Aβ (≥84th percentile). The 16th, 50th, and 84th percentiles from this sample (N = 148) correspond to baseline SUVR values of 0.957, 1.027, and 1.136, respectively. Fitted lines are plotted for each of the four subgroups (low Aβ, low-average Aβ, high-average Aβ, and high Aβ) by sex, though it should be kept in mind that Aβ was treated as a continuous variable in our model; the categorical delineation of the sample into subgroups is presented here solely for visualization purposes. Time is plotted continuously on the x-axis as years from baseline while episodic memory is plotted on the y-axis as a sample-based z-score composite. Although the main effect of sex on the episodic memory composite did not reach statistical significance, there was a notable trend (b = 0.22, p = .09) toward females showing better performance on average than males (e.g., see difference in intercepts in Panel A versus Panel B). In addition, although there was a small but statistically significant (b = −0.05, p = .046) decline in episodic memory performance over time in the overall sample (males and females combined), there was a subset of females with low Aβ who appeared to show considerable resilience to age-associated episodic memory declines, even improving over time possibly due to practice effects (see low Aβ subgroup in Panel A). By contrast, males with low Aβ showed very little change in

performance over time (see low Aβ subgroup in Panel B), suggesting that low Aβ may confer less benefit to episodic memory trajectories in males compared to females.

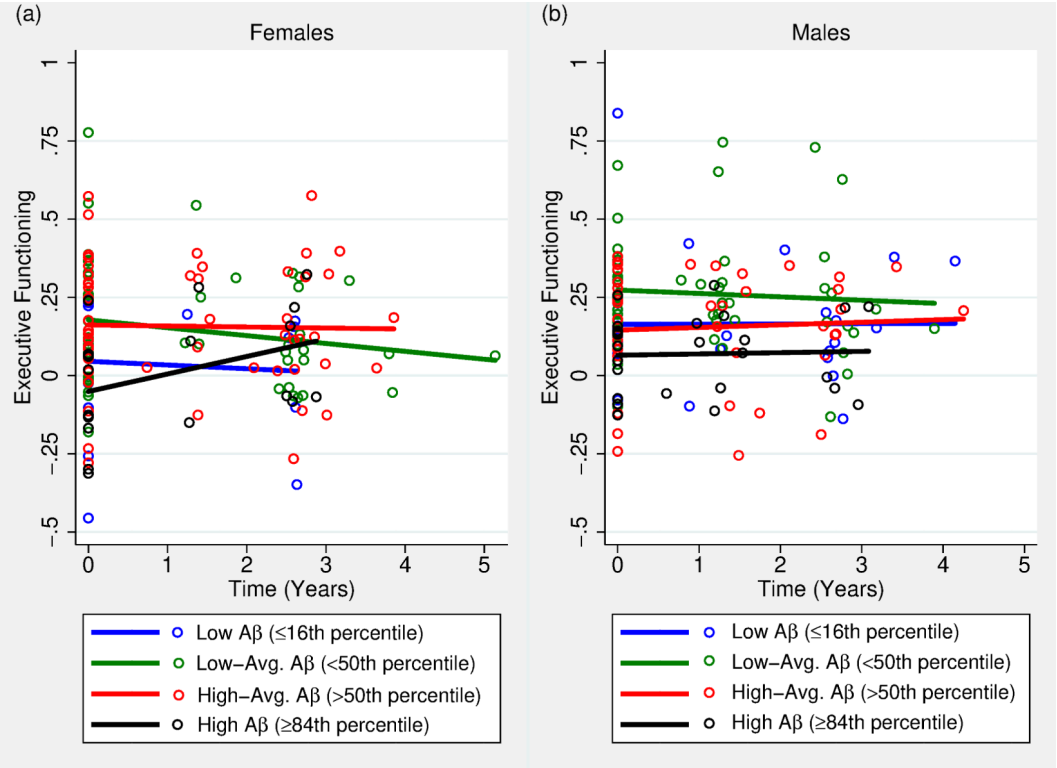

Figure 5. Relationship Between β-Amyloid and Executive Functioning Trajectories by Sex

Note. Neocortical Aβ burden (Florbetapir Standardized Uptake Value Ratio) at baseline was not significantly associated with longitudinal changes in executive functioning, regardless of sex. Demographically-adjusted predicted values from the mixed-effects regression model (Aβ × sex × time) are plotted for females (Panel A) and males (Panel B) with "low" levels of Aβ (≤16th percentile), "low-average" levels of Aβ (>16th percentile to the 50th percentile), "high-average" levels of Aβ (>50th percentile to the 84th percentile), and "high" levels of Aβ (≥84th percentile). The 16th, 50th, and 84th percentiles from this sample (N = 148) correspond to baseline SUVR values of 0.957, 1.027, and 1.136, respectively. Fitted lines are plotted for each of the four subgroups (low Aβ, low-average Aβ, high-average Aβ, and high Aβ) by sex, though it should be kept in mind that Aβ was treated as a continuous variable in our model; the categorical delineation of the sample into subgroups is presented here solely for visualization purposes. Time is plotted continuously on the x-axis as years from baseline while executive functioning is plotted on the y-axis as a sample-based z-score composite.

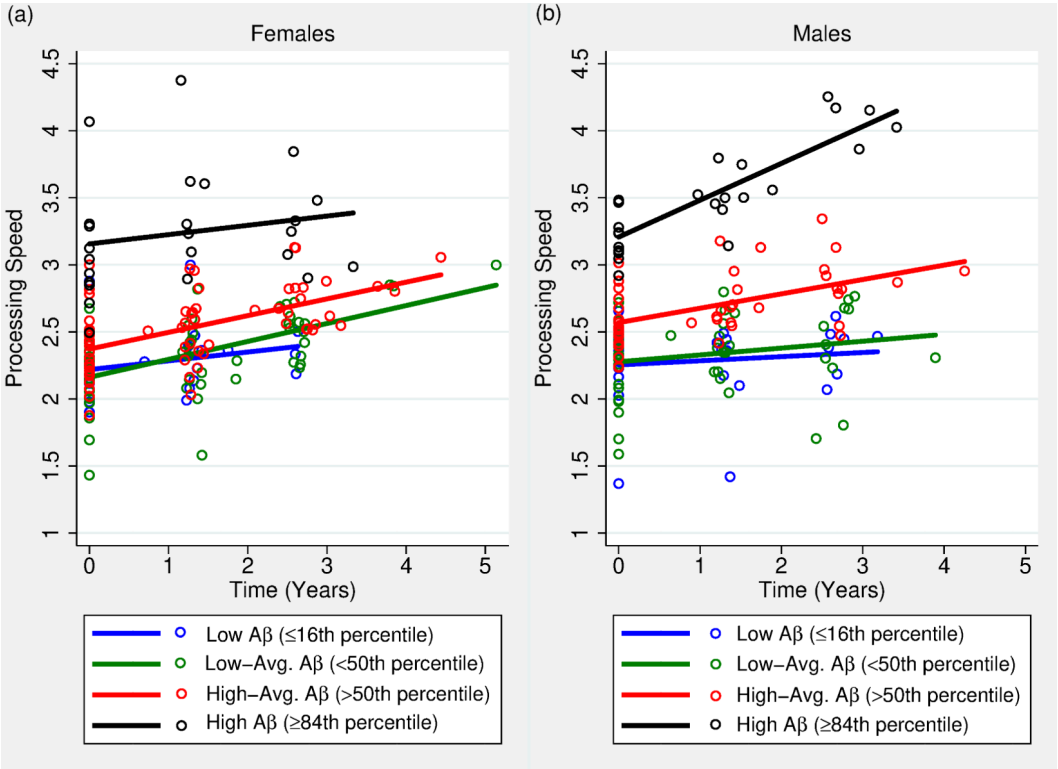

Figure 6. Relationship Between β-Amyloid and Processing Speed Trajectories by Sex

Note. Demographically-adjusted predicted values from the mixed-effects regression model (Aβ × sex × time) are plotted for females (Panel A) and males (Panel B) with "low" levels of Aβ (≤16th percentile), "low-average" levels of Aβ (>16th percentile to the 50th percentile), "high-average" levels of Aβ (>50th percentile to the 84th percentile), and "high" levels of Aβ (≥84th percentile). The 16th, 50th, and 84th percentiles from this sample (N = 148) correspond to baseline SUVR (Florbetapir Standardized Uptake Value Ratio) values of 0.957, 1.027, and 1.136, respectively. Fitted lines are plotted for each of the four subgroups (low Aβ, low-average Aβ, high-average Aβ, and high Aβ) by sex, though it should be kept in mind that Aβ was treated as a continuous variable in our model; the categorical delineation of the sample into subgroups is presented here solely for visualization purposes. Time is plotted continuously on the x-axis as years from baseline while processing speed is plotted on the y-axis as a z-score composite relative to a healthy young adult comparison group (higher scores correspond to worse performance). As represented in Figure 6, there was a statistically significant main effect of Aβ on processing speed; specifically, both males and females with higher levels of Aβ tended to show slower processing speed. In addition, males and females both demonstrated statistically significant declines in processing speed over time (main effect of time), though baseline Aβ levels did not significantly influence the observed *rates* of decline in processing speed. In other words, there was not a statistically significant interaction between Aβ and time (Aβ × time) in predicting processing speed trajectories (b = 0.47, p = .20). There was also not a statistically significant three-way interaction between Aβ, sex, and time (Aβ × sex × time) in predicting longitudinal changes in processing speed, indicating that males and females across the spectrum of Aβ levels evidenced similar rates of decline in processing speed over time (b = −0.37, p = .63).

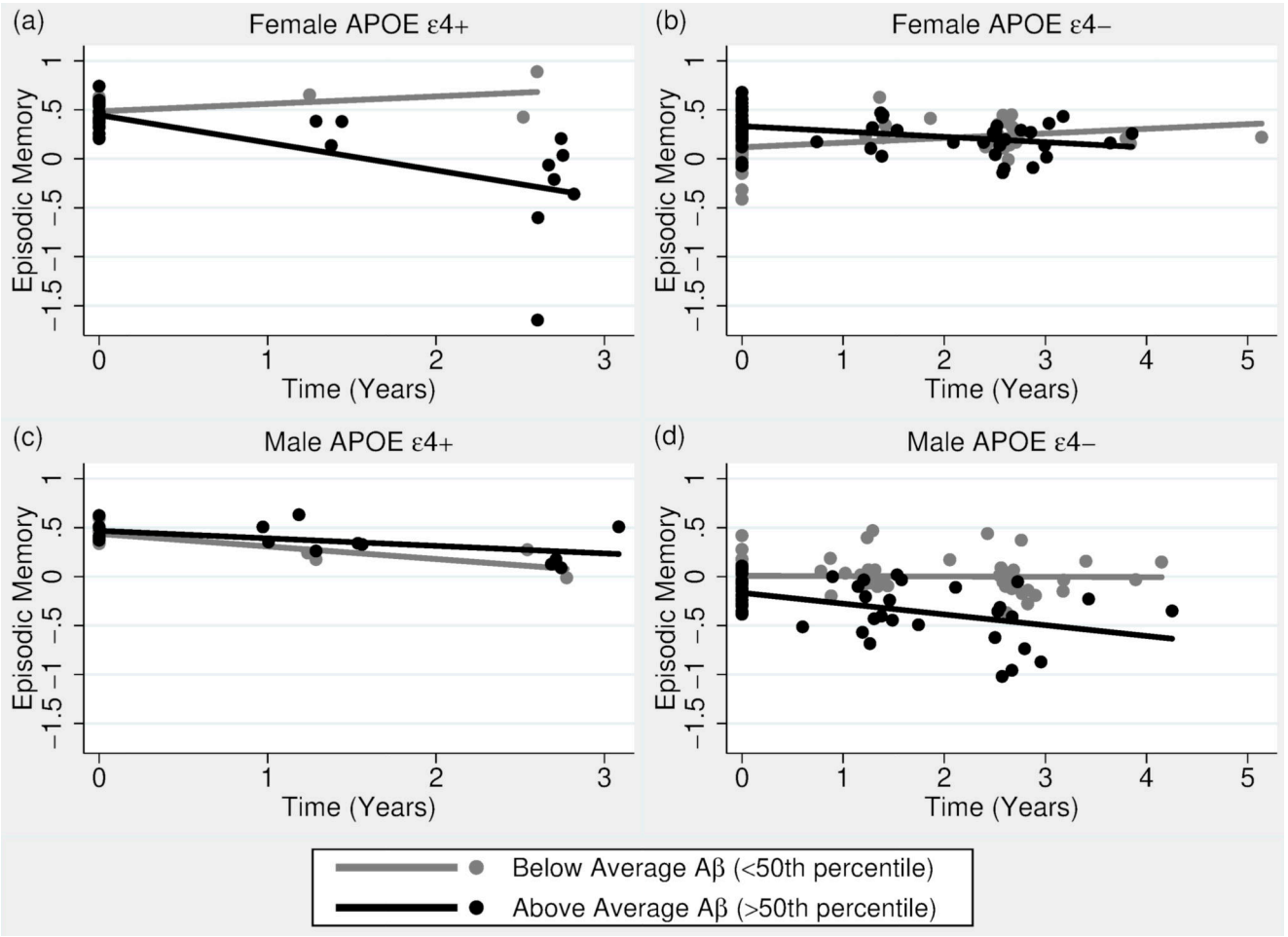

Figure 7. Sex Differences in the Effects of β-Amyloid and APOE ε4 on Episodic Memory Trajectories

Note. *APOE* ε4 status interacted with baseline neocortical Aβ burden (Florbetapir Standardized Uptake Value Ratio) in females, but not males, to predict episodic memory trajectories. To help visualize the interaction (*APOE* × Aβ × sex × time), demographically-adjusted predicted values from the mixed-effects regression model are plotted separately for female *APOE* ε4 carriers (Panel A), female *APOE* ε4 non-carriers (Panel B), male *APOE* ε4 carriers (Panel C), and male *APOE* ε4 non-carriers (Panel D). Individuals with below average levels of Aβ (less than the 50th percentile) are represented by gray filled dots while those with above average levels of Aβ (greater than the 50th percentile) are represented by black filled dots (a more detailed delineation of Aβ is not plotted due to cell size limitations, particularly among *APOE* ε4 carriers). The 50th percentile for the subset of the sample with available *APOE* data (N = 138) corresponds to a baseline SUVR value of 1.027. Fitted lines are plotted for the below-average and above-average Aβ subgroups by *APOE* status and sex, though it should be kept in mind that all of the above data were combined into a single model in our analyses and Aβ was treated as a continuous variable; the categorical delineation of the sample into subgroups is presented here solely for visualization purposes.

Time is plotted continuously on the x-axis as years from baseline while episodic memory is plotted on the y-axis as a sample-based z-score composite.

Table 1

Sample Sizes and Timeframes for Primary Longitudinal Analyses

	Episodic Memory	Processing Speed	Executive Functions
Models A (N = 148)			
# participants with 1 visit	148 (71 males)	148 (71 males)	148 (71 males)
# participants with 2 visits	98 (50 males)	118 (55 males)	98 (50 males)
# participants with 3 visits	32 (20 males)	47 (17 males)	33 (20 males)
# participants with 4 visits	5 (3 males)	1 (0 males)	5 (3 males)
Avg. # follow-up visits	2.38 (max: 4)	2.41 (max: 4)	2.39 (max: 4)
Avg. follow-up length in years	2.55 (max: 5.14)	2.27 (max: 5.14)	2.56 (max: 5.14)
Models B (N = 138)			
# participants with 1 visit	138 (64 males)	138 (64 males)	138 (64 males)
# participants with 2 visits	98 (50 males)	109 (49 males)	98 (50 males)
# participants with 3 visits	32 (20 males)	47 (17 males)	33 (20 males)
# participants with 4 visits	5 (3 males)	1 (0 males)	5 (3 males)
Avg. # follow-up visits	2.38 (max: 4)	2.44 (max: 4)	2.39 (max: 4)
Avg. follow-up length in years	2.55 (max: 5.14)	2.34 (max: 5.14)	2.56 (max: 5.14)

Note. A detailed breakdown of sample sizes comprising each of the primary longitudinal models, including the number of participants with varying numbers of study visits (range: 1–4), are presented by cognitive outcome of interest (episodic memory composite, processing speed composite, and executive functioning composite). As indicated, participants had varying numbers of follow-up visits (maximum = 4 visits) and total follow-up lengths (maximum = 5.14 years) because the Hillblom Aging Network is an active and ongoing longitudinal study with rolling enrollment (i.e., some participants enrolled more recently than others). The sample size was somewhat larger for Models A (effects of sex × time, Aβ × time, and Aβ × sex × time on cognitive trajectories) than for Models B (effects of *APOE* × time, *APOE* × sex × time, and *APOE* × Aβ × sex × time on cognitive trajectories) due to a smaller portion of the cohort having *APOE* genotyping data available.

Table 2

Descriptive Statistics at Baseline

Baseline Characteristic	Overall Sample (N = 149)	Males (N = 72)	Range for Males	Females (N = 77)	Range for Females	*p*-value (*t*-test or χ^2)
Age (years)	74.35 (6.88)	74.62 (7.11)	52.30, 90.28	74.12 (6.70)	54.94, 91.24	.653
Age Distributions						
50–59 years old	n = 5	n = 3	--	n = 2	--	--
60–69 years old	n = 28	n = 12	--	n = 16	--	--
70–79 years old	n = 86	n = 41	--	n = 45	--	--
80–89 years old	n = 27	n = 15	--	n = 12	--	--
90+ years old	n = 3	n = 1	--	n = 2	--	--
Education (years)[a]	17.36 (2.04)	17.75 (1.94)	12, 20	17.00 (2.08)	12, 20	**.026**
SUVR	1.06 (0.13)	1.06 (0.14)	0.90, 1.50	1.05 (0.12)	0.87, 1.65	.544
Episodic Memory[a]	0.13 (0.79)	0.03 (0.81)	−1.96, 1.33	0.23 (0.76)	−1.61, 1.56	.126
Executive Functions	0.14 (0.56)	0.17 (0.57)	−0.75, 1.68	0.11 (0.55)	−1.18, 1.39	.474
Processing Speed	2.40 (1.23)	2.49 (1.35)	0.35, 5.89	2.32 (1.10)	0.41, 5.90	.409
APOE (ε4/non-ε4)[b]	n = 30/108	n = 13/51	--	n = 17/57	--	.864
ε4 Heterozygous	n = 28	n = 12	--	n = 16	--	.837
ε4 Homozygous	n = 2	n = 1	--	n = 1	--	>.99

Note. Values are presented as mean (SD), range (minimum, maximum), or frequency (*n*). SUVR = standardized uptake value ratio. *APOE* = apolipoprotein E. Episodic memory, executive functioning, and processing speed are presented as z-score composites. Statistically significant differences between males and females (i.e., $p < .05$) are flagged by boldface type.

[a] N = 148.

[b] N = 138.

Table 3

Summary of Mixed-Effects Regression Models for Primary Longitudinal Analyses

	Episodic Memory			Processing Speed			Executive Functioning		
	b	**95% CI**	***p*-value**	***b***	**95% CI**	***p*-value**	***b***	**95% CI**	***p*-value**
Time[a]	−0.049	−0.097, −0.001	**.046**	0.117	0.0319, 0.202	**.007**	−0.004	−0.042, 0.035	.857
Baseline Age[a]	−0.020	−0.039, −0.002	**.034**	0.039	0.009, 0.069	**.011**	−0.023	−0.036, −0.011	**<.001**
Education[a]	0.027	−0.034, 0.087	.387	−0.038	−0.135, 0.060	.448	0.070	0.030, 0.109	**.001**
Sex[a]	0.221	−0.036, 0.478	.091	−0.132	−0.550, 0.286	.537	−0.053	−0.225, 0.118	.540
Sex × Time[a]	0.027	−0.070, 0.123	.589	0.005	−0.167, 0.178	.951	0.006	−0.071, 0.084	.875
Aβ[a]	0.112	−0.875, 1.099	.824	2.499	0.858, 4.139	**.003**	−0.327	−0.983, 0.328	.328
Aβ × Time[a]	−0.644	−1.07, −0.215	**.003**	0.466	−0.241, 1.173	.196	0.140	−0.212, 0.492	.436
Aβ × Sex × Time[a]	−1.015	−1.917, −0.114	**.027**	−0.366	−1.832, 1.100	.625	0.133	−0.617, 0.884	.728
APOE[b]	0.296	−0.023, 0.615	.069	0.349	−0.166, 0.863	.184	<0.001	−0.205, 0.205	.999
APOE × Time[b]	−0.129	−0.250, −0.007	**.038**	−0.098	−0.310, 0.115	.368	0.016	−0.081, 0.113	.743
APOE × Sex × Time[b]	−0.189	−0.432, 0.054	.127	0.112	−0.320, 0.544	.613	0.184	−0.008, 0.377	.061
APOE × Aβ × Sex × Time[b]	−2.623	−4.692, −0.555	**.013**	−0.868	−4.316, 2.579	.622	−0.207	−1.967, 1.553	.818

Note. Regression coefficients (*b*) with 95% confidence intervals (CI) are presented for primary terms of interest and covariates, by cognitive outcome (episodic memory composite, processing speed composite, and executive functioning composite). The reference group for sex is males and the reference group for *APOE* ε4 status is non-carriers. Aβ = β-amyloid (Florbetapir Standardized Uptake Value Ratio). *APOE* = apolipoprotein E status (ε4 carrier/non-carrier). Statistically significant effects (i.e., $p < .05$) are flagged by boldface type.

[a]N = 148.

[b]N = 138.