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Sex differences in blood biomarkers and cognitive performance in individuals with autosomal dominant Alzheimer's disease

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Consent Statement

This study was approved by the institutional review board at the University of Antioquia, Colombia, including procedures undertaken outside the University of Antioquia. Informed written consent for participation and the use of data and samples was obtained from cognitively unimpaired adult participants, or from a legal representative (i.e., partner or offspring) of cognitively impaired participants. Participants included a representative sample from the region of Antioquia, Colombia. Participants were not excluded in the basis of gender, race or ethnicity.

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Abstract

INTRODUCTION.—Plasma tau phosphorylated at threonine 217 (P-tau217) and neurofilament light (NfL) have emerged as markers of Alzheimer's disease (AD) pathology. Few studies have examined the role of sex in plasma biomarkers in sporadic AD, yielding mixed findings, and none in autosomal dominant AD.

METHODS.—We examined the effects of sex and age on plasma P-tau217 and NfL, and their association with cognitive performance in a cross-sectional study of 621 Presenilin-1 E280A mutation carriers and non-carriers.

RESULTS.—As plasma P-tau217 levels increase, cognitively unimpaired female carriers showed better cognitive performance than cognitively unimpaired male carriers. Yet, as disease progresses, female carriers had a greater plasma NfL increase than male carriers. There were no sex differences in the association between age and plasma biomarkers among non-carriers.

DISCUSSION.—Our findings suggest that, among *PSEN1* mutation carriers, females had a greater rate of neurodegeneration than males, yet it did not predict cognitive performance.

Keywords

Alzheimer's disease; Autosomal dominant Alzheimer's disease; blood biomarkers; P-tau217; NfL; cognition; sex differences

Background

Blood biomarkers are gaining support as sensitive, non-invasive, and relatively inexpensive biomarkers of early Alzheimer's disease (AD) pathology and neurodegeneration[1]. Among several soluble p-tau species, plasma tau phosphorylated at threonine 217 (P-tau217) has emerged as a marker of early tau pathology accumulation[2,3] that predicts the clinical diagnosis of AD[4-7]. Similarly, plasma neurofilament light chain (NfL), a marker of axonal injury and neuronal degeneration, although not specific to AD, has been shown to be elevated in preclinical and clinical AD[8,9], and is associated with markers of neurodegeneration (e.g., hippocampal atrophy or cortical thinning)[10-12]. Our group showed that Presenilin 1 (*PSEN1*) E280A mutation carriers, who are destined to develop early-onset dementia, have elevated levels of plasma P-tau217[4] and NfL[13], approximately 20 years

before symptom onset. We also showed that, in carriers, higher levels of plasma P-tau217 and NfL were associated with worse memory performance[4,14,15].

Several studies investigating sex differences in AD have shown that females may have greater neurodegeneration[16,17] and tau pathology, as measured by cerebrospinal fluid,[18] PET imaging,[19,20] and postmortem neuropathology[21,22]. Moreover, studies show that females may exhibit a cognitive resilience to early accumulation of AD-related pathology and neurodegeneration at the initial stages of the disease[23-25]; however, as the disease progresses, females exhibit faster cognitive decline[16,26] and progression to dementia[22,27-29] than males. Despite prior evidence, few studies have examined the role of sex/gender on plasma biomarkers in sporadic AD, and none in autosomal dominant AD.

Findings from community and population-based AD studies found that levels of plasma P-tau217 did not differ between males and females[2,5], while a recent study showed that higher plasma P-tau181 was associated with greater amyloid and entorhinal cortex tau accumulation, lower brain glucose metabolism, and faster cognitive decline in females, relative to males[30]. Research examining the effect of sex/gender on plasma biomarkers of neurodegeneration in AD cohort studies have also yielded mixed findings. Several studies have not found sex/gender differences in plasma NfL[5,12,31] or total tau[32,33]. In contrast, other studies found higher levels of total tau in females[31,34,35], whereas, a longitudinal study with healthy individuals with subjective concerns found higher levels of total tau in older males than younger males, but not in females[31]. Taken together, more research is needed to examine how sex/gender is associated with blood biomarkers and cognition across disease stages to further determine the usefulness of blood biomarkers in early detection, disease progression, and development of treatments in AD, and ultimately, to update current appropriate use recommendations[36].

For this study, we used available cross-sectional blood-based biomarker samples to examine sex differences in the age-related trajectory of plasma P-tau217 and NfL levels in *PSEN1* mutation carriers and age-matched non-carriers. We also examined the effect of sex on the associations between plasma biomarkers and cognitive performance among *PSEN1* mutation carriers.

Methods

Participants & Procedures

A total of 621 participants were included in the study, including 259 cognitively unimpaired mutation carriers (mean age: 31, range 24-39; %male: 45.6), 106 cognitively impaired mutation carriers (mean age: 49, range 46-52; %male: 45.3), and 256 age- and sex-matched, cognitively unimpaired non-carriers from the same kindred (mean age: 34, range 25.3-42; %male: 39.5) who were enrolled from December 2013 to February 2017 in the Colombian Alzheimer Prevention Initiative (API) Registry[37]. In brief, this registry aims to locate, enroll, genotype, and perform medical and cognitive evaluations of *PSEN1* E280A family members, and includes individuals with early-onset, potentially familial AD and healthy relatives, age 8 and older. Only those who were 18 years old or above were included in the present study.

Nearly all *PSEN1* mutation carriers develop early-onset AD, with mild cognitive impairment (MCI) symptoms emerging at a median age of 44 years and dementia at 49 years[38]. Participants were considered cognitively unimpaired if they had a MMSE[39] score ≥26 points, a functional assessment staging test (FAST)[40] score ≤2, and no cognitive impairment on the Consortium to Establish a Registry for Alzheimer's disease (CERAD) battery[41]. Cognitive impairment was defined as a FAST score of ≥3 or MCI or dementia due to AD[42,43]. Clinical diagnoses were determined by an interdisciplinary team of dementia specialists (i.e., neurologists, neuropsychologists). Individuals with significant medical, psychiatric, or neurological disorders were excluded. Participants in the study reported their sex assigned at birth (i.e., male/female).

This study was approved by the institutional review board at the University of Antioquia, Colombia, including procedures undertaken outside the University of Antioquia. Informed written consent for participation and the use of data and samples was obtained from cognitively unimpaired adult participants, or from a legal representative (i.e., partner or offspring) of cognitively impaired participants. Participants included a representative sample from the region of Antioquia, Colombia. Participants were not excluded in the basis of sex, gender, race or ethnicity. Participants and investigators acquiring and analyzing data were blind to genetic status. All participants completed clinical and cognitive assessments, and blood samples were collected within 6 months of cognitive evaluations as part of the registry procedures.

Plasma Sampling

Plasma was collected in the morning (without fasting) at the University of Antioquia. Three aliquots of 1 mL were collected. Samples were centrifuged, stored at −80°C and shipped on dry ice for analysis. Plasma NfL concentration was measured at the Clinical Neurochemistry Laboratory, University of Gothenburg, Sweden, using the NF-Light kit on a Single molecule array (Simoa) HD-X Analyzer (Quanterix, Billerica, MA) according to the manufacturer's instructions, as previously described[44]. Measurements were done by board-certified laboratory technicians. Calibrators were run in duplicates, and obvious outlier calibrator replicates were masked before curve fitting. Samples were diluted four-fold and run in singlicates. All measurements were made without information on any clinical data. The dynamic range of the assay was 1.9–1800 pg/mL. Two QC plasma samples were run in duplicates in the beginning and the end of each run. For the QC sample with a concentration of 10.8 pg/mL, repeatability was 4.8% and intermediate precision 6.2%, while for the QC sample with a concentration of 47.7 pg/mL, repeatability was 3.3% and intermediate precision 4.6%. One batch of reagents and one instrument was used to analyze all samples.

For P-tau217, concentrations of plasma P-tau217 were measured using immunoassays at Lilly Research Laboratories, using the MSD platform (Meso Scale Discovery), as previously described[4]. Biotinylated-IBA493 was used as a capture antibody and SULFO-TAG-4G10-E2 (anti-Tau) as the detector. The assay was calibrated using a recombinant tau (4R2N) protein that was phosphorylated in vitro using a reaction with glycogen synthase kinase-3 and characterized by mass spectrometry. Additional details of the plasma P-tau217 analysis are

described in Palmqvist et al., 2020, Supplemental Material. Plasma samples from study participants were analyzed in duplicates with a mean intra-assay coefficient of variation (CV) of 13.9%. The mean inter-assay CVs of quality control samples were 3.4-5.5%. The lower limit of detection of the plasma P-tau217 assay was 0.48 pg/mL.

For genetic analyses, genomic DNA was extracted from blood by standard protocols, and *PSEN1* E280A characterization was done at the University of Antioquia using methods described previously[45]. NfL analyses were supervised by co-authors Zetterberg and Blennow at the Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital (Sweden), and P-tau217 analyses by co-author Dage at Lilly Research Laboratories (USA).

Clinical & Cognitive Assessments

Clinical and cognitive assessments were undertaken at the University of Antioquia (Medellín, Colombia). Participants completed a battery of clinical and cognitive measures in Spanish, adapted by the Neurosciences Group of Antioquia (GNA) to characterize this Colombian population, including the MMSE, the Spanish CERAD battery, the Functional Assessment Staging Test, and the Geriatric Depression Scale[46]. Testing was done in Spanish by neuropsychologists or psychologists trained in neuropsychological assessment. We calculated the Alzheimer Prevention Initiative (API) global cognition composite score, which includes the MMSE (Orientation to Time), Boston Naming Test (15-item), Ravens Progressive Matrices (12-item), CERAD Word List (Delayed Recall), and Constructional Praxis (Copy). This cognitive composite score has been shown to track preclinical AD decline in autosomal dominant AD[47]. Clinical histories and neurological examinations were completed by neurologists or physicians trained in assessing neurodegenerative disorders.

Statistical Analyses

We compared demographic, clinical, neuroimaging, and cognitive data among males and females stratified by *PSEN1* mutation status (i.e., carriers and non-carriers) using t-tests. Because plasma P-tau217 and NfL data were not normally distributed, plasma biomarker data was log transformed. To examine the age-related trajectory of plasma biomarkers, a proxy for disease progression in this kindred, we used multiple linear regression models to estimate the effect of age, sex, and the interaction between sex and age on P-tau217 and NfL levels, stratified by *PSEN1* mutation carriers and non-carriers. Bivariate local polynomial regressions (LOESS) were used to characterize relationships between log-transformed plasma P-tau217 and NfL with age. We then used multiple linear regressions to examine whether sex modified the relationship between plasma biomarkers and cognitive performance among *PSEN1* carriers. Models included plasma biomarkers – P-tau217 and NfL – as the independent variable, cognitive measures – API cognitive composite score and CERAD word list delayed recall – as dependent variables, sex as a covariate of interest, and the interaction terms between sex and plasma biomarkers (i.e., Sex*P-tau217 and Sex*NfL). Subsequent models were run controlling for age. To further understand the effect of age, a proxy for disease progression among *PSEN1* mutation carriers, secondary analyses were conducted stratifying by disease stage (i.e., cognitively unimpaired carriers and cognitively impaired carriers). Analyses used a significance threshold of $p < 0.05$. Analyses were performed by a team of biostatisticians who were unblinded to genotype but had no role in

the study design or data collection. Statistical analyses were done using R (version 4.0.2, The R Foundation) and SPSS version 24. Of note, a female non-carrier participant had NfL values >2 standard deviations above the non-carrier mean and was removed from the analyses.

Results

Sample Characteristics

Overall sample characteristics of male and female *PSEN1* cognitively unimpaired carriers, impaired carriers and non-carriers are described in Table 1. There were no differences in age, years of education, MMSE score, API cognitive composite score, or CERAD word list delayed recall between male and female *PSEN1* carriers and non-carriers, and the distribution of males and females did not differ between carriers and non-carriers. Plasma P-tau217 levels did not differ between males and females among cognitively unimpaired carriers, cognitively impaired carriers, or non-carriers. Compared to males, female carriers had lower NfL levels among cognitively unimpaired, but higher NfL levels among impaired carriers.

Effect of sex in the age trajectory of plasma biomarkers

We examined the association between plasma biomarkers and age in *PSEN1* mutation carriers. There were no sex differences in the association between age and plasma P-tau217 among *PSEN1* mutation carriers; female carriers showed a trend towards higher P-tau217 levels than male carriers (Figure 1A & 1B; Age*Sex, β=1.885, p=.060). Female carriers showed a steeper slope for the association between age and plasma NfL than male carriers (Figure 1C; Age*Sex, β=2.999, p<.003). LOESS plots showed that younger female carriers have lower levels of plasma NfL, but then show a greater increase than male carriers (Figure 1D). Specifically, male and female carriers' LOESS fit confidence band separated at age 48.45. There were no differences between non-carrier males and females in the age trajectory of plasma P-tau217 or NfL (Supplemental Figure 1; Age*Sex: P-tau217, β=−.319, p=.750; NfL, β=−.797, p=.426).

Effect of sex in the association between P-tau217 & cognitive performance

We examined the effect of sex on the association between plasma P-tau217 and cognition among *PSEN1* mutation carriers. There was a significant interaction effect between sex and plasma P-tau217 in predicting cognitive performance, whereby as levels of P-tau217 increase, male carriers had worse API cognitive composite scores than female carriers (Table 2; Figure 2B; Sex*P-tau217: β=2.73, p=.007). This effect dissipated when controlling for age (Sex*P-tau217: β=1.537, p=.12507). Similarly, there was a significant interaction effect between sex and plasma P-tau217 in predicting memory performance, whereby as levels of P-tau217 increase, male carriers had worse CERAD word list delayed recall than female carriers (Figure 2A; Sex*P-tau217: β=2.093, p=.037). This effect dissipated when controlling for age (Sex*P-tau217: β=1.039, p=.299).

To further understand the effect of age in the association between P-tau217 and cognition, given that age is a proxy for disease progression in *PSEN1* mutation carriers, we conducted

secondary analyses stratified by disease stage. Results showed that among cognitively unimpaired mutation carriers, as levels of P-tau217 increase, males had worse API cognitive composite scores (Table 3; Supplemental Figure 2; Sex*P-tau217: β=3.096, *p*=.002) and worse CERAD word list delayed recall (Sex*P-tau217: β=2.454, *p*=.015) than females. In contrast, among cognitively impaired carriers, the interaction effect between sex and plasma P-tau217 did not predict API cognitive composite scores (Sex*P-tau217: β=.271, *p*=.787) or CERAD word list delayed recall (Sex*P-tau217: β=−1.164, *p*=.870).

Effect of sex in the association between NfL & cognitive performance

We examined the effect of sex on the association between plasma NfL and cognition among all *PSEN1* mutation carriers and found that the interaction effect between sex and NfL did not predict API cognitive composite scores (Figure 2D; Sex*NfL: β=0.943, p=.347; Sex*NfL, controlling for age: β=.611, *p*=.541) or CERAD word list delayed recall (Figure 2C; Sex*NfL: β=.858, *p*=.391; Sex*NfL, controlling for age: β=−.624, p=.533).

Secondary analyses stratified by disease stage showed that among cognitively unimpaired mutation carriers, the sex by NfL interaction did not predict API cognitive composite scores (Table 3; Sex*NfL: β=.610, *p*=.542) or CERAD word list delayed recall (Sex*NfL: β=.686, *p*=.493). Similarly, among impaired carriers, the sex by NfL interaction did not predict API cognitive composite scores (Sex*NfL: β=1.314, *p*=.192) or CERAD word list delayed recall (Sex*NfL: β=.731, *p*=.467).

Discussion

Plasma tau phosphorylated at threonine 217 (P-tau217) and neurofilament light (NfL) have been established as early markers of tau pathology[2-6] and neurodegeneration[8-11,48] that could be used as tools for diagnosis, disease monitoring, and clinical response to treatment[49]. Growing evidence has demonstrated sex differences in AD pathology and cognitive progression in sporadic[50] and autosomal dominant AD[51,52]. While blood biomarkers hold promise for utility in AD research and clinical trials, few studies have specifically examined the role of sex in plasma biomarkers, yielding mixed findings. To address this gap, we leveraged cross-sectional blood-based biomarker samples to examine the effect of sex in the age-related trajectory of plasma P-tau217 and NfL, and their association with cognitive performance in *PSEN1* E280A mutation carriers (*PSEN1*) and age-matched non-carriers. As nearly all *PSEN1* mutation carriers develop mild cognitive impairment at a median age of 44 years and dementia at 49 years[38], age in this sample is a proxy for disease progression, and we can estimate disease biomarker trajectories by modeling the effects of age.

Our results found a sex effect in the age-related trajectory of plasma NfL and found that female *PSEN1* mutation carriers exhibited a significantly greater rate of plasma NfL increase than male carriers, starting around age 48. Previous studies have shown that NfL levels increase with age[13]; however, there were no sex differences in the association between age and NfL accumulation among non-carriers, suggesting that this effect may be disease-related. This study is the first to provide evidence that, among *PSEN1* mutation carriers in preclinical and clinical stages of AD, females have a greater rate of neurodegeneration

than males as disease progresses. Previous research examining plasma biomarkers of neurodegeneration had yielded mixed findings, with some showing higher levels of total tau in females[15,19,20], whereas others did not find sex differences in NfL[12,31] or total tau levels[32,33]. Our findings support previous work in sporadic AD showing faster hippocampal volume loss[16] and greater brain glucose hypometabolism[17] in females, compared to males, and help clarify previous inconsistencies in plasma biomarker studies. Assay differences may have contributed to prior mixed findings, as for instance, the total tau assay used in many studies (Simoa hTau Assay) is prone to variability due to differences in pre-analytical sample handling[53]. Moreover, most studies examined cross-sectional levels of plasma NfL and did not specifically examine the interaction between sex and plasma biomarkers, highlighting the importance of examining the effect of sex on biomarker trajectories across the disease spectrum.

The mechanisms underlying the faster neurodegeneration in female *PSEN1* mutation carriers remain unknown. Several factors have been proposed to explain sex differences in sporadic and late-onset AD, including genetic factors[54,55] (e.g., *APOE4*), inflammation[56], cardiovascular disease[57], and hormonal changes[58]. Notably, sex differences in the rate of NfL accumulation were observed starting around age 48, approximately 3 years before average menopause age[59]. However, perimenopausal changes begin 8–10 years before menopause, during which sex hormones fluctuate, followed by a decline in estrogen and progesterone[60]. Previous studies showed that reduced estrogen levels were associated with increased amyloid[61,62] and tau burden[63], and greater neurodegeneration[64]. More research is needed to investigate sex-specific mechanisms of risk and resilience to AD, including the role of sex steroid hormones, cardiovascular disease (and interactive effects)[65] on AD biomarker trajectories and cognitive decline.

We also investigated the effect of sex in the age-related trajectory of plasma P-tau217 and found that there was no difference between male and female *PSEN1* mutation carriers. Our results are consistent with previous cross-sectional studies showing that males and females did not differ in plasma P-tau217 levels[2,5] in sporadic AD. Notably, these findings diverge from previous studies showing higher levels of tau pathology in females in cerebrospinal fluid[18], PET imaging [19,66-69] and postmortem data[21,22,70]. There is a possibility that our study was underpowered to detect sex differences in the age-related accumulation of P-tau217, as female carriers showed a trend towards increased plasma P-tau217 levels, consistent with prior studies in sporadic AD using non-plasma biomarkers; however, this effect did not reach statistical significance. Furthermore, recent evidence suggests that plasma P-tau217 measures the earliest accumulation of both amyloid-beta and soluble hyperphosphorylated tau concentrations[2] that occur even before insoluble tau aggregates can be detected using tau PET[3,71,72], suggesting that sex differences previously shown in tau burden may appear in more advanced disease stages, as most individuals in our study were cognitively unimpaired. Alternatively, our findings may be specific to autosomal dominant AD. These findings warrant further investigation in other autosomal dominant and sporadic AD cohorts to clarify the effect of sex on plasma biomarkers, potential sex-specific confounding measurement factors[73] (e.g., medical comorbidities), and underlying mechanisms and pathology clearance pathways[74] that may explain differences between biomarker modalities and prior findings in sporadic AD. Of note, very few *PSEN1* mutation

carriers in our sample had medical comorbidities (e.g., history of cardiovascular, renal, or hepatic conditions), as expected given their young age of symptom onset.

We then examined the effect of sex on the relationship between plasma biomarkers and cognition in *PSEN1* mutation carriers. Our findings show that, as P-tau217 levels increase, male carriers exhibited a steeper decline in global cognitive and memory performance than female carriers. Notably, this effect dissipated when adjusting for age. Given that in this kindred, age is a proxy for disease progression, we conducted secondary analyses stratified by disease stage. Results showed that the sex by P-tau217 interaction remained significant in predicting global cognitive and memory performance among cognitively unimpaired mutation carriers, but not among cognitively impaired mutation carriers, suggesting that this effect may be specific to early disease stages. In contrast, sex did not modify the relationship between NfL levels and cognitive performance, even though female carriers had a greater NfL increase with age, than male carriers. Taken together, these findings suggest a sex-specific cognitive resilience in female carriers to early accumulation of plasma P-tau217[3], that may dissipate as disease progresses. Supporting this notion, previous work in sporadic AD showed that females may have greater cognitive resilience to early AD-pathology and neurodegeneration[23-25], whereas the disease progresses, females exhibit faster cognitive decline[16,20,26] and progression to dementia[22,27-29] than males. Similarly, previous work from our group showed that among cognitively unimpaired *PSEN1* mutation carriers and non-carriers, females may have greater cognitive resilience to AD-pathology and neurodegeneration than males[51]. It is important to note that our findings may be (at least to some extent) driven by female's verbal memory advantage, as memory performance was assessed verbally, using the CERAD word list, which was also included in the API cognitive composite score to measure global cognitive performance. Our current findings expand on prior work by examining these associations using plasma biomarkers in a sample of cognitively unimpaired and impaired *PSEN1* carriers. Future work as part of the Colombia-Boston Biomarker longitudinal study of autosomal dominant AD (COLBOS), will help clarify the effect of sex and AD pathology on cognitive decline across the disease spectrum and elucidate mechanisms of AD risk and resilience.

This study has some limitations. First, this is a cross-sectional, retrospective study that leveraged available blood biomarker data. However, this study includes a large sample of cognitively unimpaired and impaired individuals from a homogeneous cohort with a single *PSEN1* mutation (E280A) who have a well-characterized clinical trajectory. As *PSEN1* E280A mutation carriers are virtually destined to develop mild cognitive impairment starting at a median age of 44 years and dementia at 49 years[38], age in this sample is a proxy for disease progression. Thus, cross-sectional assessments are analogous to the assessment of longitudinal trajectories of biomarkers and cognition. As mentioned, this study focused on plasma P-tau217 and NfL, however there are several other emerging blood biomarkers, including P-tau181, P-tau231, N-terminal fragment of tau (NT1), or glial fibrillary acidic protein (GFAP), among others. It is also worth noting that different assays were used to measure P-tau217 and NfL levels that may have contributed to our findings. In addition, this study did not examine plasma levels of sex hormones or reproductive health factors, or other data on other potential mechanisms. Further research examining sex differences in plasma P-tau217 and NfL, as well as other blood biomarkers, and its relation to cognitive

trajectories is needed to elucidate mechanisms of risk and resilience in AD, including the role of sex hormones, reproductive and neuroendocrine health factors, or genetic factors. Lastly, replication of our results in independent cohorts will be required to determine generalizability to other at-risk groups for autosomal dominant AD and sporadic AD.

Conclusion

Findings from this cross-sectional study suggest that, among *PSEN1* mutation carriers, as levels of plasma P-tau217 increase, cognitively unimpaired females showed better cognitive performance than cognitively unimpaired males. Yet, as disease progresses, female carriers had a greater plasma NfL increase than male carriers, indicative of faster rate of neurodegeneration. Our work highlights the need for further research examining sex/gender differences in blood biomarkers and their relations to cognitive decline to clarify AD pathophysiology and inform the use of blood biomarkers in clinical research, trials, and practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Cullen NC, Leuzy A, Janelidze S, et al. Plasma biomarkers of Alzheimer’s disease improve prediction of cognitive decline in cognitively unimpaired elderly populations. Nature communications. 2021;12(1):1–9.
2. Mielke MM, Frank RD, Dage JL, et al. Comparison of plasma phosphorylated tau species with amyloid and tau positron emission tomography, neurodegeneration, vascular pathology, and cognitive outcomes. JAMA neurology. 2021;78(9):1108–1117. [PubMed: 34309632]
3. Janelidze S, Berron D, Smith R, et al. Associations of plasma phospho-Tau217 levels with tau positron emission tomography in early Alzheimer disease. JAMA neurology. 2021;78(2):149–156. [PubMed: 33165506]
4. Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. Jama. 2020;324(8):772–781. [PubMed: 32722745]
5. Brickman AM, Manly JJ, Honig LS, et al. Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multi-ethnic, community study. Alzheimer's & Dementia. 2021;17(8):1353–1364.
6. Thijssen EH, La Joie R, Strom A, et al. Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. The Lancet Neurology. 2021/09/01/ 2021;20(9):739–752. doi:10.1016/S1474-4422(21)00214-3 [PubMed: 34418401]
7. Ashton NJ, Janelidze S, Mattsson-Carlgren N, et al. Differential roles of Aβ42/40, p-tau231 and p-tau217 for Alzheimer’s trial selection and disease monitoring. Nature medicine. 2022:1–8.
8. Mattsson N, Andreasson U, Zetterberg H, Blennow K, Initiative AsDN. Association of plasma neurofilament light with neurodegeneration in patients with Alzheimer disease. JAMA neurology. 2017;74(5):557–566. [PubMed: 28346578]
9. Benedet AL, Leuzy A, Pascoal TA, et al. Stage-specific links between plasma neurofilament light and imaging biomarkers of Alzheimer’s disease. Brain. 2020;143(12):3793–3804. [PubMed: 33210117]
10. Preische O, Schultz SA, Apel A, et al. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer’s disease. Nature medicine. 2019;25(2):277–283.
11. Weston PS, Poole T, Ryan NS, et al. Serum neurofilament light in familial Alzheimer disease: a marker of early neurodegeneration. Neurology. 2017;89(21):2167–2175. [PubMed: 29070659]
12. Mattsson N, Cullen NC, Andreasson U, Zetterberg H, Blennow K. Association between longitudinal plasma neurofilament light and neurodegeneration in patients with Alzheimer disease. JAMA neurology. 2019;76(7):791–799. [PubMed: 31009028]
13. Quiroz YT, Zetterberg H, Reiman EM, et al. Plasma neurofilament light chain in the presenilin 1 E280A autosomal dominant Alzheimer's disease kindred: a cross-sectional and longitudinal cohort study. The Lancet Neurology. 2020;19(6):513–521. [PubMed: 32470423]
14. Guzmán-Vélez E, Zetterberg H, Fox-Fuller JT, et al. Associations between plasma neurofilament light, in vivo brain pathology, and cognition in non-demented individuals with autosomal-dominant Alzheimer's disease. Alzheimer's & Dementia. 2021;17(5):813–821.
15. Aguillon D, Langella S, Chen Y, et al. Plasma p-tau217 predicts in vivo brain pathology and cognition in autosomal dominant Alzheimer's disease. Alzheimer's & Dementia. 2022:1–10.
16. Koran MEI, Wagener M, Hohman TJ. Sex differences in the association between AD biomarkers and cognitive decline. Brain Imaging and Behavior. 2017;11(1):205–213. [PubMed: 26843008]
17. Ramanan VK, Castillo AM, Knopman DS, et al. Association of Apolipoprotein E ε4, Educational Level, and Sex With Tau Deposition and Tau-Mediated Metabolic Dysfunction in Older Adults. JAMA Network Open. 2019;2(10):e1913909–e1913909. [PubMed: 31642932]

18. Hohman T, Dumitrescu L, Barnes L, et al. Sex-Specific Association of Apolipoprotein E with Cerebrospinal Fluid Levels of Tau. JAMA Neurology. 2018;75(8):989–998. [PubMed: 29801024]
19. Buckley RF, Mormino EC, Rabin JS, et al. Sex Differences in the Association of Global Amyloid and Regional Tau Deposition Measured By Positron Emission Tomography in Clinically Normal Older Adults. JAMA Neurology. Feb 4 2019;76(5):542–551. doi:10.1001/jamaneurol.2018.4693 [PubMed: 30715078]
20. Buckley RF, Scott MR, Jacobs HI, et al. Sex mediates relationships between regional tau pathology and cognitive decline. Annals of Neurology. 2020;88(5):921–932. [PubMed: 32799367]
21. Oveisgharan S, Arvanitakis Z, Yu L, Farfel J, Schneider JA, Bennett DA. Sex differences in Alzheimer's disease and common neuropathologies of aging. Acta Neuropathologica. 2018;136(6):887–900. [PubMed: 30334074]
22. Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA. Sex differences in the clinical manifestations of Alzheimer disease pathology. Archives of General Psychiatry. 2005;62(6):685–691. [PubMed: 15939846]
23. Sundermann EE, Biegon A, Rubin LH, et al. Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy. Neurology. 2016;86(15):1368–1376. [PubMed: 26984945]
24. Sundermann EE, Maki PM, Reddy S, Bondi MW, Biegon A, Initiative AsDN. Women's higher brain metabolic rate compensates for early Alzheimer's pathology. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2020;12(1):e12121.
25. Digma LA, Madsen JR, Rissman RA, Jacobs DM, Brewer JB, Banks SJ. Women can bear a bigger burden: Ante-and post-mortem evidence for reserve in the face of tau. Brain Communications. 2020;2(1):fcaa025. [PubMed: 32337508]
26. Buckley RF, Mormino EC, Amariglio RE, et al. Sex, amyloid, and APOE epsilon4 and risk of cognitive decline in preclinical Alzheimer's disease: Findings from three well-characterized cohorts. Alzheimer's & Dementia. Sep 2018;14(9):1193–1203. doi:10.1016/j.jalz.2018.04.010
27. Lin KA, Choudhury KR, Rathakrishnan BG, et al. Marked gender differences in progression of mild cognitive impairment over 8 years. Alzheimer's & dementia: translational research & clinical interventions. 2015;1(2):103–110.
28. Irvine K, Laws KR, Gale TM, Kondel TK. Greater cognitive deterioration in women than men with Alzheimer's disease: a meta analysis. Journal of clinical and experimental neuropsychology. 2012;34(9):989–998. [PubMed: 22913619]
29. Holland D, Desikan RS, Dale AM, McEvoy LK. Higher rates of decline for women and apolipoprotein E ε4 carriers. American Journal of Neuroradiology. 2013;34(12):2287–2293. [PubMed: 23828104]
30. Tsiknia AA, Edland SD, Sundermann EE, et al. Sex differences in plasma p-tau181 associations with Alzheimer's disease biomarkers, cognitive decline, and clinical progression. Molecular Psychiatry. 2022/06/29 2022;27:4314–4322. doi:10.1038/s41380-022-01675-8 [PubMed: 35768637]
31. Baldacci F, Lista S, Manca ML, et al. Aging and sex impact plasma NFL and t-Tau trajectories in individuals at risk for Alzheimer's disease: Biomarkers (non-neuroimaging)/plasma/serum/urine biomarkers. Alzheimer's & Dementia. 2020;16:e041792.
32. Mattsson N, Zetterberg H, Janelidze S, et al. Plasma tau in Alzheimer disease. Neurology. 2016;87(17):1827–1835. [PubMed: 27694257]
33. Dage JL, Wennberg AM, Airey DC, et al. Levels of tau protein in plasma are associated with neurodegeneration and cognitive function in a population-based elderly cohort. Alzheimer's & Dementia. 2016;12(12):1226–1234.
34. Pase MP, Beiser AS, Himali JJ, et al. Assessment of plasma total tau level as a predictive biomarker for dementia and related endophenotypes. JAMA neurology. 2019;76(5):598–606. [PubMed: 30830207]
35. Syrjanen JA, Campbell MR, Algeciras-Schimnich A, et al. Associations of amyloid and neurodegeneration plasma biomarkers with comorbidities. Alzheimer's & Dementia. 2021;18:1128–1140.

36. Hansson O, Edelmayer RM, Boxer AL, et al. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. Alzheimer's & Dementia. 2022;18:2669–2686.

37. Rios-Romenets S, Lopez H, Lopez L, et al. The Colombian Alzheimer's Prevention Initiative (API) Registry. Alzheimer's & Dementia. 2017;13(5):602–605.

38. Acosta-Baena N, Sepulveda-Falla D, Lopera-Gómez CM, et al. Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer's disease: a retrospective cohort study. The Lancet Neurology. 2011;10(3):213–220. [PubMed: 21296022]

39. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. Nov 1975;12(3):189–98. [PubMed: 1202204]

40. Reisberg B. Functional assessment staging (FAST). Psychopharmacology Bulletin. 1988;24(4):653–659. [PubMed: 3249767]

41. Aguirre-Acevedo D, Gomez R, Moreno S, et al. Validity and reliability of the CERAD-Col neuropsychological battery. Revista de Neurologia. 2007;45(11):655–660. [PubMed: 18050096]

42. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia 2011;7(3): 270–279.

43. McKhann G, Knopman D, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia. 2011;7(3):263–269.

44. Gisslén M, Price RW, Andreasson U, et al. Plasma concentration of the neurofilament light protein (NFL) is a biomarker of CNS injury in HIV infection: a cross-sectional study. EBioMedicine. 2016;3:135–140. [PubMed: 26870824]

45. Lendon CL, Martinez A, Behrens IM, et al. E280A PS-1 mutation causes Alzheimer's disease but age of onset is not modified by ApoE alleles. Human Mutation. 1997;10(3):186–195. [PubMed: 9298817]

46. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. Journal of Psychiatric Research. 1982;17(1):37–49. [PubMed: 7183759]

47. Ayutyanont N, Langbaum JB, Hendrix SB, et al. The Alzheimer's prevention initiative composite cognitive test score: sample size estimates for the evaluation of preclinical Alzheimer's disease treatments in presenilin 1 E280A mutation carriers. The Journal of clinical psychiatry. 2014;75(6):652. [PubMed: 24816373]

48. Bacioglu M, Maia LF, Preische O, et al. Neurofilament light chain in blood and CSF as marker of disease progression in mouse models and in neurodegenerative diseases. Neuron. 2016;91(1):56–66. [PubMed: 27292537]

49. Teunissen CE, Verberk IM, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. The Lancet Neurology. 2022;21(1):66–77. [PubMed: 34838239]

50. Mielke MM, Aggarwal NT, Vila-Castelar C, et al. Consideration of sex and gender in Alzheimer's disease and related disorders from a global perspective. Alzheimer's & Dementia. 2022:1–18. doi:10.1002/alz.12662

51. Vila-Castelar C, Tariot PN, Sink KM, et al. Sex differences in cognitive resilience in preclinical autosomal-dominant Alzheimer's disease carriers and non-carriers: Baseline findings from the API ADAD Colombia Trial. Alzheimer's & Dementia. 2022;18(11):2272–2282. doi:10.1002/alz.12552

52. Vila-Castelar C, Guzmán-Vélez E, Pardilla-Delgado E, et al. Examining Sex Differences in Markers of Cognition and Neurodegeneration in Autosomal Dominant Alzheimer's Disease: Preliminary Findings from the Colombian Alzheimer's Prevention Initiative Biomarker Study. Journal of Alzheimer's Disease. 2020;77(4):1743–1753.

53. Verberk IM, Misdorp EO, Koelewijn J, et al. Characterization of pre-analytical sample handling effects on a panel of Alzheimer's disease–related blood-based biomarkers: Results from the

Standardization of Alzheimer's Blood Biomarkers (SABB) working group. Alzheimer's & Dementia. 2021;18:1484–1497.

54. Neu SC, Pa J, Kukull W, et al. Apolipoprotein E genotype and sex risk factors for Alzheimer disease: a meta-analysis. JAMA Neurology. 2017;74(10):1178–1189. [PubMed: 28846757]
55. Dumitrescu L, Barnes LL, Thambisetty M, et al. Sex differences in the genetic predictors of Alzheimer's pathology. Brain. 2019;142(9):2581–2589. [PubMed: 31497858]
56. Fisher DW, Bennett DA, Dong H. Sexual dimorphism in predisposition to Alzheimer's disease. Neurobiology of Aging. 2018;70:308–324. [PubMed: 29754747]
57. Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. Endocrine reviews. 2016;37(3):278–316. [PubMed: 27159875]
58. Pike CJ, Carroll JC, Rosario ER, Barron AM. Protective actions of sex steroid hormones in Alzheimer's disease. Frontiers in Neuroendocrinology. 2009;30(2):239–258. [PubMed: 19427328]
59. Rettberg JR, Yao J, Brinton RD. Estrogen: a master regulator of bioenergetic systems in the brain and body. Frontiers in Neuroendocrinology. 2014;35(1):8–30. [PubMed: 23994581]
60. Gold EB. The timing of the age at which natural menopause occurs. Obstetrics and Gynecology Clinics. 2011;38(3):425–440. [PubMed: 21961711]
61. Kantarci K, Lowe VJ, Lesnick TG, et al. Early postmenopausal transdermal 17β-estradiol therapy and amyloid-β deposition. Journal of Alzheimer's Disease. 2016;53(2):547–556.
62. Schonknecht P, Pantel J, Klinga K, et al. Reduced cerebrospinal fluid estradiol levels are associated with increased b-amyloid levels in female patients with Alzheimer's disease. Neuroscience Letters. 2001;307(2):122–124. [PubMed: 11427315]
63. Buckley RF, O'Donnell A, McGrath ER, et al. Menopause status moderates sex differences in tau burden: a Framingham PET Study. Annals of Neurology. 2022;92:11–22. [PubMed: 35471588]
64. Mosconi L, Berti V, Quinn C, et al. Sex differences in Alzheimer risk: Brain imaging of endocrine vs chronologic aging. Neurology. 2017;89(13):1382–1390. [PubMed: 28855400]
65. Lohner V, Pehlivan G, Sanroma G, et al. The Relation Between Sex, Menopause, and White Matter Hyperintensities: The Rhineland Study. Neurology. 2022;99 (9):e935–e943. doi:10.1212/WNL.0000000000200782 [PubMed: 35768207]
66. Edwards L, La Joie R, Iaccarino L, et al. Multimodal neuroimaging of sex differences in cognitively impaired patients on the Alzheimer's continuum: greater tau-PET retention in females. Neurobiology of Aging. 2021;105:86–98. [PubMed: 34049062]
67. Wisch JK, Meeker KL, Gordon BA, et al. Sex-related differences in tau positron emission tomography (PET) and the effects of hormone therapy (HT). Alzheimer disease and associated disorders. 2021;35(2):164–168. [PubMed: 32520734]
68. Pereira JB, Harrison TM, La Joie R, Baker SL, Jagust WJ. Spatial patterns of tau deposition are associated with amyloid, ApoE, sex, and cognitive decline in older adults. European journal of nuclear medicine and molecular imaging. 2020;47(9):2155–2164. [PubMed: 31915896]
69. Palta P, Rippon B, Tahmi M, et al. Sex differences in in vivo tau neuropathology in a multiethnic sample of late middle-aged adults. Neurobiology of Aging. 2021;103:109–116. [PubMed: 33894641]
70. Liesinger AM, Graff-Radford NR, Duara R, et al. Sex and age interact to determine clinicopathologic differences in Alzheimer's disease. Acta Neuropathologica. 2018;136(6):873–885. [PubMed: 30219939]
71. Mattsson-Carlgren N, Andersson E, Janelidze S, et al. Aβ deposition is associated with increases in soluble and phosphorylated tau that precede a positive Tau PET in Alzheimer's disease. Science Advances. 2020;6(16):eaaz2387. [PubMed: 32426454]
72. Mattsson-Carlgren N, Janelidze S, Bateman RJ, et al. Soluble P-tau217 reflects amyloid and tau pathology and mediates the association of amyloid with tau. EMBO molecular medicine. 2021;13(6):e14022. [PubMed: 33949133]
73. Pichet Binette A, Janelidze S, Cullen N, et al. Confounding factors of Alzheimer's disease plasma biomarkers and their impact on clinical performance. Alzheimer's & Dementia. 2022;19:1403–1414. doi:10.1002/alz.12787

74. Stocker H, Beyer L, Trares K, et al. Association of Kidney Function With Development of Alzheimer Disease and Other Dementias and Dementia-Related Blood Biomarkers. JAMA Network Open. 2023;6(1):e2252387–e2252387. [PubMed: 36692879]

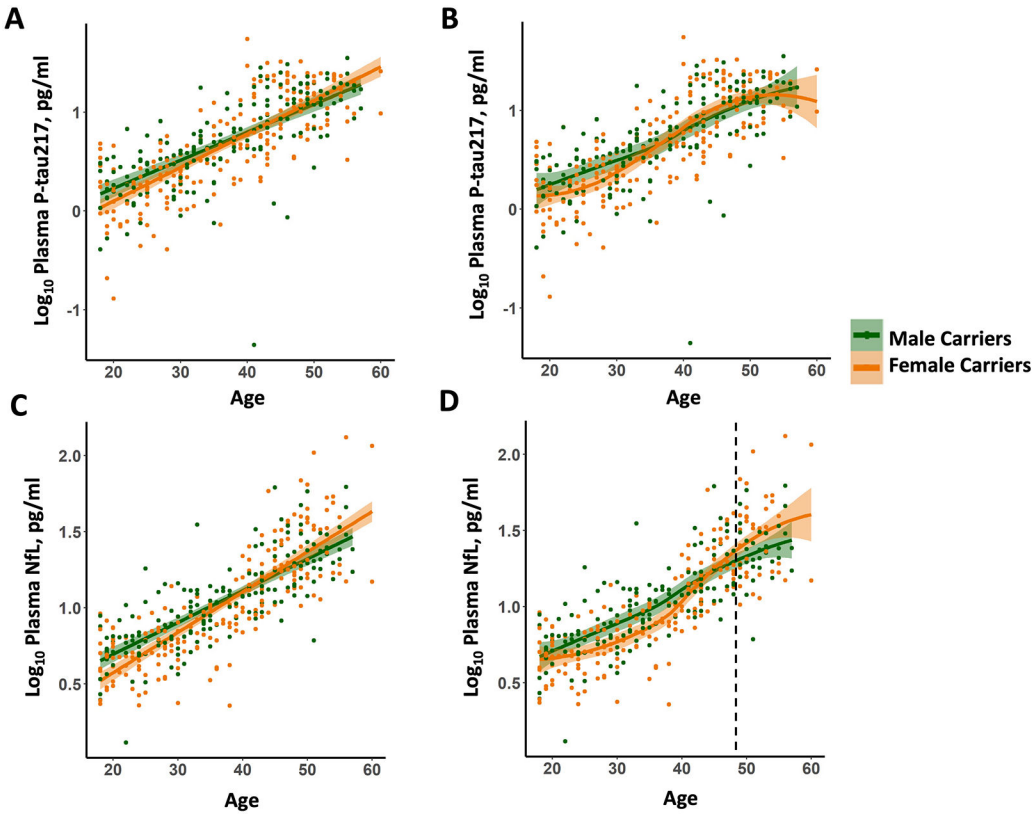

Figure 1. Age trajectories of plasma P-tau217 and NfL in male and female *PSEN1* mutation carriers.

(A) Log_{10} Plasma P-tau217 as a function of age. (B) LOESS plot of Log_{10} Plasma P-tau217 as a function of age. (C) Log_{10} Plasma NfL as a function of age. (D) LOESS plot of Log_{10} Plasma NfL as a function of age. Dashed line represents the age at which male and female carriers LOESS fit confidence band separate (age of 48.45). **Abbreviations:** NfL, Neurofilament light chain; P-tau217, Plasma-measured tau phosphorylated at threonine 217. Orange represents female carriers and green represents male carriers.

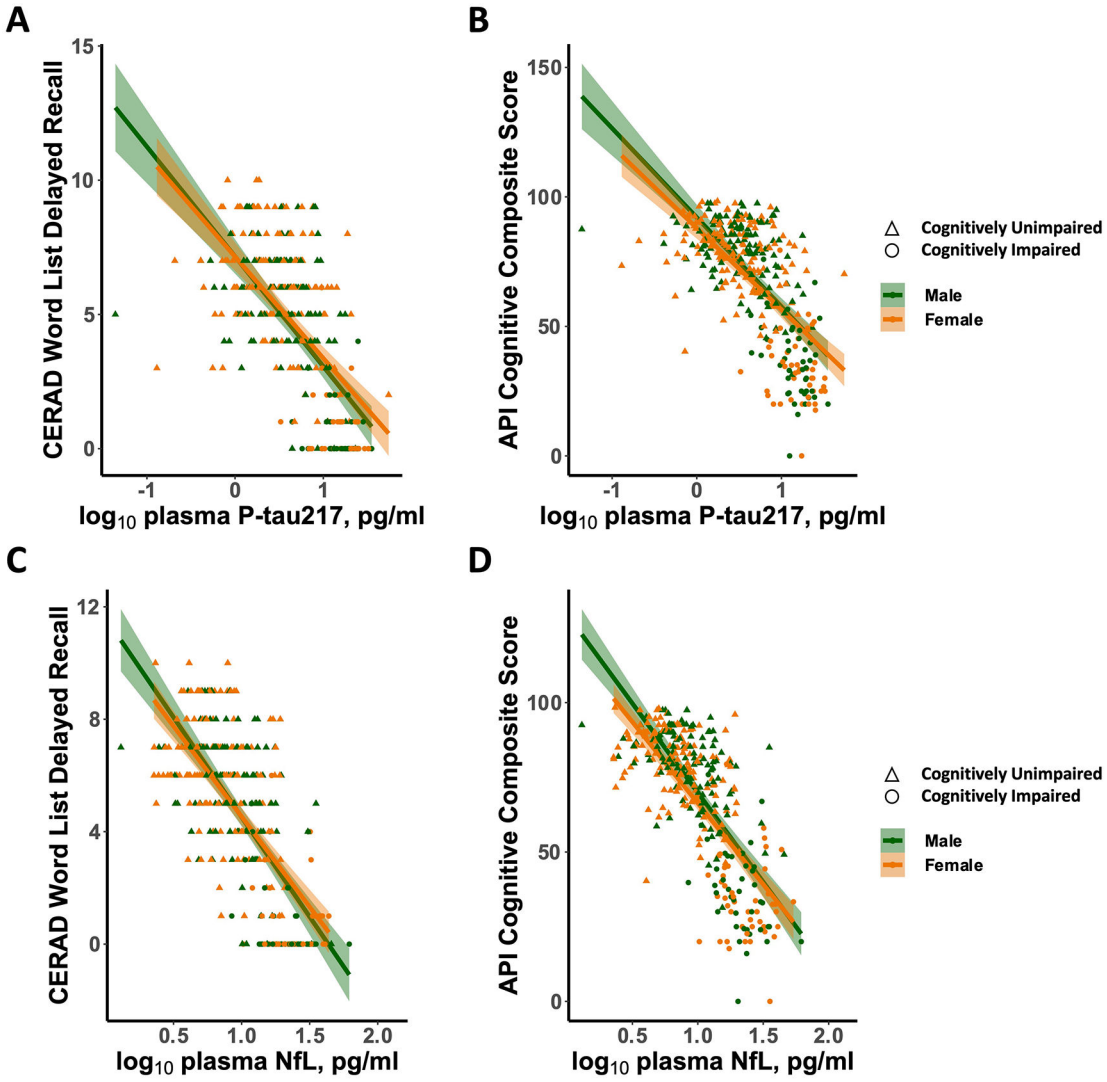

Figure 2. Associations between plasma P-tau217 and NfL and cognitive performance in male and female *PSEN1* mutation carriers.

(A) CERAD word list delayed recall as a function of Log_{10} Plasma P-tau217. (B) API cognitive composite score as a function of Log_{10} Plasma P-tau217. (C) CERAD word list delayed recall as a function of Log_{10} Plasma NfL. (D) API cognitive composite score as a function of Log_{10} Plasma NfL. **Abbreviations:** NfL, Neurofilament light chain; P-tau217, Plasma-measured tau phosphorylated at threonine 217; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; API, Alzheimer Prevention Initiative. Orange represents female carriers, and green represents male carriers. Circles represent cognitively unimpaired carriers, and triangles represent cognitively impaired carriers.

Table 1.

Demographic, clinical, cognitive, and biomarkers among male and female *PSEN1* mutation carriers and non-carriers

	Non-carriers			Cognitively Unimpaired Carriers			Cognitively Impaired Carriers		
	Mean±SD		*p* [a]	Mean±SD		*p* [b]	Mean±SD		*p* [c]
	Males n = 101	Females n = 155		Male n = 118	Female n = 141		Male n = 48	Female n = 58	
Age, years	33.42±10.29	35.08±9.53	.186	31.98±9.14	31.70±9.26	.813	49.04±4.63	48.85±4.59	.827
Education, years	8.13±4.72	8.46±4.32	.566	7.90±4.43	8.77±4.24	.109	4.85±3.78	5.36±3.66	.485
Body Mass Index, kg/m^2	22.74±2.89	23.88±3.76	.059	22.40±3.17	23.15±3.40	.142	22.51±2.79	23.47±2.57	.172
MMSE score	28.78±1.70	28.83±1.97	.846	28.80±1.55	28.67±1.87	.548	19.50±7.02	16.85±7.16	.083
API Cognitive Composite Score	82.59±11.23	81.65±10.08	.501	79.51±12.81	79.05±12.26	.768	36.75±14.74	34.63±14.28	.495
CERAD Word List Delayed Recall	6.30±1.88	6.40±2.00	.708	5.59±2.11	5.98±2.04	.136	0.76±1.37	0.88±1.45	.697
Plasma P-tau217, pg/ml	1.92±1.46	1.85±1.45	.696	4.69±3.95	4.42±5.78	.662	16.14±6.81	17.42±7.20	.352
Plasma NfL, pg/ml	7.33±3.98	6.57±2.91	.082	9.74±6.34	7.97±4.45	.009	24.92±12.11	33.32±24.12	.023

Note. Abbreviations: MMSE, Mini-Mental Status Exam; CERAD, Consortium to Establish a Registry for AD; API, Alzheimer Prevention Initiative.

[a] p-value as defined by an independent two sample t-test for male vs female non-carriers.

[b] p-value as defined by an independent two sample t-test for male vs female cognitively unimpaired mutation carriers.

[c] p-value as defined by an independent two sample t-test for male vs female symptomatic mutation carriers.

Table 2.

Regression estimates of the effect of sex on the relationship between plasma biomarkers and cognition among *PSEN1* mutation carriers with and without age as a covariate.

		Model 1		Model 2 (Adjusting for Age)	
Outcome Variable	**Predictors**	**Standardized β**	***p*-value**	**Standardized β**	***p*-value**
API Cognitive Composite Score	Sex	−2.09	**.037**	−1.524	.129
	Plasma P-tau217	−7.683	**<.001**	−4.357	**<.001**
	Sex*P-tau217	2.73	**.007**	1.537	.125
	Age	.	.	−12.142	**<.001**
CERAD Word List Delayed Recall	Sex	−.285	.775	.396	.692
	Plasma P-tau217	−6.909	**<.001**	−3.910	**<.001**
	Sex*P-tau217	2.093	**.037**	1.039	.299
	Age	.	.	−9.923	**<.001**
API Cognitive Composite Score	Sex	−1.492	.137	−1.030	.304
	Plasma NfL	−6.846	**<.001**	−3.610	**<.001**
	Sex*NfL	.943	.347	.611	.541
	Age	.	.	−8.065	**<.001**
CERAD Word List Delayed Recall	Sex	−.805	.421	−.404	.686
	Plasma NfL	−6.075	**<.001**	−3.214	**.001**
	Sex*NfL	.858	.391	.624	.533
	Age	.	.	−6.957	**<.001**

Note. Abbreviations: *PSEN1* status, *PSEN1* Carriers/Non-carriers; P-tau217, Plasma P-tau217 pg/ml; NfL, Plasma NfL pg/ml; API, Alzheimer Prevention Initiative; CERAD, Consortium to Establish a Registry for AD. Bold text represents *p*-value <.05.

Table 3.

Regression estimates of the effect of sex on the relationship between plasma biomarkers and cognition among cognitively unimpaired and impaired *PSEN1* mutation carriers.

		Cognitively Unimpaired Carriers		Cognitively Impaired Carriers	
Outcome Variable	**Predictors**	**Standardized β**	***p*-value**	**Standardized β**	***p*-value**
API Cognitive Composite Score	Sex	−2.553	**.011**	−.444	.658
	Plasma P-tau217	−4.541	**<.001**	−1.055	.294
	Sex*P-tau217	3.096	**.002**	.271	.787
CERAD Word List Delayed Recall	Sex	−.741	.459	.415	.679
	Plasma P-tau217	−4.077	**<.001**	−.967	.337
	Sex*P-tau217	2.454	**.015**	−.164	.870
API Cognitive Composite Score	Sex	−1.077	.283	−1.346	.182
	Plasma NfL	−3.303	**.001**	−2.154	**.034**
	Sex*NfL	.610	.543	1.314	.192
CERAD Word List Delayed Recall	Sex	−.575	.566	−.640	.524
	Plasma NfL	−2.917	**.004**	−1.571	.120
	Sex*NfL	.686	.493	.731	.467

Note. Abbreviations: *PSEN1* status, *PSEN1* Carriers/Non-carriers; P-tau217, Plasma P-tau217 pg/ml; NfL, Plasma NfL pg/ml; API, Alzheimer Prevention Initiative; CERAD, Consortium to Establish a Registry for AD. Bold text represents *p*-value <.05.