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

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ABSTRACT

Background: Blood-based biomarkers are a promising tool for early detection of Alzheimer's disease (AD). We recently showed that individuals with autosomal-dominant AD due to the E280A mutation in the presenilin 1 gene (*PSEN1*) showed elevated levels of plasma tau phosphorylated at threonine 217 (P-tau217) and neurofilament light chain (NfL), as early as approximately 20 years before clinical onset. We examined sex differences in the age-related trajectory of P-tau217 and NfL, and whether they predicted cognitive performance in *PSEN1* mutation carriers and non-carriers.

Methods: Cross-sectional plasma P-tau217 and NfL concentrations were measured using highly sensitive immunoassays from 622 participants, including 259 cognitively-unimpaired mutation carriers (mean age: 31 years, range 24-39; %male: 45.6), 106 cognitively-impaired mutation carriers (mean age: 49, range 46-52; %male: 45.3), and 257 age-matched non-carriers (mean age: 34, range 25.5-42; %male: 39.3). Bivariate local polynomial regressions (LOESS) were used to characterize relationships between log-transformed P-tau217 and NfL with age. Linear mixed effect models were used to estimate the fixed slope and intercept of female and male within carriers and non-carriers. Linear regressions examined the association between blood biomarkers and API cognitive composite score and CERAD word list delayed recall in carriers and non-carriers.

Results: There were no sex differences in the association between age and plasma P-tau217 among mutation carriers (Slope test, p=.055). Female carriers showed a steeper slope for the association between age and plasma NfL than male carriers (Slope test, p=.001). In contrast, there was a significant interaction between sex and plasma p-tau217 in predicting cognitive performance, in that among individuals with higher levels of P-tau217, females showed better API cognitive composite score (β = 2.989, p = .003) and CERAD word list delayed recall (β = 2.477, p = .013). Sex and the interaction between sex and plasma NfL were not significant in predicting cognitive performance.

Conclusions: Our findings suggest that, among individuals with autosomal-dominant AD, females may have greater cognitive resilience to tau pathology, while female *PSEN1* mutation carriers had a faster rate of plasma NfL increase and may be more susceptible to AD-related neurodegeneration. Further research examining sex/gender differences in blood-based biomarkers and their relations to cognitive performance is needed to understand mechanisms of risk and resilience in AD and inform the use of blood biomarkers in clinical research, trials, and clinical practice.

Introduction

Blood biomarkers have been proposed as sensitive, non-invasive, and relatively inexpensive biomarkers of early Alzheimer's disease (AD) pathology and neurodegeneration[1]. Among several 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 clinical diagnosis of AD[4-6]. Similarly, plasma neurofilament light chain (NfL), a marker of axonal injury and neuronal degeneration, though not specific to AD, has been shown to be elevated in preclinical and clinical AD[7-9], and is associated with measures of neurodegeneration (e.g., hippocampal atrophy, cortical thinning, and reduced glucose metabolism)[10-12]. Our group showed that individuals with autosomal-dominant AD due to the E280A mutation in the presenilin 1 gene (*PSEN1*), destined to develop mild cognitive impairment (MCI) at a median age of 44 years and dementia at 49 years[13], have elevated levels of plasma P-tau217[4] and NfL[14], as early as approximately 20 years before symptom onset. Moreover, we showed that, in carriers, higher plasma P-tau217 and NfL were associated with worse memory performance[4,15].

Few studies to date have examined the role of sex and gender in plasma biomarkers of tau pathology in sporadic or late-onset AD, and none in autosomal dominant AD. Levels of plasma P-tau217 did not differ between males and females in community and population-based studies[2,5]. Research examining plasma biomarkers of neurodegeneration in AD cohort studies has been mixed. Several studies have not found sex differences in NfL[16,17] or total tau[18,19], while other studies found higher levels of total tau in females[16,20,21]. Notably, Baldacci and colleagues found that total tau levels in a longitudinal sample of healthy individuals with subjective cognitive concerns were higher in older males than younger males, but not in females[16]. Therefore, more research is needed to examine how sex and gender are 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.

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 participants of the Colombian Alzheimer's Prevention Initiative Registry[22], including *PSEN1* E280A mutation carriers and age-matched non-carriers. We also examined sex differences in the associations between plasma biomarkers and cognitive performance.

Methods

Participants & Procedures

A total of 622 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 257 age- and sex-matched noncarriers (mean age: 34, range 25.5-42; %male: 39.3) who were enrolled in the Alzheimer Prevention Initiative Registry from December 2013 to February 2017.

PSEN1 mutation carriers are destined to develop early-onset AD, with mild cognitive impairment (MCI) symptoms emerging at a median age of 44 years and dementia at 49 years[13]. Participants were considered cognitively unimpaired if they had a MMSE[23] score ≥26 points, a functional assessment staging test (FAST)[24] score ≤2, and no cognitive impairment on the Consortium to Establish a Registry for Alzheimer's disease (CERAD) battery[25]. Cognitive impairment was defined as a FAST score of ≥3 or MCI or dementia due to AD[26,27]. Individuals with significant medical, psychiatric, or neurological disorders, a history of stroke, seizures, substance abuse, or other disorders that affect motor, visuospatial or cognitive abilities 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 and investigators acquiring and analyzing data were blind to genetic status.

Plasma Sampling

Plasma was collected in the morning (without fasting) at the University of Antioquia. Three aliquots of 1 mL were collected. Samples were stored at –80°C. For NfL analysis, one plasma aliquot was shipped on dry ice to the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital (Mölndal, Sweden). NfL concentration was measured using an in-house Single molecule array assay, as described previously (Quanterix, Billerica, MA, USA)[28]. The measurements were done by board-certified laboratory technicians. 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[29]. Analysis of plasma P-tau217 was performed at Eli Lilly and Company 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. Additional details of the plasma P-tau217 analysis are described in Palmqvist et al., 2020, Supplemental Material. 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[30]. 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 Hansson at the Memory Clinic, Skåne University Hospital (Sweden).

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. These included the MMSE, the Spanish CERAD battery, the Functional Assessment Staging Test, and the Geriatric Depression Scale[31]. Testing was done in Spanish by neuropsychologists or psychologists trained in neuropsychological assessment. We calculated the Alzheimer Prevention Initiative global cognition composite score, which includes the MMSE (Orientation to Time), Boston Naming Test (15-item), Ravens Progressive Matrices (12-item) and 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[32]. Clinical histories and neurological examinations were completed by neurologists or physicians trained in the assessment of dementia.

Statistical Analyses

We compared demographic, clinical, neuroimaging, and cognitive data among males and females in both *PSEN1* carriers and non-carrier groups using t-tests. Because plasma P-tau217 and NfL data were not normally distributed, blood biomarkers analyses were done after log transformation. Linear mixed effect models were used to estimate the fixed slope and intercept of female and male among carriers and noncarriers. Bivariate local polynomial regressions (LOESS) were used to characterize relationships between log-transformed plasma P-tau217 and NfL with age. Linear regressions examined whether sex modified the relationship between plasma biomarkers and cognitive performance in *PSEN1* carriers and non-carriers. Models included plasma biomarkers – P-tau217 and NfL – as the independent variable and API cognitive composite score or CERAD word list delayed recall, respectively, as dependent variables. Models included *PSEN1* status (*PSEN1* mutation carriers/non-carriers) and sex as covariates 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. 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.

Results

Sample Characteristics

Overall sample characteristics of *PSEN1* carriers and non-carriers are described in Table 1. There were no differences in the distribution of males and females between carriers and non-carriers. Demographic, clinical, cognitive, and blood biomarker data among male and female *PSEN1* carriers and non-carriers are described in detail in Table 2. There were no differences between males and females in age, years of education, MMSE score, API cognitive composite score, CERAD word list delayed recall, levels of plasma P-tau217 or NfL among *PSEN1* carriers and non-carriers.

[Insert **Table 1** here]

Sex differences in the association between blood biomarkers & age trajectories

We first 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 (**Figure 1A**; Slope test, p = .055). Female carriers showed a steeper slope for the association between age and plasma NfL than male carriers (**Figure 1C**; Slope test, p < .001). LOESS plots showed that younger female carriers have lower levels of plasma NfL but then show a faster rate of accumulation than male carriers (**Figure 1B**). 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 (Slope tests: NfL, p=.963; P-tau217, p=.867).

[Insert **Figure 1** here]

Sex differences in the association between blood biomarkers & cognitive performance

We examined the effect of sex on the relationship between plasma P-tau217 and cognition. There was a significant interaction effect between sex and plasma P-tau217 in predicting cognitive performance, whereby among individuals with higher levels of plasma P-tau217, males had worse API cognitive composite scores (**Figure 2B**; Sex*P-tau217: β = 2.989, p = .003). This effect showed a trend towards significance when controlling for age (Sex*P-tau217: β = -1.858, p = .064). Similarly, there was a significant interaction effect between sex and plasma P-tau217 in predicting memory performance, whereby among individuals with higher levels of P-tau217, males had worse CERAD word list delayed recall (**Figure 2A;** Sex*P-tau217: β = 2.477, p = .013), and this effect remained significant when controlling for age (Sex*P-tau217: β = 1.519, p = .013).

We then examined the effect of sex on the relationship between plasma NfL and cognitive performance. There was a significant effect of sex, wherein for any level of plasma NfL, females exhibited worse API cognitive composite scores than males (Sex: β =-2.072, p = .039). This effect dissipated when controlling for age (Sex, controlling for age: β = -.639, p = .523). However, the interaction effect between sex and NfL was not significant (**Figure 2D**; Sex*NfL: β= 1.488, p= .137; Sex*NfL, controlling for age: β = .326, p = .744). Similarly, sex and the interaction between sex and plasma NfL were not significant in predicting CERAD word list delayed recall (**Figure 2C;** Sex: β = -.146, p = .884; Sex*NfL: β= .194, p= .846; Sex*NfL, controlling for age: β= -.240, p= .810).

[Insert **Figure 2** here]

Discussion

Blood biomarkers of AD have been proposed as sensitive, less invasive, and cost-effective markers of early AD pathology and neurodegeneration that could be used as tools for diagnosis and monitoring in clinical trials and practice[33]. Plasma tau phosphorylated at threonine 217 (P-tau217), and plasma neurofilament light chain (NfL), a marker of axonal injury and neuronal degeneration, have emerged as early markers of tau pathology accumulation[2-6] and neurodegeneration[7-12], respectively. Few studies to date have specifically examined the role of sex and gender in plasma biomarkers and found that levels of plasma P-tau217 did not differ between males and females[2,5]. In contrast, studies examining sex differences in blood biomarkers of neurodegeneration, such as NfL or total tau, showed higher total tau levels in females[16,20,21], whereas others did not find sex differences in NfL[16,17] or total tau[18,19]. Thus, while blood biomarkers hold promise for utility in AD research studies and clinical trials, more research is needed to examine the effect of sex and gender in blood biomarker levels and age trajectories. To address this gap, we examined the effect of sex in the age-related trajectory of plasma P-tau217 and NfL levels and its effect on the associations between plasma biomarkers and cognitive performance in *PSEN1* E280A mutation carriers, who are destined to develop mild cognitive impairment at a median age of 44 years and dementia at 49 years[13], and age-matched non-carriers.

Our results show that female *PSEN1* mutation carriers exhibited a significantly faster rate of plasma NfL accumulation than male carriers, starting around age 48. This study is the first to provide evidence that, among *PSEN1* mutation carriers in preclinical and clinical stages, females have a faster rate of neurodegeneration than males, suggesting that females may be more susceptible to downstream effects of AD pathology. These findings are consistent with previous work in sporadic and late-onset AD that found faster hippocampal volume loss[34] and greater brain glucose hypometabolism[35] in females, compared to males. However, previous research examining plasma biomarkers of neurodegeneration had yielded mixed findings, with some showing higher plasma levels of total tau in females[15,19,20], whereas others did not find sex differences in NfL[16,17] or total tau levels[18,19].

The specific mechanisms underlying these findings remain unknown. Several factors have been proposed to explain sex differences in sporadic and late-onset AD, including genetic factors[36-39] (e.g., *APOEε4*[38]), inflammation,[40] cardiovascular disease,[41] or hormonal changes.[42] Notably, in our study, sex differences in the rate of NfL accumulation were observed starting around age 48, approximately 3 years before average menopause age[43]. However, perimenopausal changes begin 8-10 years before menopause[44], during which sex steroid hormones fluctuate significantly, followed by a decline in the ovarian production of estrogen and progesterone[45]. Previous studies showed that reduced estrogen levels were associated with increased amyloid burden[46,47] and greater neurodegeneration[48]. Thus, future research is needed to investigate sex-specific mechanisms of risk and resilience to AD, including the role of sex steroid hormones on AD biomarker accumulation and cognitive decline.

In contrast, our results show no differences in the age-related trajectory of plasma P-tau217 among male and female *PSEN1* mutation carriers. Our results are consistent with previous blood

biomarkers studies showing that males and females did not differ in plasma P-tau217 levels[2,5]. Nonetheless, these findings diverge from previous studies showing higher levels of tau pathology in females in PET imaging [49-53] and postmortem data[54-56]. These discrepancies warrant further investigation to elucidate the effect of sex on blood biomarkers and potential measurement factors in blood biomarkers that may explain differences between biomarker modalities.

We then examined the effect of sex on the relationship between plasma biomarkers and cognition in *PSEN1* carriers and non-carriers. Our findings show that, among individuals with higher levels of plasma P-tau271 (indicating greater tau pathology accumulation), females exhibited better cognitive and memory performance than males. However, this effect was not observed for NfL, a marker of neurodegeneration, suggesting a sex-specific cognitive resilience to tau pathology. Previous work in sporadic and late-onset AD showed that females may have greater cognitive resilience to AD-pathology and neurodegeneration[57-59], as the disease progresses, females exhibit faster cognitive decline[34,60,61] and progression to dementia[54,62-64] than males. Similarly, previous work from this group showed that among cognitively-unimpaired individuals at genetic risk for autosomal-dominant AD, females may have greater cognitive resilience to AD-pathology and neurodegeneration than males[65,66]. Current findings expand prior work as these associations were found in a sample including both cognitively-unimpaired and impaired *PSEN1* carriers, which suggests that females' cognitive resilience to tau pathology in this cohort may persist even into the early clinical stages. Future work with longitudinal biomarker and cognitive data, as part of the Colombia-Boston Biomarker study of autosomal-dominant AD (COLBOS), will help clarify the effect of sex and AD pathology on cognitive decline across the disease spectrum and potential mechanisms of risk and resilience to AD.

This study has some limitations. First, this is a cross-sectional, retrospective study that leveraged available blood biomarker data to examine the effect of sex on plasma P-tau217 and NfL and cognition. 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 MCI starting at a median age of 44 years and dementia at 49 years[13,67], age in this sample is predictive of clinical onset. Thus, cross-sectional assessments in this sample can be considered analogous to what might be expected from the assessment of longitudinal trajectories of biomarkers and cognition. As mentioned, this study focused on examining the effect of sex 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. In addition, this study did not examine plasma levels of sex steroid hormones or reproductive health data, or other data on other potential mechanisms. Further research examining sex/gender differences in P-tau217 and NfL, as well as other blood-based and fluid biomarkers, and its relation to cognitive trajectories is needed to elucidate mechanisms of risk and resilience in AD, including the role of steroid hormones, reproductive health, or genetic factors (e.g., *APOE* ε4). Lastly, replication of our results in independent cohorts will be required to determine generalizability to other at-risk groups for AD and sporadic AD.

Conclusion

Our findings suggest that females may have greater cognitive resilience to tau pathology among individuals at genetic risk for autosomal-dominant AD. In contrast, female *PSEN1* mutation carriers had a faster rate of plasma NfL increase and, thus, may be more susceptible to AD-related neurodegeneration. These results further our understanding on the effect of sex on AD pathology and cognition, and raise important considerations regarding the use of blood biomarkers in clinical research, trials, and practice.

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TABLES

Table 1. Characteristics of cognitively impaired and unimpaired mutation carriers and non-carriers.

	Cognitively Impaired Carriers (n=106)	Cognitively Unimpaired Carriers (n=259)	Non-carriers (n=257)
		Median (Interquartile Range)	
Age, years	49.0 (46.0-52.0)	31.0 (24.0-39.0)	34.0 (25.5-42.0)
Female, %	45.3	45.6	39.3
Education, years	5.0 (2.0-7.0)	9.0 (5.0-11.0)	9.0 (5.0-11.0)
MMSE score	19.0 (12.3-24.0)	29.0 (28.0-30.0)	30.0 (28.0-30.0)
API Cognitive Composite Score	33.83 (25.00-44.70)	81.36 (71.59-89.18)	84.03 (75.39-90.0)
CERAD Word List Delayed Recall	0.00 (0.00-1.00)	6.00 (5.00-7.00)	6.0 (5.0-8.0)
Plasma P-tau217, pg/ml	16.74 (11.97-21.76)	3.20 (1.76-5.65)	1.48 (.95-2.49)
Plasma NfL, pg/ml	24.15 (17.00-34.55)	7.41 (5.13-10.90)	6.25 (4.31-8.42)

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

Table 2. Demographic, clinical, cognitive, and biomarkers among male and female *PSEN1* mutation carriers and non-carriers

	Carriers (n=365)		p-value[a]	Non-carriers (n=257)		p-value[b]
	Mean±SD			Mean±SD		
	Males (n=166)	Females (n=199)		Males (n=101)	Females (n=156)	
Age, years	36.91±11.20	36.70±11.30	0.858	33.42±10.29	35.03±9.52	0.201
Education, years	7.02±4.46	7.77±4.35	0.103	8.13±4.72	8.51±4.35	0.512
MMSE score	26.36±5.60	25.76±6.41	0.360	28.78±1.70	28.83±1.96	0.820
API Cognitive Composite Score	68.29±23.09	68.12±23.03	0.947	82.59±11.23	81.78±10.16	0.562
CERAD Word List Delayed Recall	4.35±2.88	4.83±2.87	0.122	6.30±1.88	6.40±2.00	0.708
Plasma P-tau217, pg/ml	8.00±7.17	8.21±8.58	0.807	1.92±1.46	1.85±1.45	0.715
Plasma NfL, pg/ml	14.13±10.86	15.36±17.74	0.435	7.33±3.98	6.53±2.95	0.067

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

[a] p-value as defined by an independent two sample t-test for males vs females in mutation carriers.

[b] p-value as defined by an independent two sample t-test for males vs females in non-carriers.

Table 3. Regression estimates of the effect of sex on the relationship between plasma biomarkers and cognition.

Outcome Variable	Predictors	Standardized β	*p*-value
API Cognitive Composite Score	*PSEN1* status	1.612	.108
	Sex	-2.300	**.022**
	Plasma P-tau217	-9.2017	**<.001**
	Sex*P-tau217	2.989	**.003**
API Cognitive Composite Score	*PSEN1* status	4.120	**<.001**
	Sex	-1.341	.180
	Age	-13.415	**<.001**
	Plasma P-tau217	-6.406	**<.001**
	Sex*P-tau217	1.858	.064
CERAD Word List Delayed Recall	*PSEN1* status	1.689	.092
	Sex	-.385	.700
	Plasma P-tau217	-7.908	**<.001**
	Sex*P-tau217	2.477	**.013**
CERAD Word List Delayed Recall	*PSEN1* status	3.681	**<.001**
	Sex	.555	.579
	Age	-10.397	**<.001**
	Plasma P-tau217	-5.415	**<.001**
	Sex*P-tau217	1.519	**.013**
API Cognitive Composite Score	*PSEN1* status	3.871	**<.001**
	Sex	-2.072	**.039**
	Plasma NfL	-7.147	**<.001**
	Sex*NfL	1.488	.137
API Cognitive Composite Score	*PSEN1* status	6.473	**<.001**
	Sex	-.639	.523
	Age	-.929	**<.001**
	Plasma NfL	-3.269	**.001**
	Sex*NfL	.326	.744
CERAD Word List Delayed Recall	*PSEN1* status	3.663	**<.001**
	Sex	-.146	.884
	Plasma NfL	-5.472	**<.001**
	Sex*NfL	.194	.846
CERAD Word List Delayed Recall	*PSEN1* status	5.608	**<.001**
	Sex	.542	.588
	Age	-7.245	**<.001**
	Plasma NfL	-2.705	**.007**
	Sex*NfL	-.240	.810

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.

FIGURES

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

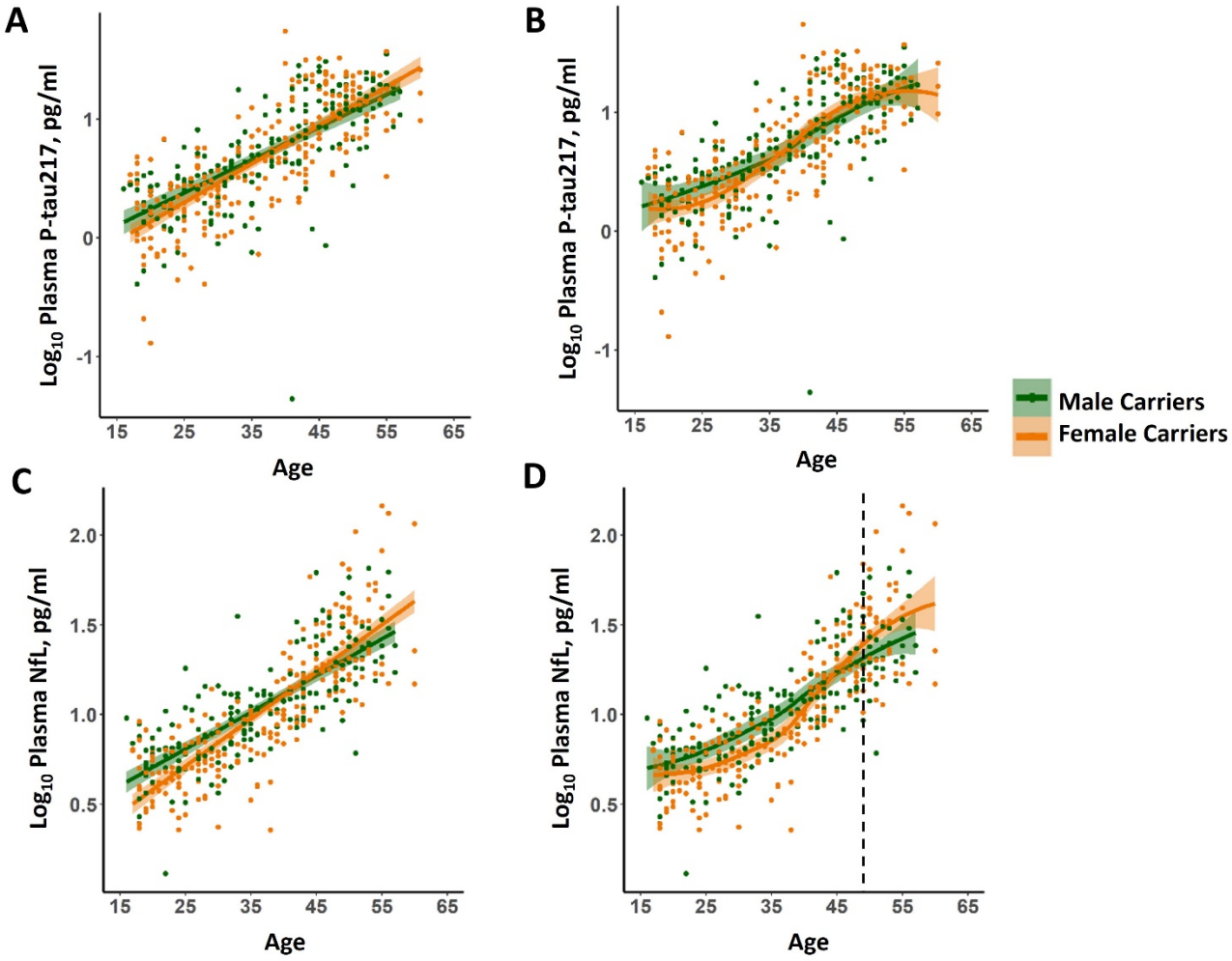

Figure 1. (A) Log_{10} Plasma P-tau217 as a function of age. (B) LOESS plot of Log_{10} Plasma P-tau217 as a function of age. (C) Log_{10} Plasma NfL as a function of age. (D) LOESS plot of Log_{10} Plasma NfL as a function of age. Dashed line represents the age at which male and female carriers LOESS fit confidence band separate (age of 48.45). **Abbreviations:** NfL, Neurofilament light chain. Orange represents female carriers and green represents male carriers.

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

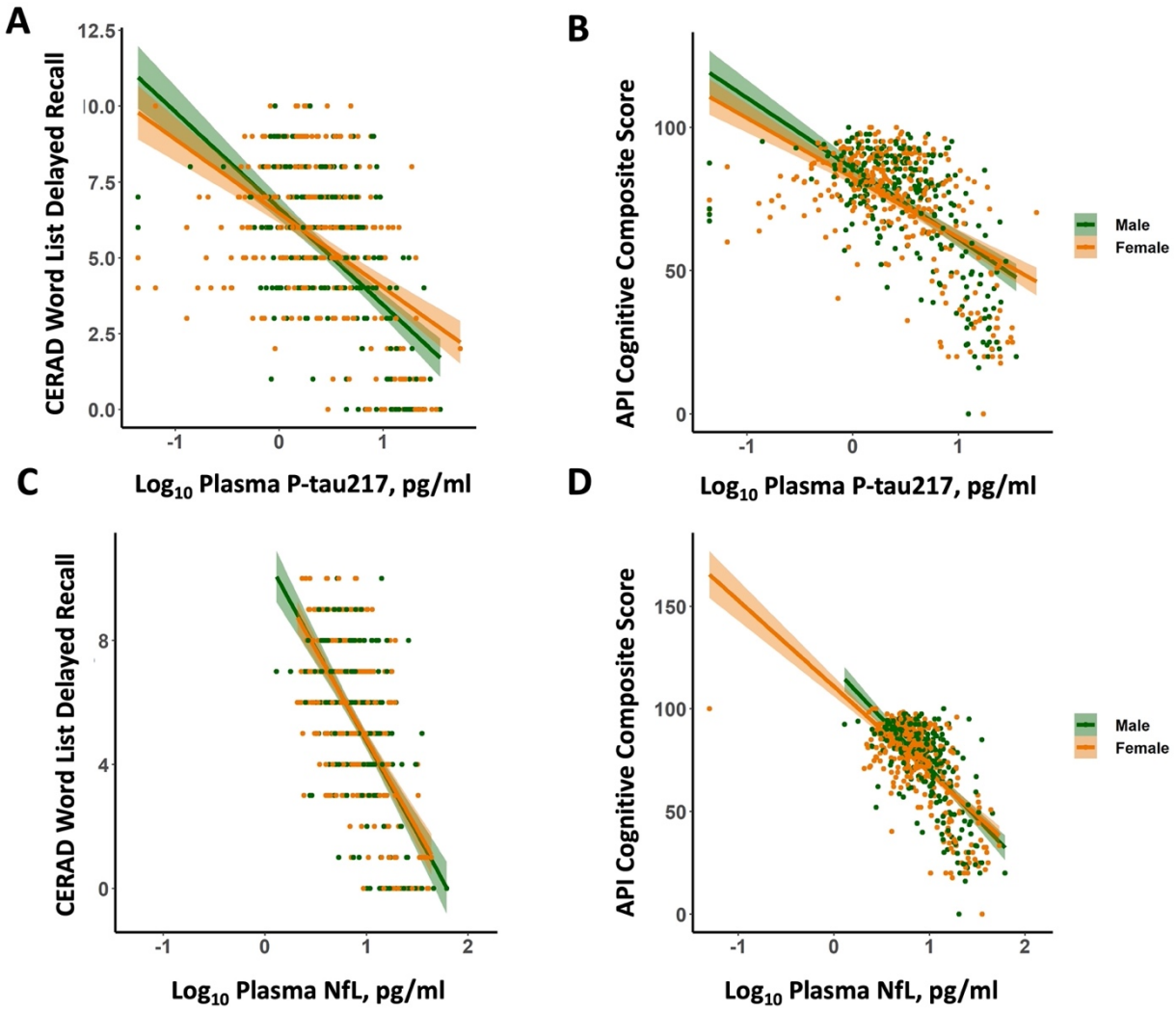

Figure 2. (A) CERAD word list delayed recall as a function of Log_{10} Plasma P-tau217. (B) API cognitive composite score as a function of Log_{10} Plasma P-tau217. (C) CERAD word list delayed recall as a function of Log_{10} Plasma NfL. (D) API cognitive composite score as a function of Log_{10} Plasma NfL. **Abbreviations:** NfL, Neurofilament light chain. Orange represents female carriers, and green represents male carriers.