

INTRODUCTION

Despite the higher risk of Alzheimer’s disease (AD) in women, sex differences in AD plasma biomarkers and their clinical utility remain understudied.

Our objective was to investigate how sex impacts AD plasma biomarker levels, their accuracy in identifying amyloid positron emission tomography (PET)-positive individuals, and their association with cognitive decline.

METHODS

Study participants: We included cognitively unimpaired (CU; CDR=0; n=768) and cognitively impaired (CI; CDR>0; n=740) ADNI participants with plasma Aβ42/40 and p-tau217 (Fujirebio Lumipulse), and GFAP and NfL (Quanterix). Amyloid PET within 1 year of plasma sampling was available for 593 CU and 526 CI participants. Longitudinal cognitive assessments (up to 5 years) were available for 504 CU and 547 CI participants.

Amyloid PET: Participants underwent ¹⁸F-florbetapir (FBP) or ¹⁸F-florbetaben (FBB) amyloid PET. Global standardized uptake value ratios (SUVRs) were calculated across cortical regions (frontal, cingulate, parietal, and lateral temporal; FreeSurfer v7.1), normalized to whole cerebellum, and converted to Centiloid values. Amyloid PET positivity cutoff: Centiloid >25.

Statistical analyses: We examined sex differences in plasma biomarker levels. For core AD plasma biomarkers (Aβ42/40, p-tau217 and p-tau217/Aβ42), Receiver Operating Characteristic (ROC) analyses were performed in the entire sample and by sex. Finally, in the sub-cohort with longitudinal cognitive follow-up participants were classified as plasma biomarker positive or negative using cutoffs derived from the whole sample, and sex differences in associations between plasma biomarker status and cognitive trajectories were examined using linear mixed-effects models with sex interactions and sex-stratified analyses.

RESULTS I

1. Participant characteristics

	Cognitively unimpaired (CDR=0)			Cognitively impaired (67.7% CDR=0.5; 32.3% CDR≥1)		
	Men	Women	<i>p</i> value	Men	Women	<i>p</i> value
Age, years	76.1 ± 7.8	72.3 ± 8.7	<0.0001	77.3 ± 8.1	75.1 ± 8.8	0.0003*
APOE-ε4 carriers, %	32.1	34.0	0.63	50.0	53.9	0.32
Ethno-racial background (NHW/NHB/Others), %	81.2/9.4/ 9.4	71.7/19.9/ 8.4	0.0004	91.9/3.2/ 4.9	78.6/ 14.2/7.2	<0.0001*
Education (High school or less/College/Postgraduate), %	5.80/37.0/ 57.3	10.3/43.6/ 46.1	0.004	15.4/42.4/ 42.2	16.0/50.6/ 33.4	0.04*
BMI, kg/m ²	27.3 ± 4.2	27.4 ± 6.1	0.72	27.0 ± 4.3	26.1 ± 5.5	0.02*
CDR-SB	0.1 ± 0.2	0.1 ± 0.2	0.52	4.0 ± 3.5	3.4 ± 3.5	0.09
ADAS-Cog 13	11.0 ± 4.9	8. 2 ± 4.6	<0.0001	24.1 ± 12.8	22.3 ± 13.4	0.14
mPACC	-0.89 ± 3.3	0.57 ± 2.9	<0.0001	-12.3 ± 10.9	-12.7 ± 9.3	0.74
Amyloid PET, Centiloid	18.7 ± 34.7	22.2 ± 34.5	0.03	53.3 ± 53.9	54.4 ± 50.7	0.49
Amyloid PET-positive, %	31.0	31.8	0.90	57.8	59.8	0.70

Table 1. Mean ± standard deviation or %. *t* tests were used to evaluate sex differences in continuous variables and Pearson χ^2 test for categorical variables. Amyloid PET Centiloid values were compared with analyses of covariance (ANCOVA) adjusting by age, and cognitive scores with ANCOVA adjusting by age and education.

RESULTS II

2. Plasma biomarker levels by sex

	Cognitively unimpaired (CDR=0)			Cognitively impaired (67.7% CDR=0.5; 32.3% CDR≥1)		
	Men	Women	<i>p</i> value	Men	Women	<i>p</i> value
Fujirebio Aβ42/40	0.090 ± 0.013	0.091 ± 0.013	0.18	0.085 ± 0.011	0.085 ± 0.012	0.041
Fujirebio p-tau217, pg/mL	0.21 ± 0.25	0.17 ± 0.17	0.24	0.43 ± 0.36	0.52 ± 0.47	0.004*
Fujirebio p-tau217/Aβ42	0.007 ± 0.009	0.006 ± 0.006	0.004*	0.016 ± 0.015	0.019 ± 0.022	0.001*
Quanterix NfL, pg/mL	20.9 ± 13.6	18.2 ± 10.4	0.85	28.0 ± 15.6	26.2 ± 15.6	0.88
Quanterix GFAP, pg/mL	155 ± 84.7	168 ± 95.6	<0.0001*	210 ± 113	245 ± 135	<0.0001*

Table 2. Mean ± standard deviation. Plasma biomarker levels were compared with analyses of covariance (ANCOVA) adjusting by age. *Statistical significance ($p<0.05$) after FDR correction for multiple comparisons. Note: differences were maintained ($p<0.05$) after adjusting for BMI (data not shown).

3. Sex differences in identifying amyloid PET-positive individuals

• Overall amyloid PET classification performance (AUC) did not differ by sex. However, p-tau217 and p-tau217/Aβ42 were more specific and had higher positive predictive value (PPV) in women among CU, with the opposite pattern observed in CI.

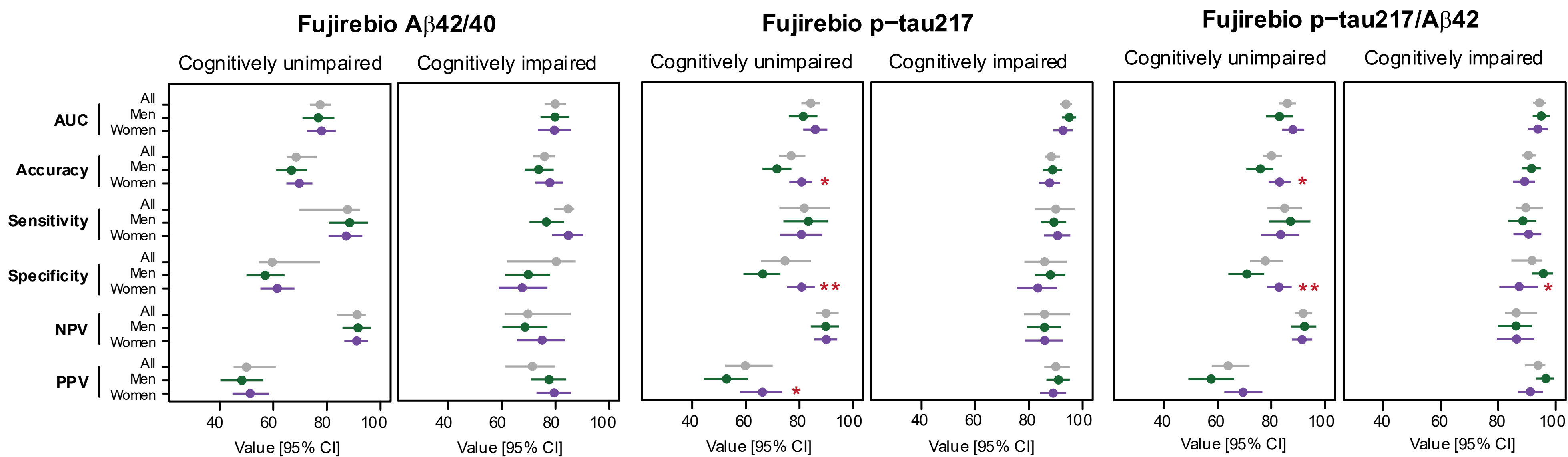


Figure 1. AUC differences were tested with DeLong test. The optimal full-sample cutoff was derived using the Youden index and applied to each sex separately. Classification metrics were calculated with 95% CIs estimated from 1,000 bootstrap resamples. Accuracy, sensitivity, and specificity were compared using Pearson χ^2 test, and PPV and NPV were compared using permutation tests (10,000 iterations). * $p<0.05$ *vs.* men; ** $p<0.01$ *vs.* men.

4. Sex differences in the association with cognitive trajectories

• In CU individuals, p-tau217 and p-tau217/Aβ42 positivity were associated with faster mPACC decline only in women.

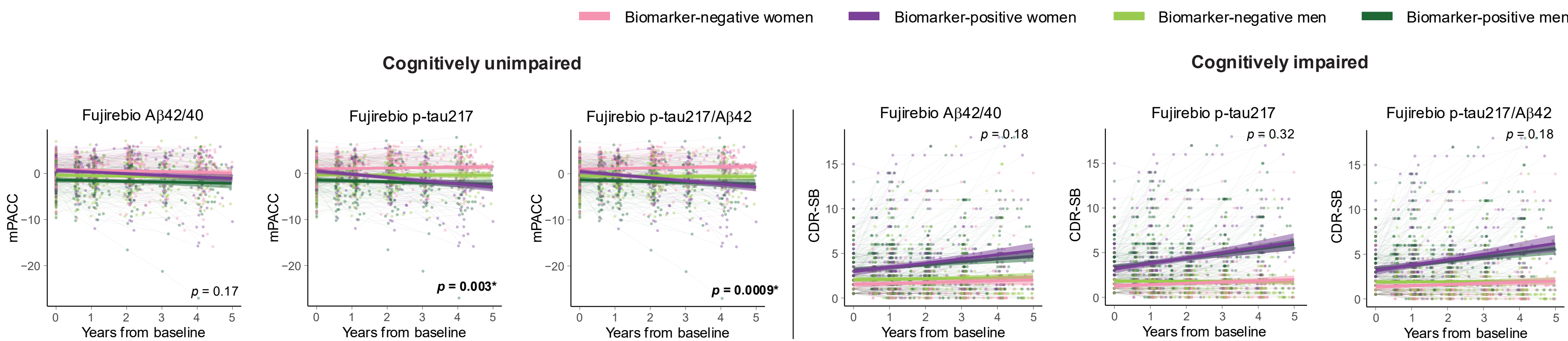


Figure 2. Longitudinal trajectories by sex and plasma biomarker status. *P*-values correspond to the 3-way interaction among sex, time, and biomarker group. Models were adjusted for the interactions of time with age, APOE-ε4 status, and education. *Statistically significant after FDR correction for multiple comparisons.

CONCLUSIONS

Sex-specific plasma biomarker cutoffs for clinical trial inclusion may not be necessary. However, sex influences plasma biomarker levels, classification accuracy and prognostic value, particularly at early disease stages, highlighting the importance of considering sex when interpreting biomarker positivity and optimizing trial enrichment strategies.

Full published article:

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