


RESEARCH ARTICLE

Association of plasma biomarkers of Alzheimer's disease and related disorders with cognition and cognitive decline: The MYHAT population-based study

Yingjin Zhang¹ | Pamela C. L. Ferreira² | Erin Jacobsen² | Bruna Bellaver² |
Tharick A. Pascoal^{2,3} | Beth E. Snitz³ | Chung-Chou H. Chang^{1,4} |
Victor L. Villemagne² | Mary Ganguli^{2,3,5} | Thomas K. Karikari² 

¹Department of Biostatistics, School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

²Department of Psychiatry, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

³Department of Neurology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

⁴Department of Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

⁵Department of Epidemiology, School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Correspondence

Thomas K. Karikari, Department of Psychiatry, School of Medicine, University of Pittsburgh, 3811 O'Hara St, Pittsburgh, PA 15213, USA.
Email: karikari@pitt.edu

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Abstract

INTRODUCTION: Plasma biomarkers of Alzheimer's disease and related dementias predict global cognitive performance and decline over time; it remains unclear how they associate with changes in different dementia syndromes affecting distinct cognitive domains.

METHODS: In a prospective study with repeated assessments of a randomly selected population-based cohort ($n = 787$, median age 73), we evaluated performance and decline in different cognitive domains over up to 8 years in relation to plasma concentrations of amyloid beta 42/40 ($A\beta_{42/40}$) ratio, phosphorylated tau181 (p-tau181), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP).

RESULTS: Cross-sectionally, memory showed the strongest associations with p-tau181, and attention, executive, and visuospatial functions with NfL. Longitudinally, memory decline was distinguishable with all biomarker profiles dichotomized according to data-driven cutoffs, most efficiently with $A\beta_{42/40}$. GFAP and $A\beta_{42/40}$ were the best discriminators of decline patterns in language and visuospatial functions, respectively.

DISCUSSION: These relatively non-invasive tests may be beneficial for clinical screening after replication in other populations and validation through neuroimaging or cerebrospinal fluid analysis.

KEYWORDS

Alzheimer's disease and related dementias, amyloid beta 42/40 ratio, attention, cognitive decline, cognitive domains, glial fibrillary acidic protein, language, memory, neurofilament light chain, phosphorylated tau181, plasma biomarkers, visuospatial functions

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Highlights

- We performed a prospective study with up to 8 years of repeated domain-specific cognitive assessments and baseline plasma Alzheimer's disease and related dementias biomarker measurements in a randomly selected population-based cohort.
- We considered distinct growth curves of trajectories of different cognitive domains and survival bias induced by missing data by adding quadratic time and applying joint modeling technique.
- Cross-sectionally, memory showed the strongest associations with plasma phosphorylated tau181, while attention, executive, and visuospatial functions were most strongly associated with neurofilament light chain.
- Longitudinally, memory and visuospatial declines were most efficiently distinguished by dichotomized amyloid beta 42/40 profile among all plasma biomarkers, while language was by dichotomized glial fibrillary acidic protein.
- These relatively non-invasive tests may be beneficial for clinical screening; however, they will need replication in other populations and validation through neuroimaging and/or cerebrospinal fluid assessments.

1 | INTRODUCTION

Positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) biomarkers are now established modalities for detecting *in vivo* biological evidence of Alzheimer's disease (AD).¹⁻³ However, their limited accessibility, high cost, and low throughput hamper their widespread applications. Plasma biomarkers are relatively non-invasive and low-cost alternatives for monitoring the biology of AD and related disorders (ADRD).³⁻⁵ Amyloid beta 42/40 (A β 42/40) ratio, phosphorylated tau at threonine-181 (p-tau181), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) are among the most extensively studied blood biomarkers of ADRD.⁶⁻¹⁵ Recent studies have shown strong correlations of plasma A β 42/40 ratio and p-tau181 with brain A β burden, as well as with concurrent and subsequent cognitive performance.^{6,16-22} Plasma p-tau181 shows good correlations with brain tau burden, while plasma NfL associates with magnetic resonance imaging (MRI)- and CSF-assessed neurodegeneration in AD and ADRD.^{11,12,23} Furthermore, plasma GFAP, measuring astrocyte reactivity, is closely related to abnormal A β accumulation as well as cognitive status in AD and, as with NfL, has been reported to be altered in non-AD dementias.²⁴⁻²⁸ Together, plasma biomarkers of ADRD are both cross-sectionally and longitudinally associated with cognitive performance.

However, cognitive performance in earlier studies was most often aggregated as global cognition by averaging results from multiple cognitive domains.^{22,25,29-32} Because different cognitive domains may become affected at various disease stages, and potentially reflect or predict distinct dementia presentations or syndromes, it is of interest

to investigate cross-sectional and longitudinal associations of plasma biomarkers with specific domains of cognition. These investigations are particularly needed in large population-based cohorts, which are: (1) unselected for memory or other cognitive disorders, (2) less exclusive of general health factors and conditions, (3) more representative of broad communities than most clinic-based studies, and (4) less well represented in the ADRD biomarker literature.

The novel aspects of the study include both population-based recruitment and domain-specific cognitive outcomes. By studying a population-based unselected cohort, relatively unaffected by selection bias, we can better understand the natural trajectory of cognitive outcomes and their associations with plasma biomarkers in a broader context. This approach is valuable for uncovering early markers of cognitive changes and informing public health strategies. By examining domain-specific cognitive outcomes, we gain a more nuanced understanding of how plasma biomarkers are associated with specific cognitive abilities, critical for tailoring interventions and treatments that target specific cognitive deficits.

We have recently reported cross-sectional findings for plasma A β 42/40 ratio, p-tau181, NfL, and GFAP in a population-based cohort of older adults, finding a bimodal distribution of A β 42/40 that separated the population into two modes differentially associated with the other biomarkers, age, Clinical Dementia Rating (CDR), and a memory composite score.³³ Building on those cross-sectional findings, we now examine associations between the same plasma biomarkers and both concurrent status and subsequent decline in performance over time in multiple cognitive domains, focusing on participants without dementia at study entry.

2 | METHODS

2.1 | Study setting and participants

The Monongahela–Youghiogheny Healthy Aging Team (MYHAT) is an ongoing population-based study cohort drawn from a Rust Belt region of southwestern Pennsylvania, USA. MYHAT participants are assessed annually for the development of cognitive decline, mild cognitive impairment (MCI), and dementia. Study recruitment took place over two time periods (2006–2008 and 2016–2019) using age-stratified random sampling from publicly available voter registration lists. Individuals were excluded if, at study entry, they were < 65 years old, not living in one of the designated towns, residing in long-term care, had severe hearing or vision loss which precluded neuropsychological testing, or lacked decisional capacity to give informed consent. The full assessment was administered to participants with normal or mildly impaired cognition (age- and education-corrected Mini-Mental State Examination scores ≥ 21)³⁴ numbering 1982 in the original cohort and 703 in the second cohort. All study procedures were approved by the University of Pittsburgh Institutional Review Board, and all participants provided written informed consent. Further details have been reported previously.³⁵

2.2 | Study assessments

Detailed assessment interviews included, but were not limited to, demographics, cognitive assessments, genotyping, and plasma biomarker measurements, all detailed in the following subsections.

2.2.1 | Demographics

Age, sex, education (less than 8th grade or 8th to 11th grade [$<$ high school, HS]; graduated from HS or General Educational Development [= HS]; some college, graduated from college program or graduate school [$>$ HS]), and self-identified race/ethnicity (White; Black or African American, more than one race [non-White]).

2.2.2 | Cognitive assessments

At baseline and each annual visit, a battery of neuropsychological tests was administered to evaluate cognitive functioning across five cognitive domains: attention/psychomotor speed (Digit Span, Trail-Making Test A), executive functions (Trail-Making Test B, clock drawing, verbal fluency for letters P&S), memory (Wechsler Memory Scale-Revised, Logical Memory, 12-item Face Name Associative Memory Exam,³⁶ and Fuld Object Memory Evaluation), language (Boston Naming Test, semantic verbal fluency, Indiana University Token Test), and visuospatial functions (Wechsler Adult Intelligence Scale-3 Block Design and Benton Visual Form Discrimination).^{37,38} To develop composite scores for each domain, we first created z scores initially standardizing each test score according to the sample baseline mean and standard deviation, and then averaging the standardized test scores within each

RESEARCH IN CONTEXT

1. **Systematic review:** The authors searched and reviewed the extant literature using traditional (e.g., PubMed) sources. There were highly limited studies on associations between domain-specific cognition composite as well as its longitudinal declines and Alzheimer's disease and related dementias and plasma biomarkers, but the relationships between global cognition and biomarkers were well studied. Those relevant citations are appropriately introduced and cited.
2. **Interpretation:** In this population-based study ($n = 787$), memory showed the strongest cross-sectional associations with plasma phosphorylated tau181, while attention, executive, and visuospatial functions had the strongest associations with neurofilament light chain. Longitudinally, after the application of data-driven cutoffs, amyloid beta 42/40 profile most efficiently distinguished memory and visuospatial functions decline patterns, while glial fibrillary acidic protein distinguished declines in language.
3. **Future directions:** Future studies will focus on: (a) the potential confounding and effect modifications among the associations between cognitive domain and plasma biomarkers; (b) the validations and replications on the data-driven cutoffs/thresholds; and (c) the biomarker method standardization, optimal panel selection, and thresholding.

domain for participants with at least one test score in that domain,³⁹ with higher composite scores indicating better cognitive performance.

2.2.3 | Clinical dementia rating

CDR was grouped into 0 = cognitively normal (CN), 0.5 = MCI, ≥ 1 = dementia, as described previously.³³

2.2.4 | Blood collection

Venous blood was collected after overnight fasting into purple-top ethylenediaminetetraacetic acid tubes as described previously³³ for genotyping and plasma biomarkers.

2.2.5 | APOE $\epsilon 4$

Apolipoprotein E (APOE) genotyping was carried out using blood or saliva samples as described previously,³³ and for this analysis was grouped into APOE $\epsilon 4$ carriers (with any $\epsilon 4$ allele) versus non-carriers.

2.2.6 | Plasma biomarker measurements

Plasma biomarker concentrations were assayed with single-molecule array (SIMOA) technology using an HD-X instrument from Quanterix at the Department of Psychiatry, University of Pittsburgh School of Medicine. Specimens were tested for p-tau181 using the p-tau181 V2 Advantage (#103714) assay. NfL, GFAP, A β 42, and A β 40 were analyzed with the Neurology 4-Plex E (#103670) commercial assays, as detailed previously.³³ We performed two sets of analyses, the primary analysis including all samples that had measurable plasma biomarker signals, and a secondary analysis limiting the biomarker concentrations to those above the manufacturer's recommended detection limit, to test the hypothesis that the concentrations would be valid independent of the detection limits.

2.3 | Statistical analysis

As previously reported, the log-transformed A β 40, A β 42, and A β 42/40 ratio were bimodally distributed in the MYHAT study cohort.³³ We applied the K-medoids unsupervised clustering method⁴⁰ for the log-transformed A β 42/40 and identified two distinct clusters, which we labeled normal and abnormal groups based on the optimal cutoff/threshold values of -2.08 (i.e., 0.1249 in raw scale). We validated these groups by examining their associations with p-tau181, NfL, and GFAP levels.

We designated as baseline the date of the annual MYHAT cognitive assessment closest to the blood draw date for plasma biomarkers, if these dates were no more than 6 months apart. We present baseline characteristics as medians (interquartile ranges [IQRs]) for continuous variables and frequencies (%) for categorical variables, both overall and by A β 42/40 groups. To compare among groups, we used the Wilcoxon rank-sum tests for continuous variables and Fisher exact test for categorical variables. We used all available outcome data from all cycles.

We used multiple linear regression models to examine cross-sectional associations between each plasma biomarker and each of the five baseline cognitive domain composite scores (memory, attention/speed, language, executive functions, and visuospatial functions). Each model evaluated one biomarker at a time, while adjusting for demographics (age, sex, race, and education) and APOE ϵ 4 genotype as they are known to affect cognitive performance.

To address the concerns about potential survival and attrition bias in the longitudinal study, we applied the joint modeling approach to analyze longitudinal relationships between plasma biomarkers and changes in domain-specific cognitive composite scores over time. First, to verify whether joint modeling is necessary and determine the shape of the growth curve in each domain, we fitted a baseline joint model without including any plasma biomarker variable for each domain. Each baseline joint model consists of two submodels⁴¹ adjusted for age, sex, race, education, and APOE ϵ 4 genotype: (1) a growth curve model of domain-specific cognitive decline, which uses a linear mixed-effects regression model (LMM) with random intercepts for participants and

random coefficients for time; and (2) an informative dropout model of time to death or becoming too ill to participate, which uses a Cox regression model, with the additional control for baseline CDR. Then, to examine the associations, we included each of the plasma biomarkers separately in the LMM submodel.

To visualize the trajectories at different biomarker levels and explore potential cutoff points, we categorized p-tau181, NfL, and GFAP based on different thresholds: at the median (resulting in two groups), at the tertiles (resulting in three groups), and at the quartiles (resulting in four groups). Subsequently, we selected the cutoff method at tertiles as it most effectively distinguished the trajectory patterns between the corresponding groups. We further combined the first two tertile groups into one, therefore dichotomizing each biomarker into two groups (lower and higher groups) at the 66.66th percentile based on the findings from the tertile group analyses.

We also conducted several sensitivity analyses to evaluate the impact on our cross-sectional and longitudinal findings of variations in (1) the cutoff for A β 42/40 (dichotomizing it using a cutoff given by another clustering method), (2) the data type of plasma biomarkers (categorical or continuous values), (3) the quality control for the biomarker values (including or excluding those below the manufacturer's detection limits), and (4) the use of A β biomarkers (clustering based on A β 42/40 ratio or on A β 42 alone; see [Method S1](#) in supporting information).

In addition, we conducted two secondary analyses to examine the potential effect modifications by sex and CDR on the associations between the rates of decline in cognitive composite scores and plasma biomarkers: (1) including three-way interaction among sex, plasma biomarker, and time in each LMM submodel, and (2) additionally adjusting for CDR levels and three-way interaction among CDR, plasma biomarker, and time in each submodel.

We applied the Benjamini-Hochberg procedure to control for the false discovery rate (FDR) in multiple hypothesis testing within the same domain.

We performed all analyses using R Statistical Software (v4.2.2; R Core Team 2022). We analyzed the joint models using the R JMBayes⁴² package, incorporating regression-spline-approximation baseline hazard functions and 40,000 iterations.

3 | RESULTS

3.1 | Sample characteristics at baseline

Among all 2685 enrolled MYHAT participants, 920 had available plasma samples.³³ Of those, we excluded 65 participants with one or more plasma biomarkers for which measurement signals (called average enzyme per bead) were assigned by the instrument but without corresponding concentration values (41 in A β 42/40, 41 in p-tau181, 38 in NfL, and 38 in GFAP). Excluding another 30 whose "baseline" visits were beyond 6 months of blood draw, 9 whose CDR > 1 at baseline and 29 whose APOE genotypes were missing, we included 787 individuals with CDR < 1 (dementia-free) in the cross-sectional analyses. Their

TABLE 1 Baseline participant characteristics according to the A β 42/40 ratio status.

	A β 42/40 normal (N = 686)	A β 42/40 abnormal (N = 101)	Total (N = 787)	
Age, median (IQR), years	73.0 (69.0, 80.0)	83.0 (78.0, 87.0)	73.0 (69.0, 80.0)	<0.001
Sex Female, N(%)	431(62.8%)	69 (68.3%)	500 (63.5%)	0.320
Race Non-White, N(%)	33 (4.8%)	3 (3.0%)	36 (4.6%)	0.609
Education, N(%)				0.018
< High School	32 (4.7%)	9 (8.9%)	41 (5.2%)	
= High School	240 (35.0%)	45 (44.6%)	285 (36.2%)	
> High School	414 (60.3%)	47 (46.5%)	461 (58.6%)	
APOE ϵ 4 carrier, N(%)	152 (22.2%)	20 (19.8%)	172 (21.9%)	
MCI group, N(%)	103 (15.0%)	14 (13.9%)	117 (14.9%)	0.881
Plasma biomarker^b, median (IQR), pg/mL				
A β 40	103.945 (83.647, 123.440)	2.153 (1.377, 3.505)	99.949 (60.702, 119.079)	<0.001
A β 42	6.825 (5.340, 8.161)	0.625 (0.380, 0.841)	6.398 (3.827, 7.918)	<0.001
A β 42/40	0.067 (0.059, 0.074)	0.237 (0.169, 0.347)	0.069 (0.060, 0.079)	<0.001
p-tau181	1.661 (1.185, 2.461)	1.533 (0.806, 2.104)	1.630 (1.151, 2.434)	0.004
NfL	21.471 (16.218, 31.333)	38.304 (28.590, 52.171)	23.147 (16.955, 34.961)	<0.001
GFAP	122.001 (85.189, 175.047)	221.199 (153.642, 341.984)	129.964 (89.084, 194.295)	<0.001
Comorbidity^c, N(%)				
Diabetes	168 (24.5%)	30 (29.7%)	198 (25.2%)	0.270
Hypertension	462 (67.3%)	77 (76.2%)	539 (68.5%)	0.085
Kidney disease	33 (4.8%)	8 (7.9%)	41 (5.2%)	0.225

Note: This table presents the characteristics of the study population by A β 42/40 status. A β 42/40 normal is defined as A β 42/40 \leq 0.1249, equivalent to exp(-2.08), while A β 42/40 abnormal corresponds to A β 42/40 > 0.1249. All continuous variables are presented as median and interquartile range: median, Q1, Q3, while categorical variables are shown as frequency and percentages: N (%). < High School: < 8th grade or 8th to 11th grade. = High School: graduated from high school or Generalized Educational Development. > High School: graduated from college, 4-year college program, or graduate school. Non-White: Black or African American, or more than one race. CN: CDR = 0, cognitive normal. MCI: CDR = 0.5, mild cognitively impaired.

Abbreviations: A β , amyloid beta; APOE, apolipoprotein E; CDR, Clinical Dementia Rating; GFAP, glial fibrillary acidic protein; IQR, interquartile range; MCI, mild cognitive impairment; NfL, neurofilament light chain; p-tau, phosphorylated tau.

^aP values represent the comparison between A β 42/40 normal and abnormal groups. For continuous variables, they were derived from the Wilcoxon rank-sum tests, and for categorical variables, they were derived from Fisher exact tests. The significant level of 0.05 was used. Significant results are indicated in bold.

^bPlasma biomarkers were raw values before standardizations.

^cParticipants self-reported having been told by a health-care professional that they had diabetes, hypertension until the collection of the plasma sample.

median age was 73 years (IQR: 69 to 83), 63.5% were female, 95.4% were White, and 58.6% had more than high school (> HS) education (Table 1).

3.2 | Characteristics of normal and abnormal A β groups

Of the 787 dementia-free participants, 101 (12.83%) with abnormal plasma A β 42/40 (A β 42/40 > 0.1249³³) were older (median age 83 vs. 73 years) and less educated (46.5% vs. 60.3% had > HS education) than those with normal A β 42/40 levels.

The abnormal group had lower A β 42 levels which agrees with the literature for CSF A β 42.^{43,44} To the contrary, the A β 42/40 ratio was higher in this group instead of the lower levels reported for CSF.^{45,46}

We attribute this disparity in A β 42/40 to the bimodal distribution of A β 40 in this population. Participants with abnormally low A β 42 values also had extremely low A β 40, resulting in a higher value of the A β 42/40 ratio in the participants with higher A β 42 (see Figure S1 in supporting information).

3.3 | Characteristics of the CN and MCI groups at baseline

In this population, 117 (14.87%) MCI participants with CDR = 0.5 at baseline were older (median age 80 vs. 73 years), less educated (45.3% vs. 60.9% had > HS education), and had a higher proportion of APOE ϵ 4 carriers (30.8% vs. 20.3%) than the CN group with CDR = 0 (Table S1 in supporting information).

TABLE 2 Missingness and availability of data in each year.

Year	baseline	1	2	3	4	5	6	7	8
Number of participants ^a , N	680	644	533	420	202	143	110	63	9
Number of informative dropouts ^b , N		24	52	72	93	91	113	115	37
Number of missing ^c , N									
Attention	11	18	15	13	9	3	7	2	1
Executive functions	2	5	7	2	4	0	4	2	1
Language	13	18	11	12	10	4	6	2	1
Memory	18	26	22	18	12	6	14	8	1
Visuospatial functions	113	219	245	203	97	78	98	52	7

^aNumber of participants with at least one cognitive score(s) available within the corresponding year.

^bNumber of participants dropped out from the study due to death or too ill.

^cNumber of missing cognitive composite scores at each year in each domain.

3.4 | Characteristics of the longitudinal sample

For the longitudinal analysis, we included 2820 records from 680 participants after excluding 107 individuals with no follow-up visits. Those included were more educated and had higher baseline attention, language, executive, and visuospatial functions composite scores than those excluded (Table S2 in supporting information). The median follow-up period was 3 years (range: 1–8 years; IQR: 2–4 years). The availability of participants, the number of informative dropout (i.e., death or too ill), and the missingness of the cognitive composite score per year are summarized in Table 2.

3.5 | Cross-sectional associations

In multivariable linear regression models evaluating the association between each plasma biomarker and domain-specific cognitive composite score (Table S3 in supporting information and Figure 1), the following results were observed:

1. Baseline mean memory composite score was significantly higher in the abnormal A β 42/40 group than in the normal A β 42/40 group ($\beta = 0.212$, 95% confidence interval [CI] -0.02 to -0.40 , adjusted $P = 0.031$).
2. Baseline mean memory composite score decreased as plasma p-tau181, NfL and GFAP increased. Memory had the strongest inverse association with higher p-tau181 ($\beta = -0.111$, 95% CI -0.17 to -0.05 , adjusted $P = 0.002$) compared to other biomarkers.
3. Baseline mean attention and executive functions composite scores were inversely associated with plasma p-tau181 and NfL. Both had stronger associations with NfL ($\beta = -0.125$, 95% CI -0.18 to -0.07 , adjusted $P < 0.001$ and $\beta = -0.107$, 95% CI -0.16 to -0.06 , adjusted $P < 0.001$) than with p-tau181.
4. Baseline mean visuospatial functions composite score only associated with NfL ($\beta = -0.134$, 95% CI -0.22 to -0.04 , adjusted $P = 0.015$).

3.6 | Longitudinal associations

As shown in Table S4 in supporting information, the presence of a significant association parameter for either the random intercept or the random coefficient indicated that the risk of informative dropout was related to the random effect in the longitudinal model, which demonstrates that joint modeling is needed. We found joint modeling was necessary for modeling each of memory, attention, executive functions, and language, while fitting LMMs was sufficient for visuospatial functions. The memory, attention/speed, and language scores showed a quadratic trajectory over time, as indicated by significant coefficients of the time-squared terms. In contrast, the executive functions and visuospatial functions scores demonstrated a linear trajectory.

3.6.1 | A β 42/40 groups

All average cognitive domain scores in the abnormal A β 42/40 group declined faster than those in the normal group (Figure 2A and Figure S2 in supporting information); however, these differences in the rate of change were statistically significant only in the domains of memory ($\beta = -0.182$, standard deviation [SD] = 0.056, adjusted $P = 0.001$) and visuospatial functions ($\beta = -0.060$, SD = 0.024, adjusted $P = 0.032$; Table 3).

3.6.2 | P-tau181, NfL, and GFAP

The best separation of different trajectory patterns was provided by tertiles, which we designated from lowest to highest as Tertile-1, Tertile-2, and Tertile-3. Rates of decline in the different cognitive domains were generally similar between Tertile-1 and Tertile-2 but both were significantly different from Tertile-3 (Figure 3, Figure S3 and Table S5 in supporting information). Therefore, we dichotomized p-tau181, NfL, and GFAP into lower (Tertile-1 and Tertile-2 combined) and higher (Tertile-3) groups at the 66.66th percentile (Figure 2 and Table 3).

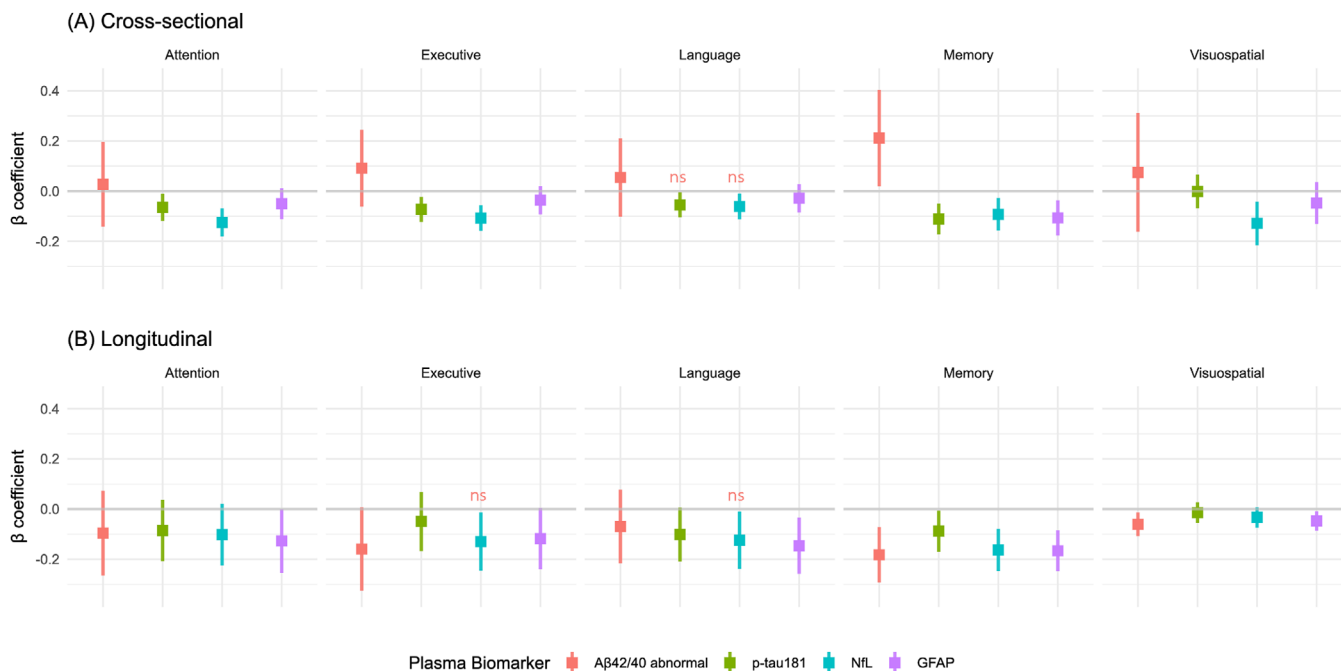


FIGURE 1 Cross-sectional and longitudinal associations between plasma biomarkers and cognitive domain composite scores. Coefficient plot was generated to visualize the association between each baseline plasma biomarker and baseline domain-specific cognitive composite score (A) and its rate of change (B). Each biomarker was individually added to a basic model adjusting for age, sex, race, education, and APOE allele. Aβ42/40 abnormal was defined as Aβ42/40 > 0.1249, equivalent to $\exp(-2.08)$. Plasma p-tau181, NfL, and GFAP were standardized to their mean values and standard deviations in the cross-sectional models (A), while were dichotomized based on their 66th percentiles in the longitudinal models (B). Estimated beta coefficients with the corresponding 95% confidence intervals were plotted for the associations of baseline plasma biomarkers with baseline or with the decline rate of neuropsychological test results. Estimates of beta coefficients in the cross-sectional models (A) are presented in terms of “The difference in the mean baseline domain-specific cognitive composite score in abnormal group compared to the mean in normal group” for Aβ42/40 or “The change in baseline domain-specific cognitive composite score per standard deviation increase in baseline biomarker value” for p-tau181, NfL, and GFAP. Estimates of beta coefficients in the longitudinal models (B) are presented in terms of “The difference between rates of change in the average domain-specific cognitive composite scores in Aβ42/40 abnormal group compared with the normal group or p-tau181, NfL, and GFAP higher groups compared to corresponding lower groups.” ns: The association became not significant after controlling for false discovery rate in multiple hypothesis testing on the same domain. Aβ, amyloid beta; APOE, apolipoprotein E; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; p-tau, phosphorylated tau.

For p-tau181, NfL, and GFAP, mean memory composite score showed 0.088 (SD = 0.042, adjusted $P = 0.041$), 0.163 (SD = 0.043, adjusted $P < 0.001$), and 0.166 (SD = 0.042, adjusted $P < 0.001$) faster declines in the higher groups, with the credible intervals well separated (Figure 2), than in the lower groups per year, respectively.

In the GFAP higher group, the mean language composite scores ($\beta = -0.146$, SD = 0.057, adjusted $P = 0.020$) and visuospatial functions ($\beta = -0.047$, SD = 0.020, adjusted $P = 0.032$) had significantly faster declines compared to those in the lower group.

No biomarkers were associated with the slopes of the attention and executive trajectories after controlling for the FDR.

3.6.3 | Comparisons within memory domain

Comparing the lower groups of p-tau181, NfL, and GFAP and the normal Aβ42/40 group (Figure 2), the shapes of the mean memory trajectories were similar. Over time, the average memory score in the

normal/lower groups initially increased before declining, suggesting practice effects⁴⁷ over earlier cycles, whereas the average score in the corresponding lower and abnormal groups consistently decreased over time.

Comparing the higher and abnormal groups of the four biomarkers (Figure 2), at baseline, the estimated mean memory score in the Aβ42/40 abnormal group was much higher (with a credible interval even above 0.5) than the mean baseline scores in p-tau181, NfL, and GFAP higher groups. However, over time, mean memory scores in the Aβ42/40 abnormal, NfL higher, and GFAP higher groups decreased to a value below -1.0 by year 8. This observation was consistent with the magnitude of effect (beta coefficient) of the interaction between Aβ42/40 abnormal and time being larger than the effects of any of the other interactions (Table 3). On the contrary, the trajectories grouped by p-tau181 appeared more parallel than those grouped by other plasma biomarkers (Figure 2), and the beta coefficient of its interaction with time was the smallest one in magnitude (Table 3).

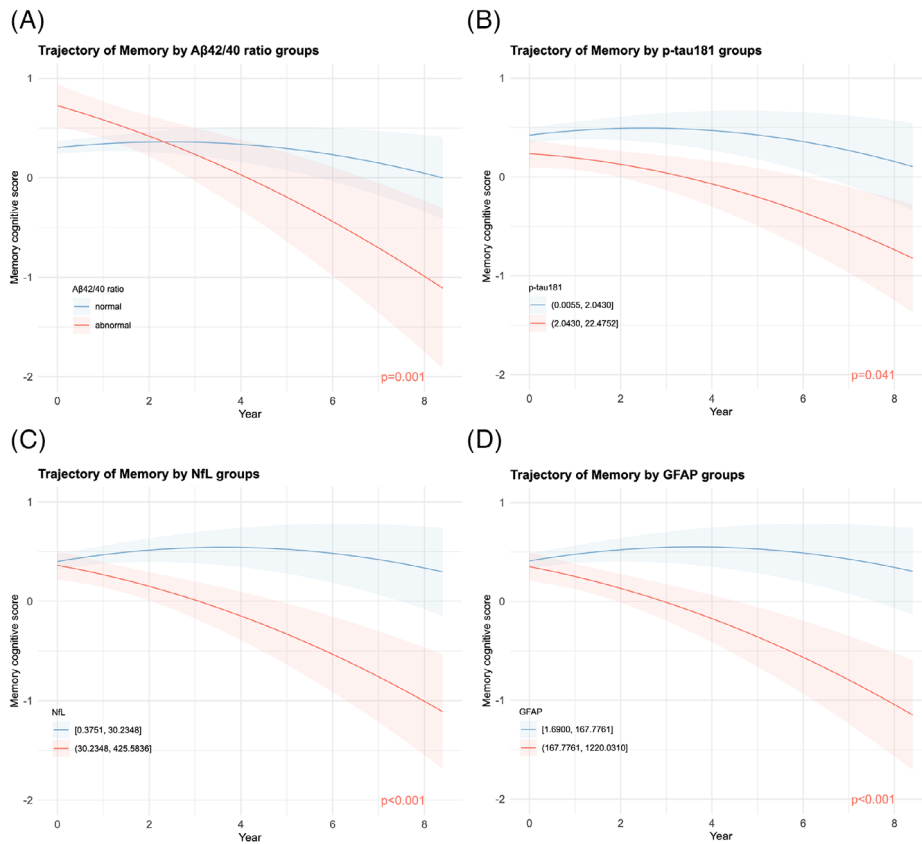


FIGURE 2 Trajectories of memory composite scores by plasma biomarker values. Trajectory plots were generated to visualize the estimated average memory composite score over the follow-up period, based on (A) A β 42/A β 40, (B) p-tau181, (C) NfL, and (D) GFAP groups. These plots were derived from linear mixed-effects submodels of the joint models, accounting for longitudinal memory composite scores and informative dropout. Each plasma biomarker was individually added to a basic random coefficients model with age, sex, race, education, and APOE allele as fixed effects and time as random effects. The shaded areas represent Bayesian 95% credible intervals. The annotated raw P value indicates the significance of differences in decline rates between the abnormal group (red) and the normal group (blue) in (A), or between the higher group (red) and the lower group (blue) in (B)-(D). The A β 42/40 abnormal group was defined as plasma A β 42/40 > 0.1249, equivalent to $\exp(-2.08)$. The cutoff values for other plasma biomarkers were their 66.66th percentile (upper tertile) and are shown in the figure legends. A β , amyloid beta; APOE, apolipoprotein E; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; p-tau181, phosphorylated tau.

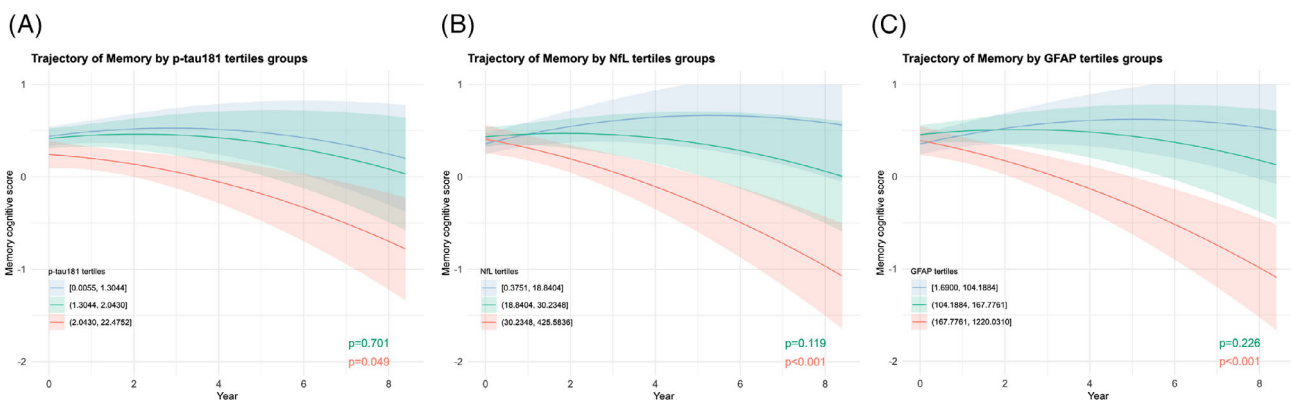


FIGURE 3 Trajectories of memory composite scores by plasma biomarker tertiles. Trajectory plots were generated to visualize the estimated average memory composite score over the follow-up period, based on (A) p-tau181, (B) NfL, and (C) GFAP tertile groups. The plots were derived from linear mixed-effects submodels of the joint models, accounting for longitudinal domain-specific composite scores and informative dropout. Each plasma biomarker was individually added to a basic random coefficients model with age, sex, race, education, and APOE carriership as the fixed effects and time as random effects. Shaded areas represent Bayesian 95% credible intervals. The annotated raw P value indicates the significance of differences in decline rates between the middle (green) or highest (red) tertile group and the lowest tertile group (blue). The cutoff values for these plasma biomarkers were based on their respective tertiles, as described in the figure legends. APOE, apolipoprotein E; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; p-tau, phosphorylated tau.

TABLE 3 Associations between baseline dichotomized plasma biomarkers and rate of change in domain-specific cognitive composite score.

Domain	Biomarker	β	SD	p value	Adjusted p value ^e
Memory	A β 42/40 abnormal ^a	-0.182	0.056	0.001	0.001
	p-tau181 T3 ^b	-0.088	0.042	0.041	0.041
	NfL T3 ^c	-0.163	0.043	<0.001	<0.001
	GFAP T3 ^d	-0.166	0.042	<0.001	<0.001
Attention	A β 42/40 abnormal ^a	-0.096	0.086	0.257	0.257
	p-tau181 T3 ^b	-0.085	0.062	0.155	0.207
	NfL T3 ^c	-0.102	0.063	0.099	0.198
	GFAP T3 ^d	-0.127	0.065	0.051	0.198
Language	A β 42/40 abnormal ^a	-0.069	0.075	0.379	0.379
	p-tau181 T3 ^b	-0.101	0.055	0.061	0.081
	NfL T3 ^c	-0.124	0.058	0.036	0.072
	GFAP T3 ^d	-0.146	0.057	0.005	0.020
Executive functions	A β 42/40 abnormal ^a	-0.159	0.085	0.066	0.088
	p-tau181 T3 ^b	-0.049	0.060	0.407	0.407
	NfL T3 ^c	-0.129	0.059	0.030	0.088
	GFAP T3 ^d	-0.118	0.062	0.054	0.088
Visuospatial functions	A β 42/40 abnormal ^a	-0.060	0.024	0.012	0.032
	p-tau181 T3 ^b	-0.014	0.021	0.493	0.493
	NfL T3 ^c	-0.033	0.021	0.110	0.147
	GFAP T3 ^d	-0.047	0.020	0.016	0.032

Note: This table shows the results of linear mixed effects submodels of the joint models to determine whether the decline rate of domain-specific cognitive score varies between plasma biomarker levels. Each submodel used a domain-specific cognitive composite score as the outcome variable and included a binarized baseline plasma biomarker in addition to a basic model containing age, sex, race, education, and APOE allele. The β coefficient represents the estimate of the effect of the interaction between each plasma biomarker and time. It is presented as "The difference in yearly change in domain-specific cognitive composite scores between the abnormal group or highest tertile (Tertile-3) and the normal group or the combination of the lowest and middle tertile groups (Tertile-1 and Tertile-2)." The comparison is made for each of A β 42/40 ratio and other biomarkers respectively. The SD represents the standard deviation of the point estimate. P value is derived from an analysis of variance comparison to the basic model, with a significant level of 0.05. Significant results are indicated in bold.

Abbreviations: A β , amyloid beta; APOE, apolipoprotein E; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; p-tau, phosphorylated tau.

^aA β 42/40 abnormal was defined as A β 42/40 > 0.1249, equivalent to exp(-2.08).

^bHighest tertile (Tertile-3/T3) of p-tau181 was (2.0430, 22.4752).

^cHighest tertile (Tertile-3/T3) of NfL was (30.2348, 425.5836).

^dHighest tertile (Tertile-3/T3) of GFAP was (167.7761, 1220.0310).

^eThe adjusted p values were calculated by the Benjamini-Hochberg procedure to control for the false discovery rates in multiple testing on the same domain.

3.7 | Secondary analyses

3.7.1 | Sex effect modification on longitudinal associations

After refitting all longitudinal joint models further including three-way interaction among sex, plasma biomarker, and time, we did not find any significant results (Table S6 in supporting information). Given the possibility of insufficient power to detect any significant effect modifications, we further looked at the estimates of those effect modifications; however, all magnitudes of the estimates were relatively small (< 0.100), suggesting the absence of modifying effect by sex.

3.7.2 | CDR effect modification on longitudinal associations

Because most of our study cohort was CN, we did not have adequate power to detect any statistically significant modifying effects of CDR level on any longitudinal association between domain-specific cognitive composite scores and plasma biomarkers (Table S7 in supporting information). Nevertheless, some relatively large (> 0.100) estimates of the effects of three-way interactions in magnitude indicated that there tended to be an effect if the sample size was large enough. For example, the difference in memory composite score declines between two A β 42/40 groups might be smaller in MCI group compared to CN; however, this difference was not statistically significant

($\beta_{interaction} = 0.152$, $P = 0.399$) based on the sample size in this study.

3.8 | Sensitivity analyses

The results of the sensitivity analyses demonstrated that: (1) both cross-sectional and longitudinal associations between domain-specific cognition and plasma biomarkers were mostly robust with minor changes in the A β 42/40 cutoff values (Result S1, Table S8, and Table S9 in supporting information); (2) several longitudinal associations lost statistical significance when treating plasma biomarkers as continuous variables (Result S1, Table S8, and Table S10 in supporting information); (3) the values that were below the manufacturer's detection limits did not substantially influence the clustering outcome despite small effects on the strength of some associations (Result S2, Table S11–S14, Figure S4, and S5 in supporting information); and (4) compared to A β 42 alone, A β 42/40 ratio gave a more narrowly defined abnormal group and more clearly separated trajectories in the memory and visuospatial functions domains (Result S3, Table S8, S9, S12, S14, S15, and Figure S6 in supporting information).

4 | DISCUSSION

In individuals without dementia in the MYHAT longitudinal population-based study of older adults, assessed annually up to 8 years after plasma collection, we found for the first time in a real-world setting that plasma measures of A β 42/40, p-tau181, NfL, and GFAP provide comparable results to those obtained in more selective cohorts, providing support to their potential widespread applicability. Further, we examined relationships of these different plasma biomarkers with specific cognitive domains—memory, attention/psychomotor, language, visuospatial functions, and executive functions—not only cross-sectionally but, more importantly, also their longitudinal trajectories, assessing which cognitive domain is the most strongly affected by a specific pathology. We show that, even in an overwhelmingly cognitively unimpaired population, these plasma biomarker profiles can distinguish the different patterns of domain-specific cognitive decline. Our results suggest differential associations of plasma biomarkers with domain-specific cognitive changes, implying that plasma biomarkers may have variable sensitivity to detecting cognitive changes arising from different domains.

We had expected A β 42/40 and p-tau181 to show the strongest associations with AD-typical memory performance and faster memory decline relative to other cognitive domains, while expecting non-AD-specific NfL and GFAP to show less differentiated associations across domains. These general patterns of results were only partially observed.

Regarding longitudinal trajectory patterns of biomarker-cognitive domain associations, memory was the only cognitive domain in which decline was significantly differentiated with the groupings of all four plasma biomarkers. Abnormal A β 42/40 and Tertile-3 GFAP also

showed faster declines in estimated mean visuospatial functions composite scores compared to normal A β 42/40 and lower group of GFAP, respectively. GFAP was associated with the rates of change across more cognitive domains than were others, given it was the only one associated with language decline. A β 42/40 was the most effective measure in distinguishing longitudinal cognitive decline in the memory and visuospatial domains between individuals with normal and abnormal biomarker profiles, while the rates of declines in memory between two p-tau181 groups were least differentiable. These findings suggest that A β 42/40 profile might be the best plasma biomarker for investigating the normal and abnormal memory decline patterns than the other biomarkers; however, plasma p-tau181 may not be well suited for separating the clinical groups according to memory decline rates. Future work will include categorical outcomes such as incident dementia and etiologic subtypes to further investigate the predictive validity and utility of these biomarkers.

Although A β 42/40 ratio is considered superior to A β 42 alone to identify AD pathophysiology in CSF,^{48–50} we examined both plasma A β 42/40 and A β 42 categorized as normal or abnormal. Note that participants with abnormally low A β 42 values also had extremely low A β 40 levels, resulting in higher A β 42/40 ratios. Cross-sectional analyses revealed robust associations between A β 42, but not A β 42/40, and the cognitive domains, as also reported by others.^{20,31,51}

A novel finding in our longitudinal models was that memory, attention, and language composite scores followed quadratic trajectories, in contrast to previous studies that only investigated linear decline.^{22,29,31,52} This finding also accounted for selective survival bias by jointly modeling cognitive decline and informative dropout to estimate unbiased cognitive trajectories.

The abnormal A β 42/40 group largely comprised individuals with lower A β 42 and higher NfL and GFAP levels, meaning they had jointly altered biomarker profiles for A β pathology, neurodegeneration, and astroglial reactivity. This group showed monotonically faster declines and continued deterioration over time in memory and visuospatial functions. This finding confirms those of previous studies in which lower plasma A β 42 was associated with faster cognitive decline, lower CSF A β 42/40, and higher neocortical A β deposition.^{7,51–53}

We characterized plasma p-tau181, NfL, and GFAP into three tertile groups based on their distributions and further dichotomized into two groups at the 66.66th percentiles, combining the two lower tertiles. All three highest tertile groups showed relatively faster declines in domain-specific cognitive composite scores compared to lower tertile groups. A faster rate of change in memory composite score was significantly associated with each of the Tertile-3 groups.^{22,25,29,32,54,55} Of note, Tertile-3 p-tau181 was associated with faster memory decline, consistent with its role as an ADRD biomarker. However, faster declines in language and visuospatial domains were only observed in the GFAP Tertile-3. Our results demonstrate the potential utility of upper tertile cutoffs of p-tau181, NfL, and GFAP to predict domain-specific cognitive changes.

In our main models, we included all individuals with measurable biomarker concentrations to avoid selection bias. However, our findings remained robust in the sensitivity analyses when we excluded

values below the manufacturer's detection limits, demonstrating that their inclusion did not significantly skew the results. Furthermore, the results of the plasma A β 42/40 clustering focusing on participants without dementia (CDR < 1) were comparable to those of our previous study that included all participants from the MYHAT cohort independent of cognitive status,³³ showing that the present results might be not significantly influenced by the exclusion of the participants with dementia.

Regarding strengths and limitations, we investigated the distribution and associations of plasma biomarkers in a population-based cohort representative of older adults in its target geographic region. Our data thus have enhanced external validity (generalizability) compared to data from cohorts of self-selected volunteers and referrals to clinical research settings. However, because the resulting cohort was largely of European descent, our findings should be investigated in more ethnographically diverse study populations. The statistical models investigated both linear and quadratic trajectories of cognitive trajectories and considered survival bias using joint modeling. We examined multiple biomarkers individually, accounting for FDR and multiple comparisons. While beyond the scope of this study, we will further evaluate associations of cognitive decline with multiple biomarkers and their mutual interactions, to identify potential confounding and effect modification.^{23,31} Our cutoffs/thresholds and clustering approaches were data-driven; they will need to be replicated in other populations and examined in relation to PET and MRI imaging data. Furthermore, some previous studies have reported that the Quanterix/Simoa plasma A β 42/40 assay used in this study may be outperformed by immunoprecipitation-mass spectrometry (IP-MS) assays.⁵⁶ Measurement of plasma A β 42/40 by IP-MS could not be performed in this study and there is currently no widely accessible IP-MS platform for the other biomarkers. Additionally, the absence of plasma p-tau217 data prevented us from examining its performance with plasma p-tau181 in this cohort.

Key critiques of clinical trials that led to the recent US Food and Drug Administration approval of anti-amyloid therapies some of which are now clinically available include enrichment for individuals with APOE ϵ 4 genotype, lack of diversity of the study population in terms of recruitment source, and uncertainty if currently available plasma biomarkers will be useful for longitudinal monitoring of patients receiving the therapies.^{57,58} The findings in this study—derived from those aged \geq 65 years in the targeted area—are relevant to addressing some of these important points. The MYHAT study—by design—included mostly cognitively normal participants at baseline, allowing us to identify individuals at risk of cognitive decline, especially with the use of plasma surrogates for brain ADRD pathology. This is underscored by recent studies presented at the Clinical Trials in AD (CTAD conference 2023⁵⁹) that have shown much stronger beneficial effects of anti-amyloid therapies when initiated among amyloid-positive individuals with normal versus impaired cognition. Moreover, the population-based design of this study reduced selection bias according to, for example, health status. This feature may potentially allow us in the future to examine the effects of disease-relevant

factors such as comorbid conditions, in the interest of personalizing treatment paradigms.

Plasma biomarkers are promising relatively non-invasive and cost-effective tools, compared to PET imaging and CSF assays, aiding in diagnosis and prognosis in various diseases that cause dementia. Population-based studies are an essential step toward validating and calibrating them for eventual clinical use outside the specialty research and tertiary care setting. Future work will focus on biomarker method standardization, optimal panel selection, and thresholding. A major future contribution of these biomarkers may be to identify individuals for different intervention trials. Our current state of knowledge suggests that these biomarkers are not yet ready for clinical applications, but steady progress is being made toward that goal. Studies in real-world populations are a step forward in that direction. Given the lack of widely available effective disease-modifying therapeutic strategies, these measures are currently inappropriate for “screening” asymptomatic individuals outside research settings. This study adds to the rapidly expanding knowledge base about the potential of plasma biomarkers as research and clinical tools, by providing population-based data from an under-resourced US community. We also provide valuable insights into the relationships between individual biomarkers and domain-specific cognitive declines.

While validating plasma ADRD biomarker performance in a population-based sample is a step forward, several other issues remain to be addressed. One is the effect of co-morbidities, both their direct effects on the different biomarkers and their independent, synergistic, or modulatory effects on cognitive trajectories over time. There is also an imperative need to assess how far the current results, mainly obtained in White individuals in the United States and Europe, can be generalized to diverse ethnic and geographic populations. Further, we need to extend the age range of these studies to examine their potential for early disease detection in the young-old as well as their performance in the oldest old. Finally, it will be necessary to determine how these biomarkers perform in, for example, under-resourced, rural, or remote populations, and how much they are affected by social determinants of health.

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CONFLICT OF INTEREST STATEMENT

VLV received consulting fees from Eli Lilly and Life Molecular Imaging, and speaker honoraria from ACE Barcelona and BRI Japan—none related to this work. MG received honoraria from the University of

Connecticut Health Center and from the *Journal of the American Geriatrics Society*, unrelated to this work. TKK has received honoraria from the University of Wisconsin Madison and the University of Pennsylvania and has an awarded patent (#WO2020193500A1), all unrelated to this work. All other authors declare that they have no conflicts of interest to disclose. Author disclosures are available in the [supporting information](#).

CONSENT STATEMENT

All human subjects involved in this study provided informed consent prior to participation.

ORCID

Thomas K. Karikari  <https://orcid.org/0000-0003-1422-4358>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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