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RESEARCH ARTICLE

Plasma Aβ42/40 and cognitive variability are associated with cognitive function in Black Americans: Findings from the AA-FAIM cohort

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Abstract

Introduction: It is critical to develop more inclusive Alzheimer's disease (AD) research protocols to ensure that historically excluded groups are included in preclinical research and have access to timely diagnosis and treatment. If validated in racialized groups, plasma AD biomarkers and measures of subtle cognitive dysfunction could provide avenues to expand diversity in preclinical AD research. We sought to evaluate the utility of two easily obtained, low-burden disease markers, plasma amyloid beta (Aβ)42/40, and intra-individual cognitive variability (IICV), to predict concurrent and longitudinal cognitive performance in a sample of Black adults.

Methods: Two hundred fifty-seven Black participants enrolled in the African Americans Fighting Alzheimer's in Midlife (AA-FAIM) study underwent at least one cognitive assessment visit; a subset of $n = 235$ had plasma samples. Baseline IICV was calculated as the standard deviation across participants' z scores on five cognitive measures: Rey Auditory Verbal Learning Test Delayed Recall, Trail Making Test Parts A and B (Trails A and B), and Boston Naming Test. Using mixed effects regression models, we compared concurrent and longitudinal models to baseline plasma Aβ42/40 or IICV by age interactions. PrecivityAD assays quantified baseline plasma Aβ42/40.

Results: IICV was associated with concurrent/baseline performance on several outcomes but did not modify associations between age and cognitive decline. In contrast, plasma Aβ42/40 was unrelated to baseline cognitive performance, but a pattern emerged in interactions with age in longitudinal models of Trails A and B and Rey Auditory Verbal Learning Test total learning trials. Although not significant after correcting for multiple comparisons, low Aβ42/40 was associated with faster cognitive declines over time.

Discussion: Our results are promising as they extend existing findings to an Black American sample using low-cost, low-burden methods that can be implemented outside of a research center, thus supporting efforts for inclusive AD biomarker research.

1 | INTRODUCTION

Black Americans are over-represented in prevalence of Alzheimer's disease and related dementias (ADRD) at approximately 1.5 to 2 times the rate of non-Hispanic Whites,[1] yet substantially under-represented in Alzheimer's disease (AD)-specific biomarker research serving to characterize the disease.[2,3] Emerging findings point toward the presence of AD pathophysiology years before clinical symptoms manifest,[4] suggesting a possible foothold for identification and intervention in a preclinical stage. Yet, compared to White individuals, Black individuals are more likely to receive medical evaluation of cognitive concerns later in the disease.[5] This would portend under-identification of preclinical disease as well. Altogether, these inequities in inclusion and access to preclinical identification will likely maintain[1] or exacerbate existing racial ADRD disparities.

To help address the disproportionate burden of ADRD in Black communities, specific tools and strategies are needed to support equitable and representative research participation. For AD biomarker research specifically, which is used to define the disease and its progression from preclinical to clinical stages (e.g., National Institute on Aging–Alzheimer's Association [NIA-AA] Research Framework Model,[6]) engaging the Black community more effectively will both ensure generalizability of existing models of preclinical AD, and allow Black Americans to trust that emerging data are personally applicable.[7]

Hallmark biomarkers of AD, amyloid beta (Aβ) deposition and neurofibrillary tau, are measurable in vivo through positron emission tomography (PET) imaging or in cerebrospinal fluid (CSF) via lumbar puncture, but several factors limit the broad use of PET and CSF

biomarkers; for example, the procedures are invasive, and aversive for many in the Black community.[8] The specialized equipment and training needed to collect these data also restricts access.

Plasma-based biomarkers hold promise as an alternative.[9–11,12] A blood draw can be performed by a range of clinic staff in multiple settings, and is generally a more acceptable procedure than lumbar puncture and PET, thereby facilitating improved inclusion in biomarker research for Black Americans.[8] However, there is sparse research on the extent to which AD biomarkers commonly associated with clinical manifestations of dementia among the non-Hispanic White population generalize to Black Americans who are more likely to present with multiple pathologies[13,14] and higher rates of cardiovascular-related AD risk factors.[15]

Identification of AD risk and disease stage in research settings typically relies on physiological markers aligned with behavioral markers—most often cognitive testing. However, given structural inequities in education, cognitive testing can be prone to bias, especially for marginalized populations. An alternative indicator of early disease is a marker of cognitive dispersion or intra-individual cognitive variability (IICV). An advantage of IICV over other cognitive markers is that it relies on intra-individual comparisons rather than standardized norms, which may unfairly evaluate performance in individuals from minoritized populations. Notably, when using standardized tests to evaluate cognitive performance, Black Americans are more likely to be misdiagnosed or over-pathologized as cognitively impaired compared to White individuals.[16,17] By contrast, IICV assesses cognitive variability rather than test performance per se and is less sensitive to cultural bias. Measured as the within-person standard deviation between

individual cognitive test scores, IICV reflects links between cognitive performance and brain structure and function, and is associated with reduced functional connectivity and network dysfunction.[18] IICV is non-invasive and easily accessible; it can be obtained via a brief cognitive evaluation in a community setting. Our group found IICV measured at baseline predicted incident cognitive impairment between 8 and 10 years later.[19–21] Moreover, predictions were comparable to standard indices such as CSF analytes and hippocampal atrophy.[19,20] A major limitation of our prior work, however, is that analytic samples were largely non-Hispanic and White. Thus, it is important to determine whether IICV predicts cognitive decline (i.e., early clinical manifestations of ADRD) in Black Americans. IICV could offer easily obtained complementary information to physiological biomarkers.

Importantly, in contrast to ancestry, which conveys biological significance regarding inherited genetics,[22] race is a social, and not a biological, construct. "Racialization" more accurately describes the process by which individuals are identified as being part of a specific racial group often based on phenotypic features.[23] Individuals racialized as Black in the United States experience substantial differences in life experiences including unequal access to quality education and healthy neighborhoods, and limits in occupational attainment, which contribute to disparities in health and disease outcomes.[24]

With an overarching goal to support timely detection of AD and improved access to prevention strategies in historically excluded groups, we sought to evaluate the ability of two easily obtained, low-burden disease markers to predict concurrent and longitudinal cognitive performance in a sample of Black middle-aged and older adults from the United States. Specifically, we compared models including baseline plasma Aβ42/40 and IICV—alone or combined. We hypothesized that lower plasma Aβ42/40 and higher baseline IICV would be associated with worse concurrent cognitive performance and with faster longitudinal cognitive decline.

2 | METHODS

2.1 | Participants

Participants were enrolled in the African Americans Fighting Alzheimer's in Midlife (AA-FAIM) study. AA-FAIM invests in community-engaged, programmatic recruitment and retention efforts while leveraging infrastructure from two ongoing longitudinal aging studies, namely, the Wisconsin Registry for Alzheimer's Prevention (WRAP) and the Wisconsin Alzheimer's Disease Research and Clinical Center (ADRC) Clinical Core. Both WRAP and ADRC studies examine risk factors associated with cognitive aging trajectories. The WRAP study enrolls cognitively unimpaired, middle-aged adults, is enriched for family history of AD, and conducts biennial study visits. The ADRC Clinical Core enrolls middle-aged and older adults spanning the AD continuum, with or without a family history of AD, and conducts annual study visits. Clinical status (cognitively normal/unimpaired, impaired, mild cognitive impairment [MCI], or AD) is adjudicated during consensus conference for each subject at each visit in both studies.

Diagnoses of MCI or dementia due to suspected AD are assigned based on NIA-AA criteria,[25,26] without reference to biomarkers. In addition to supporting recruitment into these longitudinal studies, AA-FAIM pools harmonized data from participants self-identifying as Black[27] to examine factors relevant to this population. With no overlapping in funding with the two source studies, AA-FAIM funds the science and the researchers who use data from these source studies to answer questions relevant to Black Americans' brain health and ADRD risk. For these analyses, participants were without diagnoses of Lewy body dementia, Parkinson's disease, epilepsy, or stroke. All participants (N = 257) had at least one qualifying cognitive assessment visit; in addition, a subset (n = 235) had analyzed plasma samples. On average, study participants contributed data from three cognitive testing visits and were followed for an average of 4 years. Study participants provided consent prior to all study visits. Study procedures were approved by the University of Wisconsin–Madison Institutional Review Board.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. Only a handful of studies have examined the association between plasma biomarkers and clinical factors in Black Americans. None have included cognitive variability in models predicting cognitive decline. Moreover, most include only cross-sectional data from older adults with a diagnosed cognitive disorder, for example, mild cognitive impairment or dementia. All relevant studies have been cited.

2. **Interpretation**: Cognitive variability was associated with concurrent performance on several outcomes but did not modify associations between age and cognitive decline. In contrast, plasma amyloid beta (Aβ)42/40 was unrelated to baseline cognitive performance; that is, no significant cross-sectional associations were noted, but associations emerged in interactions with age in longitudinal models of executive functioning and memory with low Aβ42/40 being associated with faster decline over time. Our findings offer clarifying support to extend targeted associations between plasma Aβ42/40 and cognitive function and between intra-individual cognitive variability and cognitive function to Black individuals

3. **Future directions**: Ongoing plasma biomarker research in Black Americans and other marginalized cohorts is critical to better understanding relationships between Alzheimer's disease proteinopathies and cognition. Larger studies should examine associations between plasma Aβ42/40, cognitive variability, and cognitive decline across racialized groups.

2.2 | Baseline plasma Aβ

PrecivityAD assays quantified baseline plasma Aβ42 and Aβ40 using a novel liquid chromatography–tandem mass spectrometry (LC-MS/MS) platform clinically and analytically validated elsewhere.[12,28,29] Mass spectroscopy, although currently of limited availability, has been shown to more effectively identify individuals with abnormal brain Aβ burden than immunoassay-based methods.[30] Concordance has been previously established among LC-MS/MS, apolipoprotein E phenotype, and evidence of brain amyloidosis from CSF and amyloid PET imaging.[29,2] For analyses, we calculated the continuous ratio Aβ42/40. Lower plasma Aβ42/40 values indicate higher likelihood of amyloid deposition or brain pathology.

2.3 | Cognitive tests and calculation of baseline IICV

Estimated baseline IICV was calculated as the standard deviation across participants' z scores on five cognitive tests/subtests, selected to pair indices sensitive to hippocampal-based memory and executive dysfunction with cognitive abilities typically well preserved in early disease stages. Specific measures included Rey Auditory Verbal Learning Test (RAVLT)[31] Total of Learning Trials, RAVLT Delayed Recall, Trail Making Test (Trails) Parts A and B,[32] and Boston Naming Test (BNT)[33] or the Multilingual Naming Test (MINT),[34] depending on the cohort. Before calculating IICV, Trails scores were log transformed and multiplied by −1 such that higher scores reflected stronger cognitive performance, consistent with other test scores. BNT scores were comprised of raw BNT scores (60 item); 30-item MINT scores were cross-walked per guidelines[35] and multiplied by two to align with BNT scores.[35] These and raw scores for remaining tests were standardized to z scores using means and standard deviations for each test using a subsample that was cognitively unimpaired and <80 years at baseline. The standard deviation across the five z scores was then calculated for each participant to obtain their baseline IICV score.

Previous examinations of IICV were conducted in largely White cohorts; therefore, to confirm IICV validity in this sample, we first examined IICV performance in relation to its component measures and three additional cognitive tests, Digit Symbol Modalities Test,[36] Logical Memory II (LM2) from the Wechsler Memory Test IV, and Mini-Mental State Examination (MMSE).[37] The MMSE score comprised a combination of raw MMSE scores or a cross-walked Montreal Cognitive Assessment[38] (MoCA) to MMSE score for subjects without MMSE.[35] These frequently used measures provide valid and familiar assessment of cognitive function not used to calculate IICV, thus reducing circularity concerns. Sample sizes were smaller for these outcomes due to changes in study protocols and testing batteries over time.

2.4 | Statistical analysis

The sample is characterized using descriptive statistics (e.g., n [%], mean (standard deviation [SD]), median [Q1, Q3]). We utilized linear regression to examine associations between baseline IICV and concurrent performance on eight cognitive outcomes (Trails A and B times were log transformed). Models were adjusted for age, self-identified sex, and years of education. We compared baseline IICV and baseline plasma Aβ to concurrent cognitive status (unimpaired/normal vs. impaired) using Mann–Whitney U tests.

To test our hypothesis that baseline IICV and/or baseline plasma Aβ42/40 moderate longitudinal cognitive trajectories, we utilized linear mixed-effects models testing IICV x age and plasma Aβ42/40 x age interactions for each of eight cognitive outcomes (Trails A and B times were log transformed). Fully adjusted models included age at each assessment, and subject-specific random intercepts, plus both IICV and plasma Aβ42/40 main effects and their interactions with age. As we had a priori concerns for age, IICV, and plasma amyloid collinearity, especially when including their interactions, all three covariates were centered to the mean value of the data before use in longitudinal analyses. For each outcome, we also ran separate submodels, including IICV x age or plasma Aβ42/40 x age interactions alone. Inference on fixed effects (including interaction terms) was performed using the Satterthwaite approximation for the estimates' degrees of freedom.[39] Adjustments for education is standard in models examining cognitive function as education is known to influence performance on cognitive testing. Likewise, women outperform men on verbal tasks. For these reasons, models were adjusted for education and self-reported sex.[40,41]

Sensitivity analyses of longitudinal models were performed by including a fixed effect of birth cohort. Decade of birth (1930's, 1940's, etc.) was included in models as a categorical predictor. Statistics and inference around the interaction of interest were calculated again, along with the significance of cohort inclusion, determined using likelihood ratio tests.

A series of Benjamini–Hochberg (BH)[42] corrections were used to control false discovery rate at 5%. BH correction was performed across the eight cognitive outcomes for a given interaction of interest (IICV x age or plasma Aβ42/40 x age) for a given model (e.g., model structure included both interactions, just IICV x age or Aβ42/40 x age).

3 | RESULTS

The baseline IICV sample included 257 AA-FAIM participants. A subset of participants (n = 235) also had plasma Aβ42/40 data, of whom 179 had longitudinal data. On average, participants were older, middle aged (mean age 62.2 years, SD = 10.1), well educated (mean education 14.5 years, SD = 2.6), predominantly female (69.6%), and cognitively unimpaired (82.9%). Table 1 provides additional participant characteristics. The cognitively unimpaired/normal group's baseline IICV was significantly lower than that of the combined impaired group (P = 0.0011; Figure S1 in supporting information). Baseline plasma Aβ42/40 did not differ between these groups (P = 0.49; Figure S2 in supporting information). Plasma Aβ42/40 values exhibited a normal distribution. Consistent with the general cognitive health of the sample, only five

TABLE 1 Participant characteristics at baseline.

Number of unique individuals included in models[a]	257	Missing
Study variables		N (%)
Age, years, mean (SD), [Q1,Q3]	62.22 (10.14) [54.72, 68.48]	0 (0)
Visit number, mean [min, max]	3.30 [1, 11]	0 (0)
Follow-up years, mean [min, max]	3.94 [0, 16.77]	0 (0)
IICV, mean (SD)	0.79 (0.36)	12 (4.7)
Aβ42/40, mean (SD)	0.11 (0.01)	22 (8.6)
Aβ42/40 under 0.089, N (%)[b]	5 (2.1)	NA
Years of education, mean (SD)	14.50 (2.58)	0 (0)
Self-identify as female, N (%)	179 (69.6)	10 (3.9)
Clinical diagnosis, N (%)[c]		0 (0)
Cognitively unimpaired	213 (82.9)	
Impaired not MCI	20 (7.8)	
MCI	15 (5.8)	
Dementia	9 (3.5)	
Apolipoprotein E genotype, N (%)		59 (23.0)
$\varepsilon2/\varepsilon2$	3 (1.2)	
$\varepsilon2/\varepsilon3$	28 (10.9)	
$\varepsilon2/\varepsilon4$	8 (3.1)	
$\varepsilon3/\varepsilon3$	79 (30.7)	
$\varepsilon3/\varepsilon4$	69 (26.8)	
$\varepsilon4/\varepsilon4$	11 (4.3)	
Boston Naming, median [Q1, Q3][d]	50.46 [48.00, 56.00]	1 (0.4)
Trails A, seconds, median [Q1, Q3][d]	38.98 [25.00, 43.25]	4 (1.6)
Trails B, seconds, median [Q1, Q3][d]	116.63 [70.00, 139.00]	1 (0.4)
RAVLT total of learning trials, mean (SD)[d]	40.13 (11.01)	1 (0.4)
RAVLT long delay, mean (SD)[d]	6.93 (3.95)	1 (0.4)
Digit symbol, no. correct, mean (SD)	42.82 (15.45)	161 (62.6)
Logical memory, delayed recall, mean (SD)	9.21 (4.54)	157 (61.1)
MMSE, median [Q1, Q3]	27.26 [26.00, 29.00]	49 (19.1)

[a]257 individuals contributed data. Models included between 56 and 245 participants.

[b]Hu et al. identified an optimal plasma Aβ42/40 cut-off value of 0.089 for differentiating brain amyloid positive versus negative status.[12]

[c]Participants' cognitive performance and functional status were adjudicated by consensus conference and diagnoses of MCI or dementia due to suspected AD were assigned based on National Institute on Aging–Alzheimer's Association (NIA-AA) criteria (Albert et al.;[25] McKhann et al.[26]), without reference to biomarkers.

[d]Denotes indices contributing to IICV index. IICV was calculated from cognitive tests measured at baseline. IICV represents an estimate of degree of dispersion in performance across cognitive domains, suggesting subtle cognitive dysfunction.

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; CIs, confidence intervals; IICV, intra-individual cognitive variability; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation; Trails, Trail Making Test, Parts A and B.

participants (2.1%) were amyloid positive using the plasma Aβ42/40 $\leq$ 0.089 cut-point (Figure S2). Plasma Aβ42/40 was not associated with any baseline cognitive test (Table 2). While some subject characteristics may differ slightly, the AA-FAIM subjects who did not make it into analyses, due to either no plasma or <2 visits, do not appear to differ substantially from those included in analyses (Table S1 in supporting information), except for age, more recent study enrollment, and number of study visits.

3.1 | Baseline IICV but not plasma Aβ42/40 is associated with concurrent cognition

Models included between 73 and 245 participants, depending on outcome (ns varied due to changes made in testing protocols over time). Linear regression showed significant associations between baseline IICV and cognitive performance for all tests except Trails A and RAVLT total, after adjusting for covariates and multiple comparisons. Addi-

TABLE 2 Cross-sectional associations between baseline IICV with cognitive outcomes without and with baseline plasma Aβ42/40 in the model (top two panels) and cross-sectional associations between plasma Aβ42/40 without and with baseline IICV in the model (bottom two panels).

Model outcome	N subject	Beta	SE	t value	P value	BH P value
IICV: Plasma Aβ42/40 NOT in models						
Boston Naming	245	−2.826	1.199	−2.357	**0.0192**	**0.0256**
log Trails A	245	0.123	0.068	1.808	0.0718	0.0718
log Trails B	245	0.211	0.077	2.721	**0.0070**	**0.0205**
RAVLT long delay	245	−1.627	0.646	−2.518	**0.0125**	**0.0205**
RAVLT learning sum	245	−3.454	1.779	−1.941	0.0534	0.0611
Digit Symbol	93	−7.568	2.916	−2.595	**0.0111**	**0.0205**
Logical Memory II	95	−2.880	1.007	−2.860	**0.0053**	**0.0205**
MMSE	195	−1.336	0.532	−2.513	**0.0128**	**0.0205**
IICV: IICV and plasma Aβ42/40 BOTH in models						
Boston Naming	220	−3.214	1.185	−2.713	**0.0072**	**0.0282**
log Trails A	221	0.162	0.076	2.135	**0.0339**	**0.0452**
log Trails B	221	0.220	0.086	2.566	**0.0110**	**0.0282**
RAVLT long delay	221	−1.713	0.724	−2.367	**0.0188**	**0.0301**
RAVLT learning sum	221	−3.801	2.002	−1.898	0.0590	0.0674
Digit Symbol	73	−7.012	4.093	−1.713	0.0913	0.0913
Logical Memory II	74	−3.624	1.438	−2.519	**0.0141**	**0.0282**
MMSE	173	−1.460	0.496	−2.942	**0.0037**	**0.0282**
Plasma Aβ42/40: IICV NOT in models						
Boston Naming	223	−47.597	43.697	−1.089	0.2773	0.7033
log Trails A	233	−3.430	2.630	−1.304	0.1935	0.7033
log Trails B	227	−2.740	2.983	−0.919	0.3594	0.7033
RAVLT long delay	234	14.082	25.562	0.551	0.5822	0.7033
RAVLT learning sum	234	34.070	67.723	0.503	0.6154	0.7033
Digit Symbol	80	110.491	160.401	0.689		0.7033
Logical Memory II	85	11.295	50.913	0.222	0.8250	0.8250
MMSE	184	15.738	18.641	0.844	0.3997	
Plasma Aβ42/40: IICV and plasma Aβ42/40 BOTH in models						
Boston Naming	220	−72.765	43.110	−1.688	0.0929	0.7431
log Trails A	221	−2.168	2.762	−0.785	0.4334	0.9920
log Trails B	221	0.348	3.119	0.111	0.9113	0.9920
RAVLT long delay	221	−0.734	26.290	−0.028	0.9777	0.9920
RAVLT learning sum	221	−0.732	72.742	−0.010	0.9920	0.9920
Digit Symbol	73	73.022	165.061	0.442	0.6596	0.9920
Logical Memory II	74	−11.333	56.760	−0.200	0.8423	0.9920
MMSE	173	9.698	18.934	0.512	0.6092	0.9920

Note: Cognitive outcomes were RAVLT Total of Learning Trials, RAVLT Delayed Recall, Trail Making Test, Part A and B, and Boston Naming Test, Digit Symbol Modalities Test, Logical Memory II from the Wechsler Memory Test IV, and MMSE or cross-walked Montreal Cognitive Assessment. All models included baseline age, self-identified sex, and baseline years of education. Multiple correction was performed using Benjamini–Hochberg (BH) corrections controlling false discovery rate at 5%. Significant adjusted *P* values are bolded.

Abbreviations: Aβ, amyloid beta; IICV, intra-individual cognitive variability; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; SE, standard error.

tionally, all beta estimates were in the hypothesized direction, that is, higher IICV was associated with worse cognitive performance (Table 2; see Table S2 in supporting information for full results). Baseline plasma Aβ42/40 was not significantly associated with any cognitive outcome (Table 2).

3.2 | Pattern suggested potential associations between baseline plasma Aβ42/40 but not IICV and longitudinal cognitive decline

Models included between 163 and 656 observations from 56 to 171 participants out of a total of 179 unique participants with plasma (ns varied due to changes made in testing protocols over time). Linear mixed effects models examining associations of IICV only with longitudinal cognitive trajectory revealed that the IICV x age interaction was not significant after adjustment for multiple comparisons for any outcome.

A pattern emerged for baseline plasma Aβ42/40 x age interaction and Trails A and B and potentially RAVLT, with lower baseline plasma Aβ42/40 associated with worse cognitive performance over time. However, these results did not survive correction for multiple comparisons (Table 3; see Table S3 in supporting information for full model results). In sensitivity analyses, decade cohort was significant in several models (Table S4 in supporting information) but had minimal impact on overall results around the IICV and plasma Aβ42/40 interactions with age; the IICV interaction findings are unchanged, and the interaction significance for plasma Aβ42/40 was reduced, but the estimate was similar. Figure 1 depicts performance over time on log Trails A and log Trails B at three levels of Aβ42/40 with and without IICV x age in the models (Figure S3 in supporting information shows the original measurement scale). Figure 2 depicts performance over time on RAVLT total at the same three levels of Aβ42/40, with and without IICV x age in the model. Model results suggested lower baseline plasma Aβ42/40 was associated with worse performance over time in all cases. All simple age slopes are calculated for women with 14 years education (sample median).

4 | DISCUSSION

In this cohort—consisting of mostly cognitively unimpaired Black Americans—baseline IICV but not baseline Aβ42/40 was associated with most tasks of concurrent cognitive function. By contrast, potential associations between baseline plasma Aβ42/40 and longitudinal trajectory of executive function and verbal learning were noted, but only before making corrections for multiple comparisons. Our results provide preliminary evidence that Aβ42/40 and IICV may play complementary roles in identifying early and subtle AD-associated changes, that is, preclinical AD.

Although findings were nonsignificant after correcting for multiple comparisons, the overall pattern of results is consistent with our group's previous findings revealing similar associations between CSF

Aβ42/40 and cognitive changes[4,43] and add to the growing body of evidence indicating that plasma Aβ42/40 is an effective means of detecting early amyloid pathology.[9–11] To our knowledge these are among the first data examining associations between plasma Aβ and longitudinal cognitive performance in a sample of Black middle-aged adults. Importantly, baseline plasma Aβ42/40 values for the sample were largely above the published cut-point indicating pathology.[29] Nonetheless, if replicated in other samples, results suggest potential associations between Aβ42/40 values and cognitive trajectory. That is, even among largely cognitively healthy individuals, baseline plasma Aβ42/40 may be associated with modest declines in performance of executive function and learning tests over time.

Partially consistent with previous findings,[19–21] baseline IICV was associated with most tasks of concurrent cognitive function, extending the relationship across racialized groups. Unexpectedly, baseline IICV was not associated with longitudinal cognitive decline. Nevertheless, we maintain that IICV offers potential as a valuable marker; cognitive evaluation provides unique and timely information about the real-world manifestation of AD in individuals. Reflecting a person's unique brain physiology, cognitive performance and variability are likely to manifest differently within and across individuals over time, perhaps explaining why IICV provided complementary information to the measurement of biological disease processes in our models. Future analyses with a larger sample, longer follow-up, or possibly different cognitive domains are needed to investigate IICV and cognitive trajectory more comprehensively across racialized groups.

Our study is novel from several perspectives. First and foremost, our findings address the broader question of whether AD biomarkers can be effectively used and consistently applied across historically under-included groups.[24] These results suggest that previously published findings regarding plasma amyloid biomarkers in predominantly non-Hispanic White samples likely apply to Black Americans as well. Notably, recent findings from another cohort of non-Hispanic Whites and Black Americans suggest that while plasma Aβ42/40 consistently predicted CSF Aβ42/40 across self-identified racialized groups, other plasma biomarkers, including phosphorylated tau (p-tau)181, p-tau231, and neurofibrillary tangle levels were not as consistently aligned.[2] Moreover, recent evidence suggesting differences in plasma Aβ42/40 levels between racialized groups carrying the same neurocognitive diagnoses (e.g., MCI and dementia) underscores the importance of this ongoing work.[3] In total, expansion of biomarker research in Black American cohorts[44] represents an essential next step to ensure that biomarkers accurately and consistently predict AD pathology across diverse populations.

Developments in disease-modifying therapies adds urgency to efforts to detect AD in its preclinical stages, allowing for early intervention. Advances in technological sensitivity could be instrumental in detecting individuals at risk for decline at very early disease stages. With refinements and confirmation across racialized groups, they offer a possible means to treat disease pathology before it manifests clinically or before it progresses. For example, plasma Aβ42/40, perhaps combined with IICV, could be used to appropriately identify patients with evolving amyloid pathology for whom interventions targeting

TABLE 3 Longitudinal associations between baseline IICV and cognitive trajectory (i.e., assessing IICV × age interactions) without and with baseline plasma Aβ42/40 and its interaction with age in the models (top two panels) and longitudinal associations between plasma Aβ42/40 and cognitive trajectory (i.e., assessing plasma × age interactions) without and with baseline IICV and its interaction with age in the model (bottom two panels).

Model outcome	N subject	N obs	Beta	SE	t value	P value	BH P value
IICV × age interactions: plasma Aβ42/40 NOT in models							
Boston Naming	159	577	−0.102	0.105	−0.966	0.3345	0.7263
log Trails A	164	596	0.012	0.007	1.713	0.0877	0.3507
log Trails B	162	575	0.013	0.007	1.726	0.0855	0.3507
RAVLT long delay	169	648	0.011	0.061	0.174	0.8620	0.8620
RAVLT learning sum	171	656	0.125	0.174	0.718	0.4737	0.7263
Digit Symbol	66	189	−0.305	0.364	−0.837	0.4038	0.7263
Logical Memory II	68	194	−0.068	0.135	−0.504	0.6156	0.7263
MMSE	157	540	−0.019	0.039	−0.475	0.6355	0.7263
IICV × age interactions: plasma Aβ42/40 x age and IICV BOTH in models							
Boston Naming	143	519	−0.148	0.122	−1.214	0.2255	0.8599
log Trails A	147	536	−0.001	0.008	−0.084	0.9335	0.9335
log Trails B	145	515	0.004	0.009	0.431	0.6665	0.8599
RAVLT long delay	155	593	0.024	0.069	0.345	0.7306	0.8599
RAVLT learning sum	156	599	0.225	0.194	1.158	0.2482	0.8599
Digit Symbol	56	163	0.145	0.460	0.316	0.7524	0.8599
Logical memory II	57	166	0.117	0.175	0.670	0.5050	0.8599
MMSE	140	482	0.031	0.047	0.654	0.5139	0.8599
Plasma Aβ42/40 × age interactions: IICV NOT in models							
Boston Naming	147	531	3.549	3.671	0.967	0.3342	0.5347
log Trails A	152	550	−0.450	0.249	−1.806	0.0719	0.2877
log Trails B	146	519	−0.685	0.261	−2.625	**0.0092**	0.0734
RAVLT long delay	158	603	0.595	2.138	0.278	0.7811	0.8927
RAVLT learning sum	159	609	8.691	6.220	1.397	0.1634	0.3269
Digit Symbol	56	163	17.858	11.777	1.516	0.1319	0.3269
Logical Memory II	58	168	−0.412	4.306	−0.096	0.9241	0.9241
MMSE	144	495	1.038	1.612	0.644	0.5205	0.6940
Plasma Aβ42/40 × age interactions: plasma Aβ42/40 and IICV BOTH in models							
Boston Naming	143	519	1.917	3.843	0.499	0.6181	0.6217
log Trails A	147	536	−0.536	0.260	−2.066	**0.0397**	0.1558
log Trails B	145	515	−0.627	0.277	−2.268	**0.0242**	0.1558
RAVLT long delay	155	593	1.091	2.209	0.494	0.6217	0.6217
RAVLT learning sum	156	599	11.941	6.282	1.901	0.0584	0.1558
Digit Symbol	56	163	20.659	13.910	1.485	0.1396	0.2793
Logical Memory II	57	166	3.002	5.492	0.547	0.5862	0.6217
MMSE	140	482	1.601	1.580	1.013	0.3121	0.4994

Note: Cognitive outcomes were RAVLT Total of Learning Trials, RAVLT Delayed Recall, Trail Making Test, Part A and B, and Boston Naming Test, Digit Symbol Modalities Test, Logical Memory II from the Wechsler Memory Test IV, and MMSE or cross-walked Montreal Cognitive Assessment. All models included age at each assessment, self-identified sex, baseline years of education, and subject-specific random intercepts and main effects for interaction components. Multiple correction was performed using Benjamini–Hochberg (BH) corrections controlling false discovery rate at 5%. Significant adjusted *P* values are bolded.

Abbreviations: Aβ, amyloid beta; IICV, intra-individual cognitive variability; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; SE, standard error.
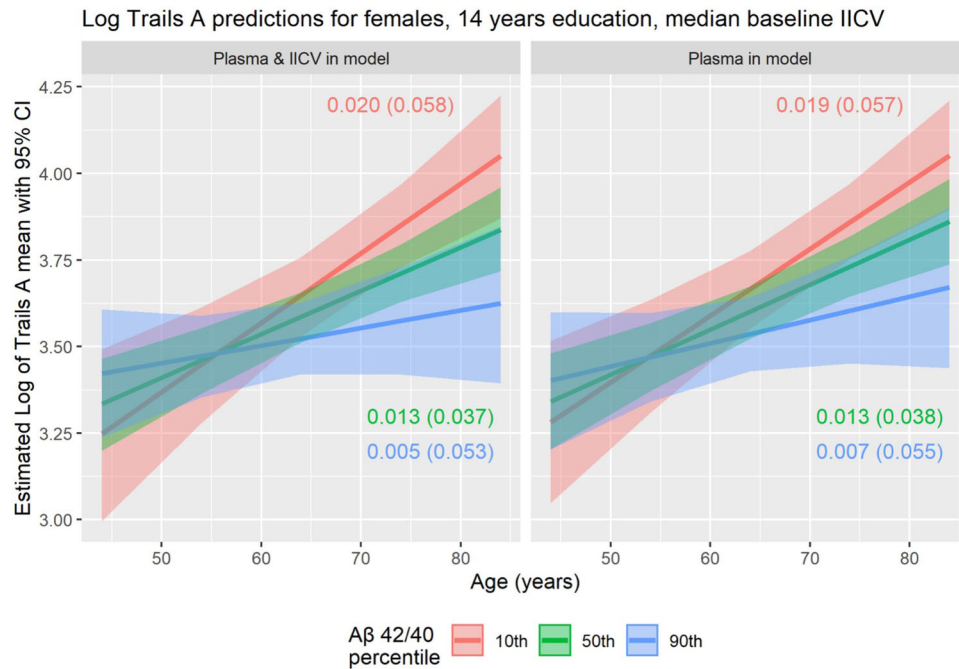
FIGURE 1 Model-predicted log Trails A and B means for varying Aβ42/40 values. Depiction of the model estimated Aβ42/40 by age interaction behavior, showing the model predicted means with 95% CIs for different ages and Aβ42/40 quantiles, while keeping self-identified sex (female) and years of education (14 years) held constant at their median values at the population level (i.e., unconditional with respect to random effects). Lower percentile represents lower Aβ42/40 ratio. For each test (Trails A and B) two panels display the estimated behavior for model with IICV accounted for and set to the median in the data (main effects and its interaction with age; Panels A and C), versus models in which IICV is not included in any covariate (Panels B and D). Trails A and B performances measured as time to complete. Longer time (higher value) represents worse performance. Figures are annotated to indicate simple age slope (SE) at each level of Aβ42/40 (SE is calculated at the sample mean age of 64 years). A woman with 14 years education whose Aβ42/40 value was equal to the 10th percentile would be expected to take approximately 7 seconds longer to complete Trails A at age 70 then she did at age 60 and 30 seconds longer to complete Trails B. If she had Aβ42/40 values equal to the 90th percentile she would be expected to take 2 more seconds to complete trails A and 2.5 more seconds to complete Trails B by age 70. Aβ, amyloid beta; CIs, confidence intervals; IICV, intra-individual cognitive variability; SE, standard error; Trails, Trail Making Test, Parts A and B

amyloid would be most efficacious. Ensuring accurate preclinical identification for Black Americans will be essential to address the ADRD disparities.

Advances in blood-based biomarkers and the use of cognitive assessments to inform associations present an opportunity to move data collection out of the laboratory and into the community. In contrast to neuroimaging and CSF collection, which are invasive, expensive, time consuming, and require specialized staff and equipment, blood draw is readily accessible. The AA-FAIM study recently started collecting blood at community locations, implementing preanalytical processing protocols,[45] and demonstrating the feasibility of expanding access to blood-based biomarkers. Additionally, estimating risk using IICV could be accomplished with remote or technologically assisted assessments—a process even more readily disseminated than blood collection. Thus, blood-based biomarker research with brief cognitive assessment could offer a practical, low cost, non-invasive, person-centered strategy for broad population assessment, and a means to mitigate significant barriers to participation in AD biomarker research,[8,46] the desired outcome of which would be reduced disease burden for Black Americans.

Our study's limitations warrant acknowledgement. Our present sample size is small, and we did not have reference standards for most AA-FAIM participants (i.e., amyloid status confirmed by PET or CSF). Given available assay methods, we focused on Aβ42/40, but acknowledge that future analysis of additional biomarkers such as p-tau may be fruitful. Still, Aβ42/40 is likely to be included with future efforts to measure tau isoforms, making it still important to clarify its predictive value. Another limitation is that the mean age of participants was relatively young, reducing the likelihood of subsequent cognitive decline in the 4-year study period, and observed cognitive decline was modest. Our AA-FAIM cohort was established relatively recently; we anticipate that as our sample size increases and the cohort ages, data will become increasingly informative about preclinical disease in Black Americans. For example, Black Americans made up 4.4% of the sample on which C$_2$N Diagnostics developed their recommended Aβ42/40 threshold (see Hu et al.[12]), calling into question the generalizability of that threshold. In the future, we will have the opportunity to address this knowledge gap by validating plasma biomarkers with amyloid PET imaging. While the theoretical concepts behind IICV are well established, the battery of cognitive tests used to construct IICV and the reference standard for test score standardization are not yet established and vary across studies. Here we relied on methods used in our previous work.[19–21] Additionally, we tried to maximize power at each stage by using all available data, with the trade-off that the
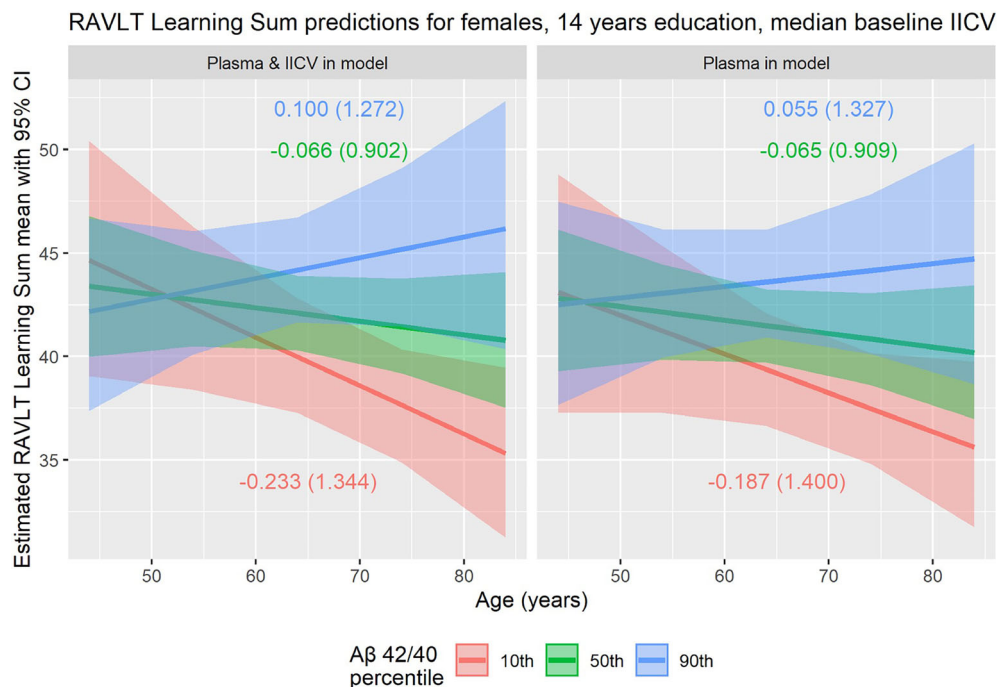
FIGURE 2 Model-predicted RAVLT Total of Learning Trials means for varying Aβ42/40 values. Direction of the model estimated by Aβ42/40 by age interaction behavior, showing the model predicted means with 95% CIs for different ages and Aβ42/40 quantiles, while keeping self-identified sex (female) and years of education (14 years) held constant at their median values, at the population level (i.e., unconditional with respect to random effects). The two panels in the figure display the estimated behavior for models with IICV accounted for and set to the median in the data (main effects and its interaction with age, Panel A), versus the model where IICV is not included in any covariate (panel B). RAVLT performance measured as number correct. Lower number correct (lower value represents worse performance). Figures are annotated to indicate simple age slope (SE) at each level of Aβ42/40 (SE is calculated at the sample mean age of 64 years). A 60-year-old woman with 14 years education whose Aβ42/40 was equal to the 10th percentile would be expected to decline by 2 points on RAVLT total by age 70; if the woman's Aβ42/40 was equal to the 90th percentile she would be expected to gain 1 point over 10 years. Aβ, amyloid beta; CIs, confidence intervals; IICV, intra-individual cognitive variability; RAVLT, Rey Auditory Verbal Learning Test; SE, standard error

variable N between models with and without plasma and/or IICV can make it difficult to fully understand differences between results. Ninety-three subjects could not be included in analyses for various reasons, with the vast majority of these participants only having one visit (73/93), and thus our sample is biased to exclude recent recruitment into the study (Table S1). Results need to be interpreted knowing that participants were predominantly cognitively healthy, and mostly outside published ranges defining pathological plasma Aβ42/40 levels. Also, while cohort effects were not the focus of this paper, inclusion of birth decade cohort is commonly significant in longitudinal models; in our analyses, cohort inclusion appeared mainly to affect findings around the plasma x age interactions for the Trails A outcome (Table S4). Still, trajectory effects discussed in this paper should be considered a mixture of aging and cohort effects. As noted, the findings regarding longitudinal decline described above were nonsignificant after multiple comparisons. Finally, participants were highly educated, representing a convenience sample from a university town, albeit a largely community-based sample. Additional research is needed to further examine how these findings generalize to the larger Black community. Notably, racialized group membership is not an exact reflection of one's experiences and exposures, and socially

assigned race is just one axis of identity. Future AD research will need to leverage participants' multiple intersecting identities.

Using data from a sample comprised entirely of self-identified Black Americans offers a step toward reducing racial disparities in AD research and provides the basis for further examination of AD in Black Americans using blood-based biomarkers. In taking this step we argue that the research community can no longer be satisfied with non-inclusive samples; studies must fully represent the population to which they are intended to generalize. Importantly, we move away from positioning non-Hispanic Whites as the standard to which under-represented groups should be compared, while acknowledging that given well known recruitment biases, no one sample can generalize to all Black Americans.[47] While improved recruitment efforts have been used in AA-FAIM and other ADRC-related grants, time is needed to build trust and gain greater and longer participation, as indicative of our relatively small and young sample. Altogether, this and continued analyses are needed for Black participants and patients to be reassured that AD biomarker findings are relevant for them.[8]

To conclude, these preliminary findings suggest that in a largely cognitively unimpaired Black cohort, an initial pattern emerged linking plasma Aβ42/40 and executive function and memory trajectory but did

not survive correction for multiple comparisons. On the other hand, IICV was associated with most tasks of concurrent cognitive function. Our findings are promising; if replicated they suggest that with a 30 minute visit individuals could provide practical information to identify potential AD disease risk. By facilitating accessible research and continuing to recruit Black Americans, we will improve confidence that findings apply to the entire population and more effectively identify and treat preclinical ADRD for populations currently caught between under-inclusion in research and over-representation in disease burden.

AUTHOR CONTRIBUTIONS

The authors wish to thank the participants and staff who made this work possible. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

CONFLICT OF INTEREST STATEMENT

K.K., M.H., M.M., V.V., T.W., P.V., and K.Y. are each employed by and have equity interest in C$_2$N Diagnostics. D.G. is a board member of Schizophrenia International Research Society (SIRS), President of NAMI-Dane County Board, Deputy Editor of *Psychiatry Research* (honorarium paid), and advisory board member of Black Leaders for Brain Health. B.F. has nothing to disclose. C.V.H. has nothing to disclose. R.L.K. has nothing to disclose. D.N. has nothing to disclose. M.Z. has nothing to disclose. M.W. has nothing to disclose. A.J. has nothing to disclose. N.L. has nothing to disclose. T.J. has nothing to disclose. S.B. has nothing to disclose. F.C. has nothing to disclose. H.S. has nothing to disclose. C.C. has nothing to disclose. S.J. has nothing to disclose. S.A. has nothing to disclose. C.G. has nothing to disclose. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Study participants provided consent prior to all study visits. Study procedures were approved by the University of Wisconsin–Madison Institutional Review Board.

REFERENCES

1. Power M, Bennett E, Turner R, Dowling M, Ciarleglio A, Gymour M, Gianattasio K. Trends in relative incidence and prevalence of dementia across non-Hispanic Black and White individuals in the United States, 2000-2016. *JAMA Neurol.* 2020;78(3):275-284. doi:10.1001/jamaneurol.2020.4471

2. Schindler SE, Karikari TK, Ashton NJ, et al. Effect of race on prediction of brain amyloidosis by plasma Abeta42/Abeta40, phosphorylated tau, and neurofilament light. *Neurology.* 2022;99(3):e245-e257. doi:10.1212/WNL.0000000000200358

3. Hall JR, Petersen M, Johnson L, O'Bryant SE. Characterizing plasma biomarkers of Alzheimer's in a diverse community-based cohort: a cross-sectional study of the HAB-HD cohort. *Front Neurol.* 2022;13:871947. doi:10.3389/fneur.2022.871947

4. Betthauser TJ, Koscik RL, Jonaitis EM, et al. Amyloid and tau imaging biomarkers explain cognitive decline from late middle-age. *Brain.* 2020;143(1):320-335. doi:10.1093/brain/awz378

5. Tsoy E, Kiekhofer RE, Guterman EL, et al. Assessment of racial/ethnic disparities in timeliness and comprehensiveness of dementia diagnosis in California. *JAMA Neurol.* 2021;78(6):657-665. doi:10.1001/jamaneurol.2021.0399

6. Jack CR, Jr., Bennett DA, Blennow K, et al.Research Framework NIA-AA: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018

7. Gilmore-Bykovskyi A, Croff R, Glover CM, et al. Traversing the aging research and health equity divide: toward intersectional frameworks of research justice and participation. *Gerontologist.* 2022;62(5):711-720. doi:10.1093/geront/gnab107

8. Howell JC, Parker MW, Watts KD, Kollhoff A, Tsvetkova DZ, Hu WT. Research lumbar punctures among African Americans and Caucasians: perception predicts experience. *Front Aging Neurosci.* 2016;8:296. doi:10.3389/fnagi.2016.00296

9. Song F, Poljak A, Valenzuela M, Mayeux R, Smythe GA, Sachdev PS. Meta-analysis of plasma amyloid-beta levels in Alzheimer's disease. *J Alzheimers Dis.* 2011;26(2):365-375. doi:10.3233/JAD-2011-101977

10. Doecke JD, Perez-Grijalba V, Fandos N, et al. Total Abeta42/Abeta40 ratio in plasma predicts amyloid-PET status, independent of clinical AD diagnosis. *Neurology.* 2020;94(15):e1580-e1591. doi:10.1212/WNL.0000000000009240

11. O'Connor A, Pannee J, Poole T, et al. Plasma amyloid-beta ratios in autosomal dominant Alzheimer's disease: the influence of genotype. *Brain.* 2021;144(10):2964-2970. doi:10.1093/brain/awab166

12. Hu Y, Kirmess KM, Meyer MR, et al. Assessment of a plasma amyloid probability score to estimate amyloid positron emission tomography findings among adults with cognitive impairment. *JAMA Netw Open.* 2022;5(4):e228392. doi:10.1001/jamanetworkopen.2022.8392

13. Barnes L, Leurgans S, Neelum A, et al. Mixed pathology is more likely in black than white decedent with Alzheimer's disease. *Neurology.* 2015;85:528-534. doi:10.1212/WNL.0000000000001834

14. Howell JC, Watts KD, Parker MW, et al. Race modifies the relationship between cognition and Alzheimer's disease cerebrospinal fluid biomarkers. *Alzheimers Res Ther.* 2017;9(1):88. doi:10.1186/s13195-017-0315-1

15. Bravata DM, Wells CK, Gulanski B, et al. Racial disparities in stroke risk factors: the impact of socioeconomic status. *Stroke.* 2005;36(7):1507-1511. doi:10.1161/01.STR.0000170991.63594.b6

16. Patton DE, Duff K, Schoenberg MR, Mold J, Scott JG, Adams RL. Performance of cognitively normal African Americans on the RBANS in community dwelling older adults. *Clin Neuropsychol.* 2003;17(4):515-530. doi:10.1076/clin.17.4.515.27948

17. Manly JJ, Jacobs DM, Sano M, et al. Cognitive test performance among nondemented elderly African Americans and whites. *Neurology.* 1998;50(5):1238-1245. doi:10.1212/wnl.50.5.1238

18. Lin SS, McDonough IM. Intra-individual cognitive variability in neuropsychological assessment: a sign of neural network dysfunction.

Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2022;29(3):375-399. doi:10.1080/13825585.2021.2021134

19. Gleason CE, Norton D, Anderson ED, et al. Cognitive variability predicts incident Alzheimer's disease and mild cognitive impairment comparable to a cerebrospinal fluid biomarker. *J Alzheimers Dis.* 2018;61(1):79-89. doi:10.3233/JAD-170498

20. Anderson ED, Wahoske M, Huber M, et al. Cognitive variability-A marker for incident MCI and AD: an analysis for the Alzheimer's Disease Neuroimaging Initiative. *Alzheimers Dement (Amst).* 2016;4:47-55. doi:10.1016/j.dadm.2016.05.003

21. Koscik RL, Berman SE, Clark LR, et al. Intraindividual cognitive variability in middle age predicts cognitive impairment 8-10 years later: results from the wisconsin registry for Alzheimer's prevention. *J Int Neuropsychol Soc.* 2016;22(10):1016-1025. doi:10.1017/S135561771600093X

22. Fontanarosa PB, Race BH, Ancestry, and medical research. *JAMA.* 2018;320(15):1539-1540. doi:10.1001/jama.2018.14438

23. Caulfield T, Fullerton SM, Ali-Khan SE, et al. Race and ancestry in biomedical research: exploring the challenges. *Genome Med.* 2009;1(1):8. doi:10.1186/gm8

24. Gleason CE, Zuelsdorff M, Gooding DC, et al. Alzheimer's disease biomarkers in Black and non-Hispanic White cohorts: a contextualized review of the evidence. *Alzheimers Dement.* 2021. doi:10.1002/alz.12511

25. 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. *Alzheimers Dement.* 2011;7(3):270-279. doi:10.1016/j.jalz.2011.03.008

26. McKhann GM, Knopman DS, 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. *Alzheimers Dement.* 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005

27. Graff-Radford NR, Besser LM, Crook JE, Kukull WA, Dickson DW. Neuropathologic differences by race from the National Alzheimer's Coordinating Center. *Alzheimers Dement.* 2016;12(6):669-677. doi:10.1016/j.jalz.2016.03.004

28. Kirmess KM, Meyer MR, Holubasch MS, et al. The PrecivityAD test: Accurate and reliable LC-MS/MS assays for quantifying plasma amyloid beta 40 and 42 and apolipoprotein E proteotype for the assessment of brain amyloidosis. *Clin Chim Acta.* 2021;519:267-275. doi:10.1016/j.cca.2021.05.011

29. West T, Kirmess KM, Meyer MR, et al. A blood-based diagnostic test incorporating plasma Abeta42/40 ratio, ApoE proteotype, and age accurately identifies brain amyloid status: findings from a multi cohort validity analysis. *Mol Neurodegener.* 2021;16(1):30. doi:10.1186/s13024-021-00451-6

30. Janelidze S, Teunissen CE, Zetterberg H, et al. Head-to-head comparison of 8 plasma amyloid-β 42/40 assays in Alzheimer disease. *JAMA Neurol.* 2021;78(11):1375-1382. doi:10.1001/jamaneurol.2021.3180

31. Rey A. L'examen clinique en psychologie. Presses Universaires de France; 1964.

32. Battery AIT. Manual of Directions and Scoring. War Department, Adjutant General's Office; 1944.

33. Kaplan E, Goodglass H, Weintraub S. Boston Naming Test. Lea & Febiger; 1983.

34. Gollan TH, Weissberger GH, Runnqvist E, Montoya RI, Cera CM. Self-ratings of spoken language dominance: a multi-lingual naming test (MINT) and preliminary norms for young and aging Spanish-English Bilinguals. *Biling (Camb Engl).* 2012;15(3):594-615. doi:10.1017/S1366728911000332

35. Monsell S, Dodge H, Xiao-Hua Z, et al. Results from the NACC uniform data set neuropsychological battery crosswalk study. *Alzheimer Dis Assoc Disord.* 2016;30(2):134-139. doi:10.1097/WAD.000000000000011

36. Smith A. Digit Symbol Modalities Test Manual. Western Psychological Services.

37. Folstein MFS, McHugh P. Mini-mental state'': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-198.

38. Nasreddine Z, Phillips N, Bedirian V, et al. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J American Geriat Soc.* 2005;53(4):695-699. doi:10.1111/j1532-5415.2005.53221.x

39. Satterthwaite F. An approximate distribution of estimates of variance components. *Biometrics Bulletin.* 1946;2:110-114. doi:10.2307/3002019

40. Elias MF, Elias PK, D'Agostino RB, Silbershatz H, Wolf PA. Role of age, education, and gender on cognitive performance in the Framingham Heart Study: community-based norms. *Exp Aging Res.* 1997;23(3):201-235. doi:10.1080/03610739708254281

41. Lezak M, Howieson D, Bigler E, Tranel D. *Neuropsychological Assessment.* 5th ed. Oxford University Press; 2012.

42. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and pwoerful method to multiple testing. *J RSS, Series B (Methodolo).* 1995;57(1):289-300.

43. Koscik RL, Betthauser TJ, Jonaitis EM, et al. Amyloid duration is associated with preclinical cognitive decline and tau PET. *Alzheimers Dement (Amst).* 2020;12(1):e12007. doi:10.1002/dad2.12007

44. Deniz K, Ho CCG, Malphrus KG, et al. Plasma Biomarkers of Alzheimer's Disease in African Americans. *J Alzheimers Dis.* 2021;79(1):323-334. doi:10.3233/JAD-200828

45. O'Bryant SE, Waring SC, Cullum CM, et al. Staging dementia using clinical dementia rating scale sum of boxes scores: a Texas Alzheimer's research consortium study. *Arch Neurol.* 2008;65(8):1091-1095. doi:10.1001/archneur.65.8.1091

46. George S, Duran N, Norris K. A systematic review of barriers and facilitators to minority research participation among African Americans, Latinos, Asian Americans, and Pacific Islanders. *Am J Public Health.* 2014;104(2):e16-e31. doi:10.2105/AJPH.2013.301706

47. Gleason CE, Norton D, Zuelsdorff M, et al. Association between enrollment factors and incident cognitive impairment in Blacks and Whites: data from the Alzheimer's Disease Center. *Alzheimers Dement.* 2019;15(12):1533-1545. doi:10.1016/j.jalz.2019.07.015

SUPPORTING INFORMATION

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