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RESEARCH ARTICLE

Plasma biomarkers predict cognitive trajectories in an ethnoracially and clinically diverse cohort: Mediation with hippocampal volume

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Abstract

Introduction: We examine whether the association between key plasma biomarkers (amyloid β [$a\beta$] 42/40, total tau (t-tau), neurofilament light [NfL]) and cognitive trajectories (executive function [EF] and episodic memory [EM]) is mediated through neurodegeneration.

Methods: All participants were recruited from the University of California, Davis-Alzheimer's Disease Research Center ($n = 473$; baseline age range = 49–95 years, 60% women). We applied an accelerated longitudinal design to test latent growth models for EF and EM, and path and mediation analyses. Age was centered at 75 years, and all models were adjusted for sex, education, and ethnicity.

Results: HV differentially mediated the association $a\beta$ 42/40 and NfL on EF and EM level and change. Hippocampal volume (HV) did not mediate the association between t-tau and cognitive performance.

Discussion: Neurodegeneration as represented with HV selectively mediates the association between key non-invasive plasma biomarkers and cognitive trajectories in an ethnoracially and clinically diverse community-based sample.

KEYWORDS

Alzheimer's disease, amyloid β 42/40, cognition, hippocampal volume, neurofilament light, plasma biomarkers, total-tau

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1 | INTRODUCTION

Biomarkers to identify older adults at risk of dementia and accelerated cognitive decline are central to early and accurate diagnosis of neurodegenerative diseases.¹ There is an urgent need for easily implemented multi-ethnic community-based biomarkers for earlier detection of at-risk individuals. Current research on fluid and neuroimaging biomarkers has undergone rapid development.¹ For example, recently developed non-invasive, cost effective and highly accurate plasma assays^{1,2} have been shown to correlate significantly with the standard cerebrospinal fluid (CSF) or positron emission tomography (PET) biomarkers for Alzheimer's disease (AD) diagnosis.^{3,4}

Specifically, amyloid β ($a\beta$) 42 and $a\beta$ 40 are markers of $a\beta$ plaque accumulation, phosphorylated and total tau (p-tau and t-tau, respectively) are important indicators of neurofibrillary tangles, and neurofilament light (NfL) represents degeneration of myelinated axons. Lower plasma $a\beta$ 42/40,⁵ higher p-tau and t-tau,⁶ and higher NfL⁷ have been associated with lower cognitive performance, steeper cognitive decline, increased dementia risk,^{6,8} and neurodegeneration in cognitively unimpaired older adults⁹ and dementia patients¹⁰ in study cohorts of predominantly non-Hispanic white individuals. Although recent studies have identified racial differences between CSF $a\beta$ 42, t-tau, and p-tau,¹¹ plasma t-tau and NfL results are just starting to be examined in ethnoracially diverse populations.¹² This includes older adults who may be at higher risk (i.e., African Americans and Hispanics) for accelerated cognitive¹³ and functional decline,¹⁴ and are more likely to have mixed neuropathology¹⁵ as a cause for dementia.

Given the important role of neurodegeneration in Alzheimer's disease and related dementias (ADRD)¹⁶ and cognitive decline, in combination with the strong potential of plasma biomarkers for future use in clinical settings,¹⁷ it is essential to understand how and whether neurodegeneration mediates the association between key plasma biomarkers and cognition in ethnoracially diverse populations. We selected a robust and multifaceted brain morphometry region in cognitive aging and ADRD research for two key reasons. First, hippocampal volume (HV) has been shown to discriminate not only AD but also normal aging from mild cognitive impairment (MCI).⁴⁹ Second, HV has been associated with not just episodic memory (EM) but also processing speed, working memory, and executive function (EF)¹⁸ in older adults and is a sensitive marker for early AD detection.¹⁹ Thus, hippocampal atrophy, a well-documented aging process was optimally suited for our purposes.

In the present study, we examine whether three robust plasma biomarkers ($a\beta$ 42/40, t-tau, NfL) predict performance and change in two key cognitive domains (EF and EM) and whether neurodegeneration typically observed in AD (as measured by HV), explains these association in an ethnoracially and clinically diverse population. We hypothesized that HV would mediate the association between each plasma biomarker (lower $a\beta$ 42/40, higher t-tau, and higher NfL) and cognition (poorer EF and EM performance and steeper decline).

RESEARCH IN CONTEXT

1. **Systematic review:** We reviewed the literature (e.g., PubMed) on plasma biomarkers and cognitive decline with a focus on synergistic associations between key dementia plasma biomarkers and brain morphometry. Specifically, whether the association between plasma amyloid beta 42/40, total-tau, and neurofilament light (NfL), and cognitive decline is mediated through brain morphometry. We did not find any such reports.
2. **Interpretation:** Our findings suggests that hippocampal volume (HV) (key marker of neurodegeneration) selectively mediates the association between plasma biomarkers and episodic memory (EM) and executive function (EF) trajectories in clinically heterogenous and ethnoracially diverse population.
3. **Future directions:** Our findings provide support and direction to make relevant comparisons with more established cerebrospinal fluid (CSF) and amyloid and tau positron emission topography markers across a broad range of cognitive domains and neurodegenerative markers.

2 | METHODS

2.1 | Participants

We used data from the University of California, Davis-Alzheimer's Disease Research Cohort (UCD-ADRC),²⁰ an ethnoracially diverse longitudinal study representing community dwelling older adults who are cognitively normal or diagnosed as MCI or demented. The UCD-ADRC and all data collection are in full and certified compliance with the human/institutional review board. Written informed consent was obtained from all participants or their legal representatives. Ethnicity and racial status were self-reported, and standard criteria and methods were followed for cognitive status diagnosis.²¹ Participants received a multidisciplinary clinical evaluation using the Uniform Data Set battery.^{21,22} For the present study, we used a subsample of participants with plasma biomarker data ($N = 493$) and at least one neuropsychological assessment ($n = 20$ were excluded). Accordingly, 473 participants (mean age = 74.80 (7.22) years old, baseline age range = 49–95 years old) were included (see Table 1), of these, 444 individuals had Magnetic Resonance Imaging (MRI) hippocampal measures and did not meet a biomarker definition of AD. UCD-ADRC cohort follows a rolling-enrollment design and the present study uses 10 follow-ups of data on participants differing in baseline age.

TABLE 1 Baseline characteristics by ethnicity and diagnosis

	Race/ethnicity				Diagnosis			p
	Total	African American	Hispanic	White	Normal	MCI	Demented	
N	473	189	175	98	295	102	76	-
Age	74.80 (7.216)	75.76 (6.973)*	73.77 (7.373)*	74.46 (7.218)	73.48 (6.895)**	76.85* (7.229)	77.20* (7.250)	<.001
Sex (M/W)	187/286	52/137**	69/106*	61/37***	105/190	48/54	34/42	.206
Education	12.507 (4.904)	13.524 (3.136)*	9.400 (5.541)*	15.867 (2.987)*	13.271 (4.548)	11.618 (5.078)	10.737 (5.385)	.022
Ethnicity (African American/ Hispanic/White)	189/175/98	-	-	-	110/108/66	52/32/18	27/35/14	.173
Diagnosis (Normal/MCI/ Demented)	295/102/76	110/52/27	108/32/35	66/18/14	-	-	-	-
a β 42/40	0.044 (0.011)	0.045 (0.011)	0.046 (0.012)	0.041 (0.011)	0.045 (0.011)**	0.045 (0.012)*	0.040 (0.012)***	<.001
t-tau (pg/mL)	3.150 (1.484)	3.215 (1.355)	3.222 (1.688)	2.874 (1.198)	2.985 (1.332)*	3.462 (1.849)*	3.373 (1.423)	.004
NFL ^a (pg/mL)	-0.007 (0.435)	-0.076 (0.403)	-0.044 (0.382)	0.077 (0.503)	-0.080 (0.389)***	0.132 (0.588)*	0.222 (0.291)*	<.001
Hippocampal volume (residuals) cc	0.014 (0.720)	-0.057 (0.684)	0.070 (0.677)	0.010 (0.852)	0.243 (0.588)*	-0.218 (0.713)*	-0.664 (0.735)*	<.001
EF factor score	-0.210 (0.704)	-0.218 (0.631)*	-0.513 (0.682)*	0.266 (0.568)*	0.056 (0.570)*	-0.454 (0.591)*	-0.921 (0.708)*	<.001
EM factor score	-0.251 (0.957)	-0.200 (0.859)**	-0.552 (0.939)***	0.107 (1.018)*	0.178 (0.818)*	-0.701 (0.661)*	-1.326 (0.629)*	<.001

Abbreviations: a β , amyloid β ; EF, executive function; EM, episodic memory; MCI, mild cognitive impairment; NFL, neurofilament Light; t-tau, total tau.

Note: Means and standard deviations are in brackets. $n = 11$ did not have data on ethnicity and are not represented in the table. p represents significance for all three levels for both ethnicity and diagnosis.

^aNatural log transformation applied for normal distribution.

*Post-hoc Tukey significance $p < .05$.

**Post-hoc Tukey significance $p < .05$.

2.2 | Plasma biomarkers

2.2.1 | Sample collection

Blood samples were randomly obtained, processed within 2 hours, and stored in 250 μ L aliquots at -80°C using previously reported standard procedures.²³ Methodological details for $\text{a}\beta$, t-tau, and NfL are in the supplementary methods.

2.3 | Magnetic resonance imaging (MRI) acquisition protocols and processing

Structural MRI scans for 118 participants were obtained at the UCD MRI research center on a 3T Siemens (Munich, Germany) Magnetom Trio Syngo System with an eight-channel head coil. Acquired images included a T1-weighted volumetric magnetization-prepared rapid gradient echo (repetition time [TR] 2500, echo time [TE] 2.94 or 2.98, inversion time [TI] 1100, with 1 mm^3 isotropic resolution) and a fluid-attenuated inversion recovery (FLAIR) scan (TR 5000, TE 403, TI 1700, with $1.00 \times 1.00 \text{ mm}^2$ in-plane resolution and 2.00 mm slice thickness). MRI scans using a 1.5T GE (Cleveland, OH) Signa Genesis system at the UCD were obtained from 209 individuals. Each session included a T1-weighted 3D spoiled gradient recalled echo scan (TR 9, TE 1.9, with $0.98 \times 0.98 \text{ mm}^2$ in-plane resolution and 1.5 mm slice thickness) and a FLAIR scan (TR 11002, TE 147, TI 2250, with $0.98 \times 0.98 \text{ mm}^2$ in-plane resolution and 3.00 mm slice thickness). Finally, MRI scans from 110 subjects were performed on a Philips Eclipse 1.55T machine consisting of a T1 weighted rapid imaging protocol (TR 9, TE 2.4 with $1 \times 1 \times 1.5 \text{ mm}$ resolution) and a FLAIR protocol (TR 11000, TE 140, TI 2250 with $0.86 \times 0.86 \times 3.0 \text{ mm}$ resolution). Complete details on acquisition and imaging processing are available elsewhere.^{24,25} MRI scan information for $n = 7$ were missing. For the present study, HVs were calculated using a multi-atlas hippocampal segmentation algorithm²⁶ implemented in the Imaging of Dementia and Aging (IDeA) laboratory at UC Davis. All HVs measurements were corrected for total cerebrum cranial volume (TCV) for each participant (using the residual method where we regress HV on TCV brain volumes and save the residuals). The mean time lag between HV measurements and blood draw used to derive plasma biomarkers was minimal (mean = 0.58 ± 1.03 years; range = 0 to 6 years). A total of 348 of 444 participants (78%) had 0 years of difference, and 4 cases with > 5 years of differences (<1%). The mean time lag from initial assessment to MRI was 0.13 ± 0.14 years.

2.4 | Neuropsychological assessments

We examined two key domains to study cognitive performance and change. EF and EM composite scores have extensively been tested and applied in the UCD-ADRC diversity cohort using the Spanish and English Neuropsychological Assessment Scale (SENAS).^{24,27} EM is derived from a verbal score based on a multi-trial word list learning test and EF is a composite measure of category fluency, phonemic flu-

ency (letter), and working memory (digit span backward, visual span backward, list sorting). Both scores have been shown to be invariant between ethnic groups and longitudinally invariant.²⁸ Relevant procedure and psychometric characteristics of the SENAS battery are available.²⁷ Follow-ups were approximately 1.2 to 1.5 years.

2.5 | Statistical analysis

Baseline participant characteristics were compared by ethnicity and diagnosis using analysis of variance for continuous variables and a chi-squared test for categorical variables. Continuous measures (i.e., age) were summarized using means and standard deviations, whereas categorical measures were summarized using counts and percentages. We used structural equation modeling (SEM) for all analyses in Mplus Version 7.4. Latent growth models in SEM account for unique trajectories of each individual and are not limited to specific directions of change for latent factors. All missing values for EF and EM measures were assumed to be missing at random and were estimated using maximum likelihood. Cases with missing predictor values were removed using list-wise deletion in Mplus 7.4. Age instead of wave was used as the metric of change and accounted for any variability associated with age directly in the model.²⁹

2.5.1 | Latent growth models for EF and EM

We applied latent growth modeling and determined the best latent growth model for the EF and EM composite scores using age as the metric of time for 10 follow-ups. We used the same methodology as the one employed in a previous study²⁹ for latent growth modeling.

2.5.2 | Path analysis

Path analyses were conducted to test the association between each plasma biomarker and cognitive performance and change. Specifically, EF and EM level and slope were regressed on $\text{a}\beta$ 42/40, t-tau, and NfL. Sex, education (years), and ethnicity (African Americans, Hispanics, and Whites) were added as covariates in all models.

2.5.3 | Mediation analyses

Only significant associations between plasma biomarker and cognitive performance and change were further tested for mediation with HV. Specifically, HV was added as a mediator to test whether the association between plasma biomarker and cognition is explained by HV (see conceptual model in Figure 1). The mediation model in Mplus Version 7.4 calculates the indirect effect with bias-corrected bootstrapped 95% confidence intervals (CI) method, where the dataset is resampled with replacement over 5000 iterations,³⁰ to test the mediation effect for each path analysis. Significant mediation was determined by

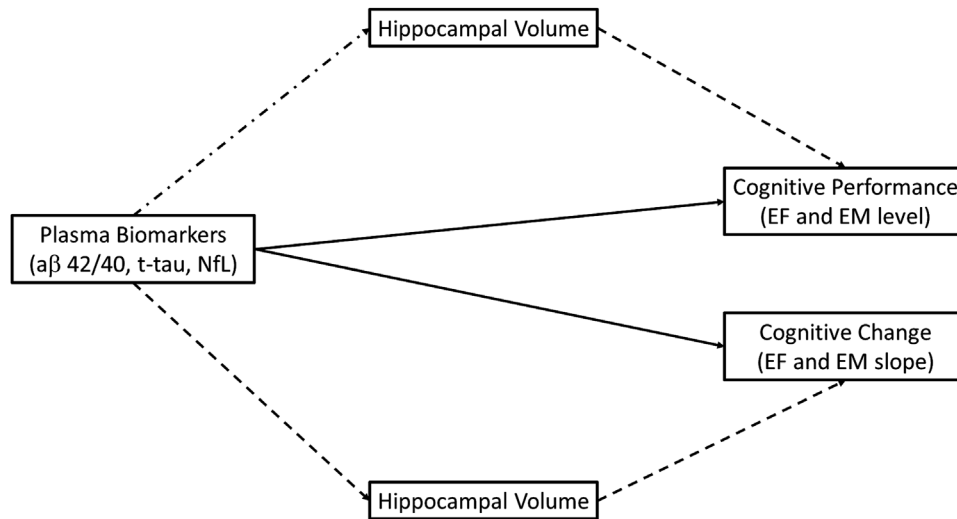


FIGURE 1 Conceptual mediation model. Association between plasma biomarkers (amyloid β 42/40 [$a\beta$ 42/40], total-tau [t-tau], neurofilament light [NfL]) and cognitive trajectories (executive function [EF] and episodic memory [EM]) are mediated by hippocampal volume

examining the model indirect pathway for significance ($P < .05$). Sex, education, and ethnicity were added as covariates in all models. All models were identified as completely mediated when the association between plasma biomarker and cognition was no longer significant and partially mediated when both the association and the mediation was significant.

3 | RESULTS

3.1 | Demographics

Descriptive statistics for all baseline characteristics and comparisons by ethnicity and diagnosis are presented in Table 1. Mean baseline age of participants was 74.80 (7.22) years with 60% female and average education of 12.51 (4.90) years. $a\beta$ 42/40 levels were significantly lower in Whites compared to Hispanics and African Americans. $a\beta$ 42/40 levels also were significantly lower in the demented group compared to MCI or cognitively normal group. The t-tau levels were significantly lower in the cognitively normal group compared to MCI. NfL levels were significantly lower in cognitively normal compared to the MCI or the demented group (see Table 1).

3.2 | Latent growth modeling

To find the best fit approximation of level and change in cognition, we tested five separate models, including non-linear estimates. Using traditional fitting metrics of AIC and BIC, we found stepwise significant improvement of the model by adding a random intercept and slope. We observed that the random intercept (level) and random slope growth model provided the best fit to our EF and EM scores (Supplementary Table S1). Adding a quadratic estimate of change did not improve the model. The random intercept and random slope model showed that

participants varied in their EF and EM level (at 75 years) and slopes over time (Supplementary Figure S1). All level and slope estimates of EF and EM were saved and used as dependent variables in our subsequent models.

3.3 | Path analysis for EF and EM

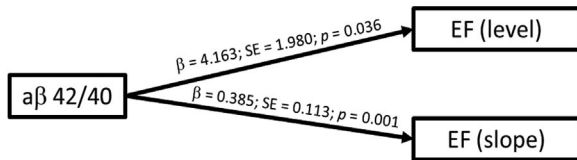
We observed that plasma biomarkers were differentially associated with EF and EM performance and change. First, lower $a\beta$ 42/40 levels were associated with poorer EF (level: $\beta = 4.163$, SE = 1.980, $p = .036$) and EM performance (level: $\beta = 6.902$, SE = 2.957, $p = .020$) and steeper EF (slope: $\beta = 0.385$, SE = 0.113, $p = .001$) and EM (slope: $\beta = 0.272$, SE = 0.128, $p = .034$) decline. We note that to be consistent in our presentation of all three plasma biomarker results, we reversed the association of $a\beta$ 42/40 levels where, higher $a\beta$ 42/40 levels corresponding to higher cognitive performance and less decline is represented as lower $a\beta$ 42/40 levels were associated with lower cognitive performance and steeper decline. Second, higher t-tau was associated with lower EF (level: $\beta = -0.042$, SE = 0.015, $p = .005$) and EM (level: $\beta = -0.050$, SE = 0.022, $p = .025$) performance but did not predict change in cognition. Third, higher NfL was associated with lower EF (level: $\beta = -0.164$, SE = 0.062, $p = .008$) and EM (level: $\beta = -0.263$, SE = 0.094, $p = .005$) performance and steeper EF (slope: $\beta = -0.009$, SE = 0.004, $p = .026$) and EM (slope: $\beta = -0.019$, SE = 0.005, $p < .001$) decline.

3.4 | HV mediations

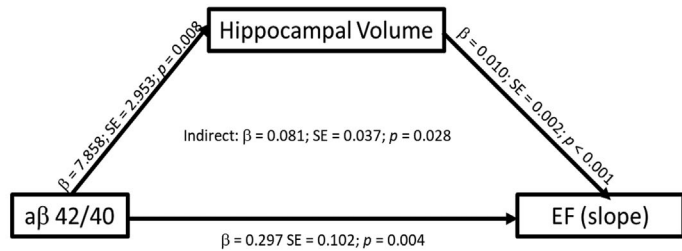
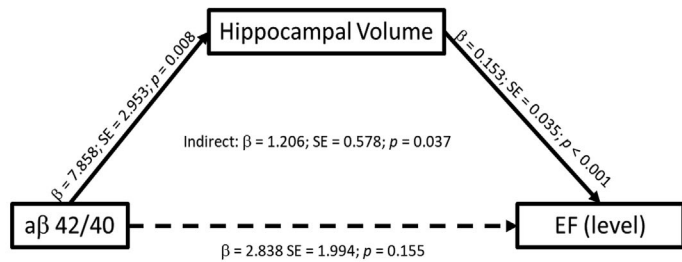
HV differentially mediated the association between each plasma biomarker and cognitive performance and change (Figure 2A–C). First, HV completely mediated the association between lower $a\beta$ 42/40 levels and poorer EF performance and partially mediated steeper EF

A. $a\beta$ 42/20

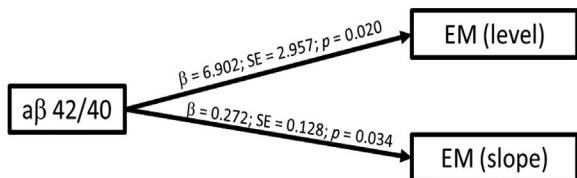
Path Analysis:



Hippocampal Mediation:



Path Analysis:



Hippocampal Mediation:

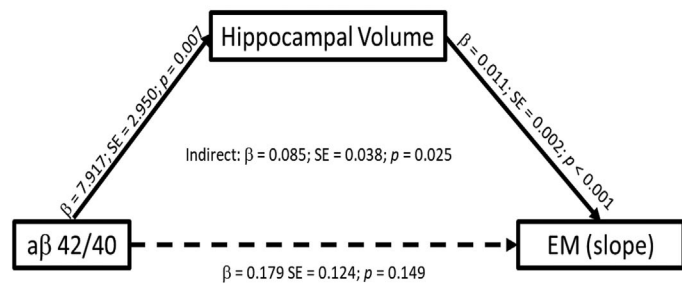
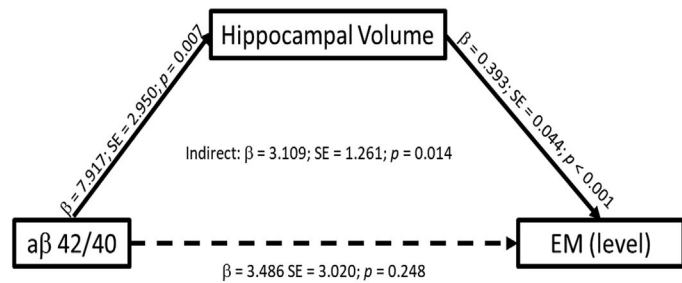
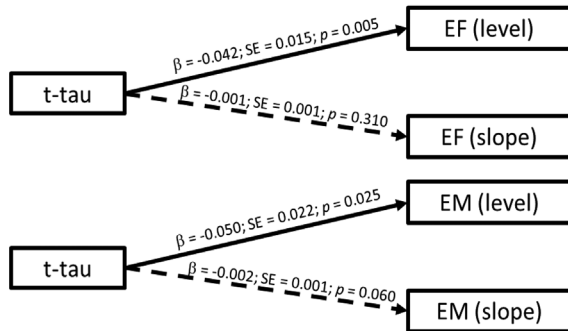


FIGURE 2 Path analysis and hippocampal mediation models for (A) amyloid β 42/40 ($a\beta$ 42/20), (B) total-tau (t-tau), and (C) neurofilament light (NfL) on executive function (EF) and episodic memory (EM) performance (level) and change (slope).

Note: Solid arrows represent significant results and dashed arrows depict insignificant results.

B. t-tau Path Analysis:



Hippocampal Mediation:

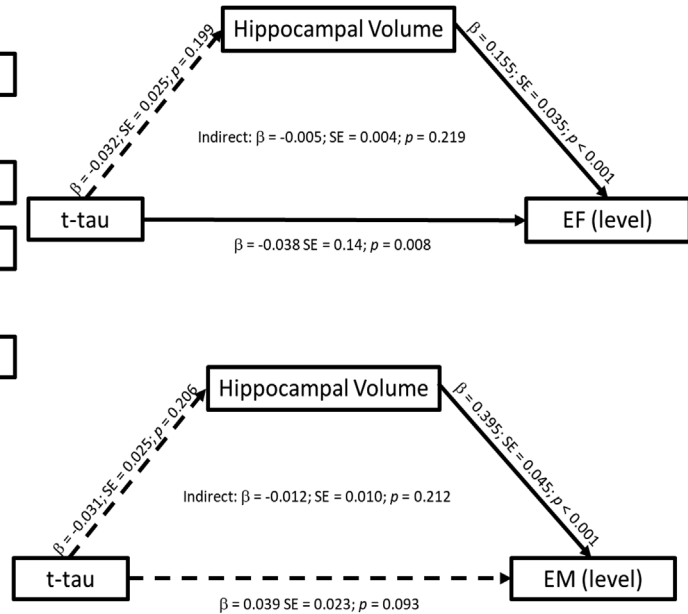


FIGURE 2 Continued

decline. Second, HV completely mediated the association between lower $a\beta$ 42/40 levels and poorer EM performance and steeper decline. For complete details see Supplementary Table S2. Third, there were no significant HV mediations for t-tau with EF or EM performance. Fourth, HV completely mediated the association between higher NfL and steeper EF decline and poorer EM performance (Supplementary Table S2 and Figure 2). Fifth, HV partially mediated the association between higher NfL and steeper EM decline (Supplementary Table S2). We note that time difference in MRI scan and plasma collection as a covariate did not change our overall mediation results.

4 | DISCUSSION

We observed neurodegeneration (represented by HV) selectively mediated the association between key plasma biomarkers on cognitive trajectories in an ethnographically diverse community-based sample. First, lower plasma $a\beta$ 42/40, higher t-tau, and higher NfL predicted lower EF and EM performance, and lower $a\beta$ 42/40 and higher NfL predicted steeper EF and EM decline. Second, this association was partially or completely explained by HV for (1) $a\beta$ 42/40 and EF performance and decline, (2) $a\beta$ 42/40 and EM performance and decline, (3) NfL and EF decline, and (4) NfL and EM performance and decline. Our findings in this cohort suggest that (1) plasma NfL and $a\beta$ 42/40 levels are more sensitive than t-tau in predicting cognitive decline and (2) HV mediates the association between $a\beta$ 42/40 levels and cognition for both EF and EM performance and decline whereas, the association between NfL and EF performance was not mediated. In the paragraphs below, we highlight five aspects related to the importance and significance of these findings.

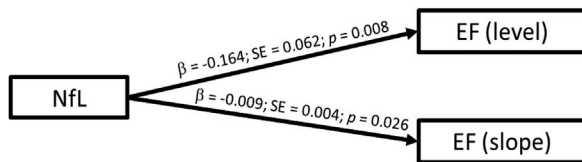
First, the current study is an extension of previous work on plasma NfL³ to detect differences and changes across cognitive domains. Both EF and EM are important for early identification of older adults at risk of accelerated decline and differential diagnosis of dementia.³¹ NfL is hypothesized to be a key marker of axonal injury and neurodegeneration, and plays an important role in nerve conduction velocity of myelinated axons³² and may be sensitive to vascular or AD white matter neurodegeneration.³³ As our cohort included individuals along the spectrum of cognitive performance, we observed significantly lower NfL levels in our cognitively normal group compared to the MCI and demented groups. With sample size limitation in each group, we did not perform mediation analyses as stratified by diagnoses. However, these mean group differences further support our findings for higher NfL (observed in the MCI and demented group) with poorer EF and EM performance and steeper decline.

Second, we note that t-tau was significantly related to cognitive performance but did not predict cognitive change. Although the concentration of $a\beta$ 42/40, p-tau, t-tau, and NfL in plasma are much lower than in CSF,³⁴ recent studies using a range of ultrasensitive assays have shown significant associations with each of the four plasma biomarkers and cognition.^{9,34,35} Our findings suggest that compared to $a\beta$ 42/40 and NfL, plasma t-tau may not fully capture high risk cognitive decline profiles⁸ in an ethnographically diverse group or early clinical phase of dementia.³⁶

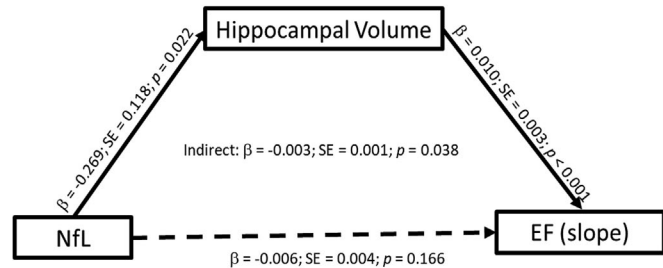
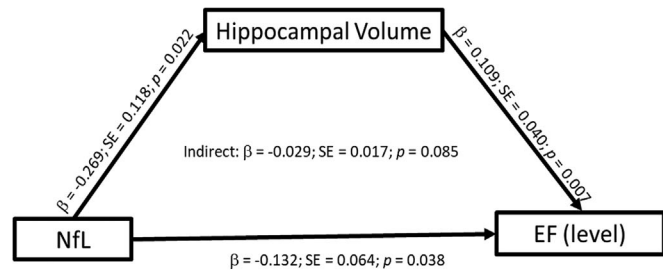
Third, $a\beta$ 42/40 is a key player in AD pathogenesis,³⁷ and as expected, we observed lower plasma $a\beta$ 42/40 levels predicted lower cognitive performance and steeper decline even in our ethnographically diverse cohort. Although inconclusive, our results suggest that plasma $a\beta$ 42/40 levels are representative of both EF and EM

C. NFL

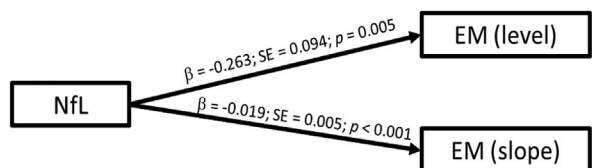
Path Analysis:



Hippocampal Mediation:



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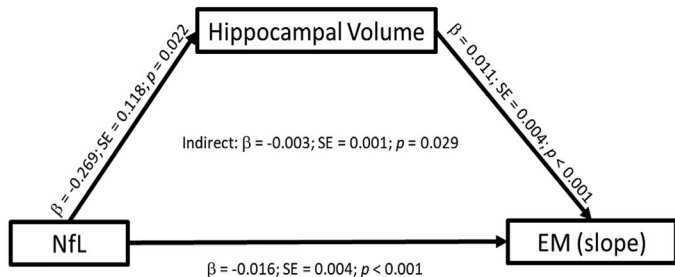
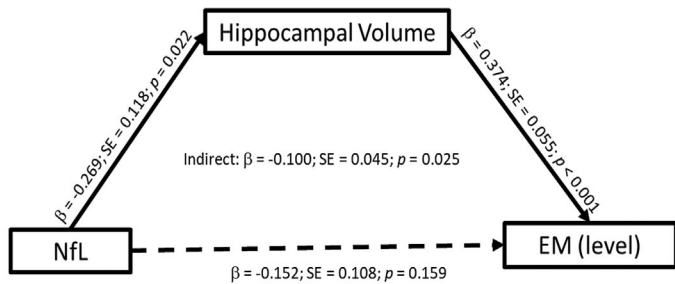


FIGURE 2 Continued

changes. Future work should consider examining how plasma $a\beta$ 42/40 levels associate with amyloid in the brain and how decline in other cognitive domains may be partially affected or possibly even precede memory deterioration.³⁸ We also observed that $a\beta$ 42/40 levels were lower in Whites compared to Hispanics and African Americans in our cohort. This finding suggest $a\beta$ 42/40 levels may

be reflective of different underlying neuropathological mechanisms influencing cognitive trajectories in different racial/ethnic groups^{11,12} as previously shown by our group.¹⁵ While previous studies report that plasma $a\beta$ 42/40 are positively correlated with CSF $a\beta$ 42/40⁴ and amyloid PET positivity,³⁹ our findings raise the question of whether plasma $a\beta$ 42/40 biomarkers are similarly correlated with

established CSF and PET biomarkers of dementia in different racial/ethnic groups.⁴⁰

Fourth, we observed the association between $a\beta$ 42/40 levels and cognition is partially or fully explained through HV. Hippocampal atrophy, an important indicator of neurodegeneration in ADRD and memory decline,⁴¹ may provide a pathway through which $a\beta$ 42/40 levels are associated with EF and EM performance and decline. It is also important to note this pathway may be more sensitive to EM decline than EF decline, since EF decline was only partially mediated through HV. Previous reports have focused on a global cognitive measure⁹ as the primary outcome to examine plasma $a\beta$ 42/40 and cognitive associations. We extend this work and provide novel insight on potential underlying differences between plasma biomarkers across cognitive domains (EF versus EM trajectories) in a clinically and ethnographically heterogeneous population.

Fifth, HV selectively mediated the association between NfL and our two cognitive domains. Specifically, HV completely explained the association between NfL and EM performance and EF decline, and partially explained the association between NfL and EM decline in our cohort. Elevated NfL levels, which reflects greater axonal degeneration and injury, in combination with hippocampal atrophy, may represent higher risk of EF decline and lower EM performance. In previous research, elevated plasma NfL has been shown to predict right hippocampal atrophy in AD patients⁴² and is highly correlated with CSF NfL,³ t-tau, p-tau, and $a\beta$ 42/40.⁴³ Recent work also suggest low plasma NfL levels protect against prodromal AD through elevated cortical microglial activation.⁴⁴ Hippocampal atrophy is highly associated with EM performance⁴⁵ and, in synergy with elevated NfL, may explain the observed steeper EF decline and poorer EM performance and decline. In our findings, HV did not mediate the association between NfL and EF performance. This suggests the mediation for NfL and EF (level) associations may occur through other brain structures (e.g., frontal lobes; white matter injury) and should be considered in future work. Although high NfL levels are not considered to be disease specific but reflects overall neurodegeneration, our finding with higher NfL predicting lower EF and EM performance and steeper decline, suggests that NfL mediation with hippocampal atrophy may indicate processes beyond white matter injury that influences multiple cognitive domains and longitudinal change.

Our study has strengths as well as limitations. A first strength is that our plasma biomarker findings replicated the cognitive decline observed with more established CSF ($a\beta$, t-tau, NfL) and PET (amyloid and tau) results. We extended this finding by showing that a key neurodegenerative marker, HV, selectively mediates this association for two important cognitive domains in a large ethnographically and clinically diverse cohort of community based older adults. Second, in our longitudinal data analyses, we examined age as the metric of time, which allowed us to incorporate chronological age directly into our analyses. This approach allowed us to account for any variability associated with age on the two cognitive domains and examine change across a 50-year band of aging. Third, we included two well established cognitive domains (EF and EM) in cognitive aging and dementia research. Both cognitive factors include a range of standard neuropsychological tests

and have been extensively validated to be invariant, both across ethnic groups and longitudinally.²⁷ Fourth, although, the present work is limited to plasma biomarkers, we observed similar findings in the literature with corresponding CSF and PET biomarkers, which are highly invasive and expensive AD biomarkers.

Regarding limitations, first, inconsistent and negative results have been observed between plasma and CSF $a\beta$ 42 levels in AD,⁴⁶ suggesting these differences may be due to assay techniques and the smaller concentration present in blood versus CSF. Future work should consider including CSF biomarkers in addition to amyloid and tau PET markers to make relevant comparisons.⁴⁷ Second, we did not examine our mediation models with other brain regions,⁴⁸ nor as stratified by clinical diagnoses, ethnicity, and *Apolipoprotein E* ϵ 4 status. Future studies with larger sample sizes are needed to account for differential plasma biomarker levels and brain morphometry and to make accurate conclusions regarding ethnicity, clinical, and genetic differences. Third, we did not analyze p-tau levels in addition to our t-tau measures. Previous studies have reported inconsistent findings between plasma p-tau and t-tau in AD⁵⁰ and future studies with the availability of both p-tau and t-tau should consider investigating both biomarkers to elucidate these discrepancies as p-tau may be more sensitive to detect changes in cognition.³⁵ Fourth, our plasma biomarkers data were only measured at baseline, and longitudinal data as well as post-mortem diagnoses to denote the underlying pathophysiology of dementia biomarkers are needed to provide an in-depth understanding of the association between change in plasma biomarkers with cognitive changes in a heterogeneous population.

In sum, we observed that the associations of plasma $a\beta$ 42/40 and NfL, with cognitive performance and trajectory, is differentially mediated by HV in an ethnographically and clinically diverse cohort. Future work should consider examining the underlying molecular pathways to understand how neurodegeneration may mediate the risk observed with non-invasive plasma biomarkers in dementia. Understanding the underlying neural and pathological mechanisms for blood-based biomarker pathways may lead to early identification of high dementia risk profiles in clinical practice and person-centered intervention programs in diverse populations.

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CONFLICT OF INTEREST

All authors report no disclosures relevant to the manuscript. Author disclosures are available in the supporting information.

AUTHOR CONTRIBUTIONS

Shraddha Sapkota drafted the manuscript, participated in the study concept and design, analyzed, and interpreted the data. Kelsey Erickson, Danielle Harvey, Tiffany Kautz, and Danielle Parent contributed towards plasma biomarker analysis. Charles DeCarli obtained funding, designed the study, participated in the analysis,

and critical review of the final manuscript. All authors revised the manuscript.

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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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