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RESEARCH ARTICLE

Association of cardiovascular risk factors and blood biomarkers with cognition: The HABS-HD study

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Abstract

Introduction: To determine if cardiovascular risk factor (CVRF) burden is associated with Alzheimer's disease (AD) biomarkers and whether they synergistically associate with cognition.

Methods: We cross-sectionally studied 1521 non-demented Mexican American (52%) and non-Hispanic White individuals aged ≥50 years. A composite score was calculated by averaging the z-scores of five cognitive tests. Plasma β-amyloid (Aβ) 42/40, total tau (t-tau), and neurofilament light (NfL) were assayed using Simoa. CVRF burden was assessed using the Framingham Risk Score (FRS).

Results: Compared to low FRS (< 10% risk), high FRS (≥ 20% risk) was independently associated with increased t-tau and NfL. High FRS was significantly associated with higher NfL only among Mexican American individuals. Intermediate or high FRS (*vs.* low FRS) were independently associated with lower cognition, and the association remained significant after adjusting for plasma biomarkers. Hypertension synergistically interacted with t-tau and NfL ($p < 0.05$).

Discussion: CVRFs play critical roles, both through independent and neurodegenerative pathways, on cognition.

KEYWORDS
amyloid, blood biomarkers, cardiovascular risk factors, cognition, Hispanic, Mexican American, neurofilament light, tau

1 | BACKGROUND

An estimated 6.2 million Americans age 65 years and older are living with Alzheimer's disease (AD) related dementia (ADRD).[1] Cardiovascular risk factors (CVRFs), including hypertension, dyslipidemia, diabetes mellitus, obesity, and smoking, are key modifiable risk factors for ADRD.[2,3] CVRFs may contribute to cognitive decline and dementia through vascular pathways such as small vessel diseases, which commonly co-occur with AD-related pathology in older adults.[4,5] However, it is less well understood whether CVRFs are directly associated with neurodegenerative pathways specifically associated with AD. Previous studies on the association between CVRFs and AD pathology (e.g., amyloid and tau deposition) have been inconsistent.[6–10]

Findings from neuroimaging and pathological studies indicate that vascular pathology may lower the threshold of AD pathology for cognitive impairment, suggesting that the combination of CVRFs and AD pathology may have a greater impact on cognition than their additive effect.[11,12] However, findings from small cohort studies have been mixed regarding whether CVRFs and AD pathology additively or synergistically contribute to cognitive aging.[9,13,14] Evidence from large, population-based studies is lacking. Furthermore, studies in ethnically diverse cohorts are lacking, although CVRFs and AD disproportionately impact ethnic minorities, such as Mexican Americans (MAs).[15–17]

Recently, key plasma biomarkers based on the AT(N) framework, including β-amyloid (Aβ), tau, and neurofilament light (NfL), have emerged as less invasive and inexpensive tools to detect and diagnose AD.[18–21] The availability of plasma biomarkers, including Aβ, total tau (t-tau), and NfL, in the Health and Aging Brain Study: Health Disparities (HABS-HD) allows us to study the relationship of CVRFs with Aβ and neurodegenerative pathways and their interactions in a large, bi-ethnic population of middle-aged and older adults. The goal of this study is to investigate whether (1) CVRF burden is associated with plasma biomarker levels, and (2) CVRFs and plasma biomarkers synergistically associate with cognition in middle-aged and older adults.

RESEARCH IN CONTEXT

1. **Systematic Review**: Several studies have evaluated the associations between cardiovascular risk factors (CVRFs) and Alzheimer's disease (AD) biomarkers, and the findings have been mixed. Findings on the synergistic association of CVRFs and β-amyloid (Aβ) were inconsistent. Less is known about tau and neurofilament light (NfL).
2. **Interpretation**: CVRF burden is associated with increased plasma total tau and NfL levels, but not Aβ 42/40, suggesting the contribution of CVRF to neurodegenerative pathways. The differential association between CVRF burden and NfL indicates the presence of ethnic-specific mechanisms. CVRFs may contribute to worse cognition partially through associations with neurodegeneration and, more importantly, through other pathways that may synergistically interact with neurodegeneration.
3. **Future Directions**: The Health and Aging Brain Study: Health Disparities is an ongoing study; therefore, longitudinal associations and synergistic interactions between CVRFs and AD biomarkers in middle-aged and older adults will be critical to understand the mechanisms of CVRF in cognitive aging.

2 | METHODS

2.1 | Study population

We cross-sectionally analyzed baseline data from the HABS-HD study.[16] Briefly, the HABS-HD study is an ongoing, community-based cohort study of cognitive aging among MA and non-Hispanic White (NHW) older adults at the University of North Texas Health Science Center, Fort Worth, Texas. Since 2017, 1705 MA and NHW individuals, aged ≥ 50 years who were willing to provide blood samples and capable of undergoing neuroimaging studies have enrolled. Individuals with type 1 diabetes, severe mental/physical illness that could impact study participation, and active alcohol/substance abuse were excluded. Participants were invited to complete a clinical interview, neuropsychological assessment, functional examination, and blood draw for clinical and biomarker analysis. The HABS-HD study is conducted under institutional review board–approved protocols, and all participants and/or caregivers sign written informed consent. The HABS-HD study data are publicly available through the University of North Texas Health Science Center Institute for Translational Research website.

Of the 1705 MA and NHW individuals in HABS-HD, 116 (6.8%) were diagnosed with dementia and were excluded from our analysis. Dementia diagnoses were adjudicated at consensus review based on the clinician-administered Clinical Dementia Rating Scale (CDR) sum of boxes ≥2.5 or cognitive z-scores at least 2 standard deviations (SD) below the mean on two or more neuropsychological tests.[16] Participants with mild cognitive impairment were not excluded. Of the 1589 non-demented participants, 59 (3.7%) and 9 (0.6%) participants were missing all plasma biomarkers and blood cholesterols, respectively. For the current study, we analyzed 1,521 non-demented, community-dwelling MA and NHW individuals, aged ≥50 years.

2.2 | Cognitive function assessment

A standard battery of cognitive tests was administered consisting of the Trail Making Test, Parts A and B (measures of attention and executive function),[22] the Digit-Symbol Substitution Test (a measure of processing speed),[23] verbal fluency tests of FAS and Animal Naming,[23] and the Spanish English Verbal Learning Test, 30 min-delayed recall (a measure of verbal memory).[24] We computed a cognitive composite score by averaging the z-standardized test scores of all tests.

2.3 | Cardiovascular risk factors

At baseline, CVRFs were classified during the HABS-HD consensus review based on lab values, objective measures, self-report, and current medication use.[16] We defined hypertension as at least two readings of systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or with a medical history and use of medications. We defined diabetes as hemoglobin A1c (HbA1c) ≥ 6.5% or with a medical history and use of medications. We defined dyslipidemia as low-density lipoprotein (LDL) cholesterol ≥120 mg/dL, total

cholesterol ≥240 mg/dL, triglycerides ≥200 mg/dL, or with a medical history and use of medications. Cigarette smoking was based on self-reported current smoking. We used height and weight from the baseline exam to calculate body mass index (BMI) and defined obesity as a BMI ≥30 kg/m^2. Participants underwent a collection of fasting blood at baseline, which was then assayed for a comprehensive metabolic panel, lipid panel, and HbA1c. Information on systolic and diastolic blood pressure, HbA1c, height and weight, LDL cholesterol, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were collected at the baseline exam.

We assessed aggregated CVRF burden using the Framingham Risk Score (FRS),[25] a sex-specific algorithm based on age, total cholesterol, HDL cholesterol, systolic and diastolic blood pressures, smoking, and diabetes. FRS was initially developed to assess risk of coronary heart disease (CHD),[25,26] and has been shown to be associated with cognitive decline and brain pathology.[27–29] We defined low, intermediate, and high FRS as having 10-year CHD risk of <10% (female FRS <10; male FRS <6), 10% to 19% (female FRS 10-14; male FRS 6-8), and ≥ 20% (female FRS ≥15 male FRS ≥9), respectively.[25]

2.4 | Plasma biomarkers

Baseline fasting blood collection was completed within 2 hour (stick-to-freezer).[30] The ultra-sensitive Quanterix Simoa (single molecule array) HD-1 platform was used for the assay of plasma Aβ 40, Aβ 42, and t-tau (three-plex plate), as well as NfL. The detection limit is 0.196 pg/ml for Aβ 40, 0.045 pg/ml for Aβ 42, 0.019 pg/ml for t-tau, and 0.038 for NfL. More than 5000 assays have been conducted for the samples, and the mean coefficients of variation for all assays were ≤ 5%.

2.5 | Covariates

Demographic characteristics (age, sex, ethnicity), socioeconomic status (SES; marital status, insurance, household income), and education were from self-report. Hazardous/dependent alcohol use was assessed by the Alcohol Use Disorders Identification Test (AUDIT) questionnaire at baseline interview (AUDIT score ≥8).[31] Physical activity was assessed by the Rapid Assessment of Physical Activity (RAPA) questionnaire and dichotomized as physically active (RAPA score ≥6). Depression was assessed using the Geriatric Depression Scale (GDS) and defined as GDS ≥10 or with medical history. Apolipoprotein E (APOE) genotype and serum creatinine was ascertained at baseline using standard techniques. Self-reported medical history, including coronary heart disease and stroke/transient ischemic attack (TIA), were collected from interview.

2.6 | Statistical analysis

Descriptive statistics for participant characteristics, plasma biomarker levels, and cognitive performance were compared by low, intermediate, and high FRS using χ^2 and Kruskal-Wallis tests. Because of skewness, serum creatinine, and plasma biomarkers were natural log-transformed in models. The associations between FRS with plasma biomarkers were estimated using linear regression models adjusting for confounders. To identify a minimally sufficient set of measured confounders to be adjusted for,[32,33] we constructed directed acyclic graphs (DAGs) considering factors associated both with FRS and plasma biomarkers (Table 1, Supplemental Table and Figure). We conceptualized that SES may be associated with plasma biomarkers and cognition primarily through its association with CVRFs, education, behavior factors (physical activity and alcohol use), and depression. In a preliminary analysis, SES was not independently associated with plasma biomarkers or cognition when other factors were adjusted for. Therefore, we determined that adjustment for demographics (age, sex, ethnicity), education, APOE, behavior factors, renal function, and depression was minimally sufficient to control for confounding in estimating the associations between FRS and biomarkers. Parameter estimates were back-transformed to represent the percent increase in each biomarker, comparing participants with intermediate or high versus low FRS. Ethnic differences in the FRS-biomarker associations were also assessed.

To determine whether CVRFs and plasma biomarkers synergistically associate with cognition, we first estimated the independent associations of FRS with the composite cognitive score using multivariable-adjusted linear regression with additional adjustment for plasma biomarkers. We then examined the presence of an interaction between FRS and each plasma biomarker one at a time, adjusting for covariates (e.g., composite cognitive score ~ FRS + Aβ 42/40 + FRS x Aβ 42/40 + covariates). The presence of interactions between each biomarker and individual CVRFs, including hypertension, diabetes, dyslipidemia, obesity, and current smoking, were also assessed one at a time (e.g., composite cognitive score ~ hypertension + Aβ 42/40 + hypertension x Aβ 42/40 + covariates). Additionally, we conducted stratified analyses to estimate the association between biomarkers and cognition by FRS levels or CVRF when a significant interaction between FRS or a CVRF and a biomarker was present. Similarly, we determined using DAGs that the minimally sufficient set of measured confounders included demographics, education, behavior factors, renal function, physical activity, and depression (Table 1, Supplemental Table and Figure). In sensitivity analysis, we further adjusted for the other CVRFs when an individual CVRF was assessed; excluded participants with stroke/TIA or with plasma biomarker levels at the 1st and 99th percentiles (to limit the impact of extreme values). Two-sided statistical tests were conducted, and $p < 0.05$ was considered statistically significant. Statistical analyses were conducted with SAS (version 9.4).

3 | RESULTS

The mean age of the 1521 participants (61% female and 52% MA individuals) was 66.3 ± 8.7 years. The median FRS was 8 (interquartile range [IQR], 5 to 10), with 36% and 15% having intermediate and high FRS, respectively. Compared to participants with low FRS, those with higher FRS were more likely to be older, male, MA individuals, APOE

TABLE 1 Characteristics of the 1521 HABS-HD participants by low, intermediate, and high FRS

	Low FRS $n = 740$	Intermediate FRS, $n = 547$	High FRS, $n = 234$	p-value*
Age, years, median (IQR)	65 (57.5-72)	66 (61-72)	69 (63-73)	< 0.001
Female, n (%)	585 (79)	284 (52)	61 (26)	< 0.001
Mexican American, n (%)	311 (42)	326 (60)	150 (64)	< 0.001
Education ≥ high school, n (%)	576 (79)	369 (68)	148 (64)	< 0.001
Hazardous/dependent alcohol use, n (%)	17 (2)	24 (4)	12 (5)	0.042
Physically active, n (%)	261 (35)	177 (32)	64 (27)	0.07
APOE ε4 carrier, n (%)	195 (26)	100 (18)	47 (20)	0.002
Hypertension, n (%)	356 (48)	395 (72)	201 (86)	< 0.001
Diabetes, n (%)	61 (8)	179 (33)	131 (56)	< 0.001
Dyslipidemia, n (%)	433 (59)	389 (71)	177 (76)	< 0.001
Current smoking, n (%)	16 (2)	31 (6)	35 (15)	< 0.001
Obesity, n (%)	263 (36)	289 (53)	111 (48)	< 0.001
Creatinine, mg/dL, medium (IQR)	0.78 (0.67-0.91)	0.85 (0.7-1)	0.92 (0.78-1.09)	< 0.001
Coronary heart disease, n (%)	28 (4)	30 (5)	13 (6)	0.28
Stroke/TIA, n (%)	29 (4)	27 (5)	10 (4)	0.68
Depression, n (%)	235 (32)	186 (34)	68 (29)	0.38

Abbreviations: APOE, apolipoprotein E; FRS, Framingham Risk Score; HABS_HD, Health and Aging Brain Study: Health Disparities; IQR, interquartile range; TIA, transient ischemic attack.

*Chi-squared test for categorical variable and Kruskal-Wallis tests for continuous variables. Participants with missing information: education 15 (1%), APOE 5 (0.3%), physical activity 1(0.1%).

ε4 non-carrier, have hazardous/dependent alcohol use and higher creatinine levels, and with lower education (Table 1). Participants with intermediate and high FRS had significantly lower mean composite cognitive scores (intermediate *vs.* low: -0.29; 95% confidence interval [CI], -0.37 to -0.22; high *vs.* low: -0.45; 95% CI -0.55 to -0.35) than those with low FRS (both $p < 0.001$). Plasma biomarkers and cognitive score by subgroups of participants were compared in Tables SI and SII.

3.1 | Association of cardiovascular risk factor burden with plasma biomarkers

After adjusting for demographics, APOE, and education, high (*vs.* low) FRS was associated with increased t-tau (8.5%, 95% CI 1.9% to 15.6%) and NfL (14.2%, 95% CI 5.8% to23.2%). Those with intermediate and low FRS were not significantly different in t-tau and NfL levels, and FRS was not associated with Aβ 42/40 levels ($p > 0.05$). The associations of FRS with t-tau and NfL remained largely unchanged with additional adjustments for alcohol use, physical activity, and depression (Table 2). High (*vs.* low) FRS remained significantly associated with increased NfL (10%, 95% CI 2.4% to 18.2%, $p = 0.009$) and marginally significantly associated with increased t-tau (5.7%, 95% CI -0.6% to 12.4%, $p = 0.07$) after further adjustment for serum creatinine. The interaction between FRS and ethnicity was significant for NfL ($p = 0.012$). Specifically, participants with high FRS had a significantly higher NfL only in MA individuals (20.9%, 95% CI 8.6% to 34.7%) but not in NHW individuals (4.4%, 95% CI -6.2% to 16.2%). There was no evidence of an interaction between FRS and ethnicity for Aβ 42/40 or t-tau (both $p > 0.05$).

3.2 | Assessment of synergistic associations between cardiovascular risk factors and plasma biomarkers

Intermediate and high (vs. low) FRS were significantly associated with lower cognitive performance (intermediate: β = -0.09, 95% CI -0.15 to -0.03; high: β = -0.13, 95% CI -0.22 to -0.05) after adjusting for demographics and education. Further adjusting for alcohol use, physical activity, depression, and serum creatinine did not appreciably change the results. The association between FRS and lower cognitive performance remained significant after adjusting for Aβ 42/40, t-tau, and NfL (intermediate *vs.* low: β = -0.09, 95% CI -0.15 to -0.03; high *vs.* low: β = -0.11, 95% CI -0.20 to -0.03), indicating that the contribution of CVRF to worse cognition was independent of biomarkers.

In the extended models, the interactions between FRS and each plasma biomarker were not statistically significant ($p > 0.05$ for interactions). However, when individual CVRF (hypertension, diabetes, dyslipidemia, obesity, and current smoking) was assessed separately with Aβ 42/40, t-tau, and NfL one at a time, the interactions of hypertension with t-tau and NfL were statistically significant ($p = 0.047$ and 0.002, respectively, Figure 1) after adjusting for all covariates,

TABLE 2 Multivariable-adjusted association of Framingham Risk Score (FRS) with Alzheimer's disease biomarkers

	Model 1 β (95% CI)		Model 2 β (95% CI)	
	Intermediate vs. Low FRS	High vs. Low FRS	Intermediate vs. Low FRS	High vs. Low FRS
Aβ 42/40, $n = 1512$	−0.3% (−3.2% to 2.8%)	−2.1% (−6.1% to 2.1%)	−0.4% (−3.3% to 2.7%)	−2.1% (−6.1% to 2.1%)
Total tau, $n = 1513$	4.5% (−0.1% to 9.3%)	8.5% (1.9% to 15.6%)	4.1% (−0.5% to 8.9%)	7.7% (1.1% to 14.7%)
Neurofilament light, $n = 1508$	−0.9% (−6.2% to 4.6%)	14.2% (5.8% to 23.2%)	−1.7% (−6.9% to 3.8%)	13.4% (5.1% to 22.3%)

Note: Model 1 adjusted for demographics (age, sex, and ethnicity), APOE, and education; Model 2 additionally adjusted for physical activity, alcohol use, and depression. Estimated associations (β) were derived from the regression coefficients and back transformed to represent the percent difference in biomarkers comparing participants with Intermediate (10% to 19% risk) or high (≥ 20% risk) FRS with low FRS (< 10% risk). Abbreviations: Aβ, β-amyloid; CI, confidence interval.

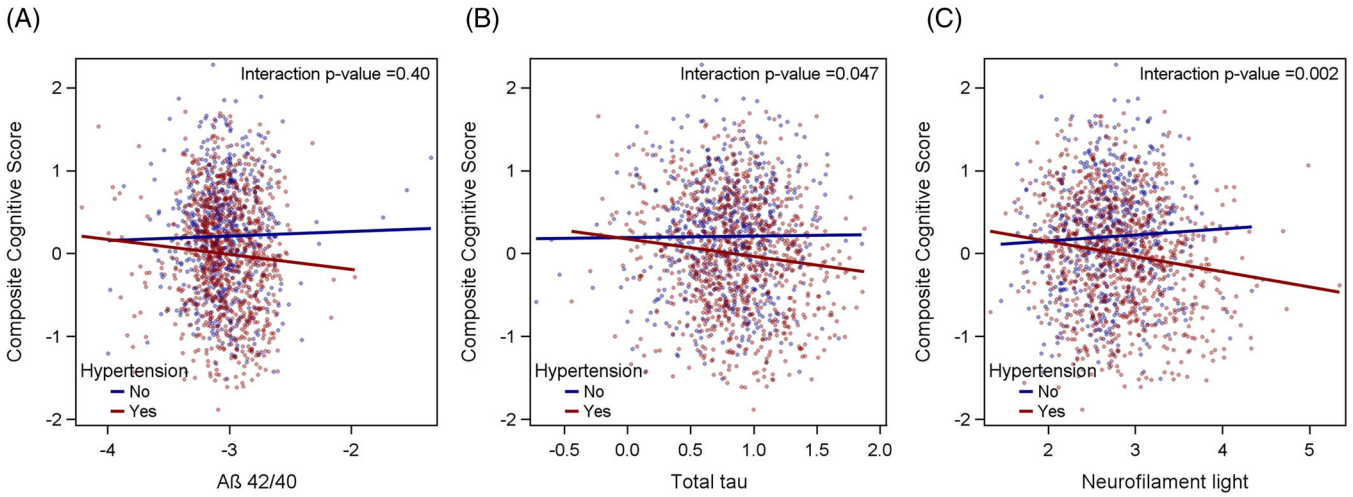

FIGURE 1 Hypertension interacts with plasma biomarkers on cognitive performance. Associations of plasma Aβ 42/40, total tau, and neurofilament light with the composite cognitive score in participants with and with hypertension. Abbreviations: Aβ = β-amyloid.

suggesting that hypertension together with increased t-tau and NfL were associated with worse cognition more than their additive effect. The interaction between hypertension and Aβ 42/40 was not significant ($p = 0.40$). Further adjustment for other CVRFs and excluding participants with stroke/TIA or extreme biomarker values (1st and 99th percentiles) did not appreciably change the results. In stratified analysis, 1 unit increase in t-tau and NfL (both natural log-transformed) was more strongly associated with worse cognitive performance in participants with hypertension (t-tau: β = -0.11, 95% CI -0.20 to -0.02; NfL: β = -0.14, 95% CI -0.22 to -0.07) than in without hypertension (t-tau: β = 0.06, 95% CI -0.06 to 0.19; NfL: β = -0.01, 95% CI -0.1 to 0.13). Diabetes, dyslipidemia, obesity, and current smoking had no significant interaction with plasma biomarkers (all $p > 0.05$).

4 | DISCUSSION

In this bi-ethnic cohort of nondemented, middle-aged and older adults, we found that greater CVRF burden measured by FRS was cross-sectionally associated with higher plasma t-tau and NfL, but not Aβ 42/40, which was independent of demographics, education, APOE, physical activity, alcohol use, and depression. The association between FRS and NfL was only in MA individuals but not NHW individuals. FRS was also associated with cognition, independently of plasma biomarkers. We also found synergistic interactions of hypertension with t-tau and NfL, whereby t-tau and NfL were primarily associated with cognition among those with hypertension. These results suggest that CVRFs may contribute to worse cognitive performance partially through their association with neurodegenerative pathways involving these biomarkers, more importantly, through other potential comorbid changes that may synergically interact with neurodegeneration.

Previous studies on the association between CVRF and AD biomarkers have mainly focused on Aβ with mixed findings. CVRF burden has been linked to Aβ deposition in late life. A study from the Atherosclerosis Risk in Communities (ARIC) found that a higher number of CVRFs in midlife was associated with elevated Aβ measured using positron emission tomography (PET) at 76 ± 5.3 years.[6] However, a study in the British 1946 birth cohort did not find an association between FRS

and PET Aβ among people aged 69 to 71 years.[8] Less is known about other biomarkers, such as tau and NfL. A CVRF count was not associated with CSF t-tau and phosphorylated tau (p-tau) levels among middle-aged adults (56 ± 11 years).[9] However, a study among slightly older adults (61±8.5 years) found that the Cardiovascular Risk Factors, Aging and Dementia Study (CAIDE) risk score (without APOE) was associated with CSF t-tau levels.[10] Our findings on the association of FRS with plasma t-tau and NfL align with results from the Alzheimer's Disease Neuroimaging Initiative, where cerebrovascular disease was associated with plasma t-tau and neurofibrillary pathology severity.[34]

Most prior studies have focused on PET and CSF biomarkers. Our findings add to the standing debate on whether CVRF contributes to the accumulation of Aβ. Our results support the recent findings that CVRF burden was not associated with PET and CSF Aβ among middle-aged and older adults.[8,9] Our results need to be interpreted with caution. Although plasma Aβ using Simoa (Neurology 3-Plex) HD-1 platform has been shown to have modest-high sensitivity and specificity in detecting abnormal CSF-amyloid status and PET Aβ positivity,[35,36] plasma biomarkers, including Aβ, have both central and peripheral sources, and the role of peripheral biomarkers in AD-related pathologies is not well understood.[37] Plasma biomarkers may be less sensitive to changes compared to CSF biomarkers.[35] Differences between cohorts, especially the age of neuroimaging or biomarker assessment, race and ethnic diversity, as well as measurement used for CVRF burden, might contribute to different findings.

Importantly, we also found synergistic interactions of hypertension with plasma t-tau and NfL, suggesting that the presence of vascular risk factor and neurodegenerative biomarkers in combination may be associated with a greater risk of cognitive aging than their additivity. Previous neuropathological and neuroimaging studies have suggested a synergistic effect of infarction and AD pathology (plaques and neurofibrillary tangles), or white matter hyperintensities and plasma tau, on cognition or AD diagnosis.[11,12,34,38,39] Findings on aggregated CVRF burden and with Aβ were mixed. A synergistic effect between FRS and PET Aβ burden on cognitive decline has been reported in a longitudinal cohort (aged 74 ± 6 years followed up for 3.7 ± 1.2 years),[7] while others found the combined effect of CVRF burden with CSF Aβ to be no more than additive.[9,14,40] Our findings aligned with the results from neuropathological studies, although we also did not find a significant interaction between FRS and Aβ levels suggesting that the mechanism of the synergistic interaction may be specific to individual CVRF and neurodegenerative biomarkers.

The mechanisms underlying the association of CVRFs with plasma biomarkers and a synergistic interaction are unclear but may involve mixed vascular and neurodegenerative pathways. Our findings indicate that the association between CVRF burden and cognition may be partially attributable to the direct association with tau and neurodegenerative pathology. Cerebrovascular diseases, such as white matter hyperintensities, infarction, lacunes, and microbleeds, resulting from long-term exposure to CVRFs, may directly contribute to tau and neurofibrillary pathology but also synergistically interact with tau-related pathology in relation to dementia.[11,12,34,39,41] Hypoperfusion occurs in hypoxia-ischemia-induced white matter injury and may both promote tau pathology and enhance its impact on AD expression.[34,42] CVRF may independently be associated with cortical atrophy, contributing to neurodegeneration.[10] More research is needed to elucidate the specific mechanisms for individual CVRF in modifying the clinical expression of AD.

Recently, plasma biomarkers have emerged as inexpensive and minimally invasive tools to identify individuals with increased risk of AD. Our findings on the association between CVRF and cognition, both dependent and independent of neurodegenerative biomarkers, as well as their synergistic interactions, raise the question of whether CVRF needs to be considered as a confounder and effect modifier when utilizing plasma neurodegenerative biomarkers in risk stratification for AD. Our findings need to be confirmed in additional studies, especially in diverse populations, where CVRF burden may be greater and more strongly associated with neurodegeneration. The observed ethnic differences in the association between FRS and NfL suggest that ethnic-specific mechanisms may be present in vascular contributions to neurodegeneration. Critical questions remain regarding whether this may contribute to the ethnic disparities in cognitive aging. More studies on racially and ethnically diverse populations are warranted.

Our findings in the associations with plasma biomarkers are novel but may need to be interpreted with caution. Compared with PET and CSF biomarkers, such as Aβ and p-tau, the role of plasma t-tau and NfL in AD is less clear. Although plasma t-tau is an indicator of neurofibrillary tangles and neuronal damage, it may not be AD-specific.[43–46] Biomarkers more specific to AD, such as CSF and plasma p-tau, were only weakly associated with t-tau.[44,46] Plasma NfL correlates with CSF NfL and has diagnostic accuracy for AD.[47] However, it reflects nonspecific axonal damage and may elevate in other neurodegenerative disorders. Therefore, our findings on plasma t-tau and NfL but not Aβ 42/40 more likely reflect neurodegeneration rather than AD-specific pathways.

This is one of the largest population-based studies examining the association of CVRFs with AD biomarkers and their synergistic interaction in diverse communities. We found robust associations of aggregate CVRF burden with t-tau and NfL in a relatively young community of older adults, whereas prior studies focused mostly on Aβ later in life.[6,48] We also detected a significant synergistic interaction of hypertension with t-tau and NfL, further supporting the critical and multimodal roles of CVRFs in cognitive aging. With a large number of MA individuals, we found an ethnic-specific association between CVRF burden and NfL, highlighting the importance of considering ethnic-specific pathways in cognitive aging research.

Several limitations of our study also require consideration. Data on plasma p-tau and PET Aβ, which were more AD-specific, was not available at the time of analysis but will be analyzed when data collection is complete. Interpreting the time course of CVRFs occurrence and biomarker elevation is challenging given the cross-sectional design, and we conceptualized the relationship between CVRF and plasma biomarkers as associations rather than causation. Large population-based studies that validate the use of FRS in MA individuals are lacking, and it is possible that we overestimated CVRF burden in MA individuals.[49] We do not have information on complications

associated with CVRFs, such as peripheral neuropathy, although the ethnic differences in complications may have contributed to the differential association between FRS and NfL by ethnicity. We may still be underpowered to detect the association of FRS with Aβ, as well as additional synergistic interactions between CVRFs (or FRS) and biomarkers,[50] which may take time to exert their impact as biomarkers accumulate over the life course. We did not examine the use of medications, although a follow-up assessment on the impact of antihypertensive treatment on plasma biomarkers is warranted. Our findings may not be generalizable to other racial/ethnic groups as our cohort only included MA and NHW individuals.

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CONFLICT OF INTEREST

None. Author disclosures are available in the supporting information.

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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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APPENDICES A

Collaborators

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