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Original Article

Association of cardiac biomarkers with longitudinal cognitive changes in the general population

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ABSTRACT

Background: Little is known about the association of high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) with changes in cognitive performance over time.
Objectives: To investigate the association of cardiac biomarkers with cognitive changes over time.
Participants: The study population consisted of 2540 stroke-free participants (56.1 % women; 21.2 % Black; mean age, 74.5 years) enrolled in the Atherosclerosis Risk in Communities study.
Measurements: Associations of the changes in the Mini Mental State Examination (MMSE) scores with the log-transformed cardiac biomarkers were modelled using multivariable linear and restricted cubic spline regression.
Results: Over 6.6 years (median), the MMSE score decreased by 0.57 (95 % CI, 0.46–0.67) and the frequency of an MMSE score <24 increased from 5.339 % to 9.69 % ($P < 0.001$). In multivariable-adjusted models, the cardiac biomarkers measured at baseline were linearly related to absolute MMSE changes with association sizes amounting to 0.47 (0.27–0.66) and 0.58 (0.19–0.97) for NT-proBNP and hs-cTnT, respectively. Classification-by-cardiac biomarker interactions were significant for race, age group and diabetes in relation to NT-proBNP ($P \leq 0.031$) and for race, age group and hypertension in relation to hs-cTnT ($P \leq 0.041$). For both biomarkers, associations were stronger in Blacks than Whites and in older than younger individuals; for NT-proBNP in diabetic than non-diabetic participants; and for hs-cTnT in normotensive than hypertensive individuals.
Conclusion: NT-proBNP and hs-cTnT were associated with MMSE changes. Although association studies cannot prove causality, the clinical implication might be that targeting the heart within the framework of a multifactorial approach might be strategy in reducing cognitive decline.

1. Introduction

Dementia is a major global health problem and affects more than 55 million individuals worldwide [1,2]. Given that the exact underlying etiology of dementia remains limited [3], increasing attention has turned towards prevention strategies targeting modifiable risk factors [4–6]. Cardiovascular disease is often associated with cognitive impairment [7,8] and the development and progression of dementia [9,10]. The heart-brain axis refers to the complex bidirectional connections between cardiovascular and cerebrovascular diseases, mediated by shared risk factors and common pathogenetic mechanisms [11]. Some novel biomarkers (i.e., epigenetic changes and omics-based biomarkers)

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increasingly attract attention for their role in cardiovascular disease [12] and cognitive impairment as measured by Mini Mental State Examination (MMSE) [13]. High-sensitivity cardiac troponin T (hs-cTnT) [14] and N-terminal pro-B-type natriuretic peptide (NT-proBNP) [15] act as well-established biomarkers of subclinical cardiac injury. Previous studies have demonstrated associations of NT-proBNP with Alzheimer's disease [16] and cognitive impairment [16,17], whereas few studies evaluated those cardiac biomarkers in relation to longitudinal cognitive trajectories. To address the above issues, we investigated the association of NT-proBNP and hs-cTnT with longitudinal cognitive change as measured by MMSE using data from the Atherosclerosis Risk in Communities (ARIC) study [18,19].

2. Methods

2.1. Study population

The ARIC study is a community-based prospective study that recruited Black and White participants aged 45 to 64 years from 1987 to 1989 (visit 1) from 4 US communities: Jackson, Mississippi; Washington County, Maryland; suburbs of Minneapolis, Minnesota; and Forsyth County, North Carolina. The study aimed to evaluate atherosclerosis and its risk factors. The participants were repeatedly followed up and gave informed written consent at each contact in 1990–1992 (visit 2), 1993–1995 (visit 3), 1996–1998 (visit 4), 2011–2013 (visit 5), and 2017–2019 (visit 7) [18]. The Institutional Review Boards at all participating institutions approved the study protocol, as described in detail in the online Supplementary Information. Previous publications describe the objectives and design in detail [18]. Blood samples were collected to measure hs-cTnT and NT-proBNP at visit 5 [20]. At visit 5 and visit 7, cognitive performance was assessed by MMSE score [19]. Of 6538 participants who attended ARIC visit 5, 3058 participants had MMSE score available at visits 5 and 7 (Supplementary Fig. 1). We excluded 518 participants because of prevalent stroke at visit 5 ($n = 86$) or due to missing data on cardiac biomarkers ($n = 227$) or because of missing data on covariables ($n = 205$). Thus, a total of 2540 individuals were included in our analysis.

2.2. Clinical measurements

Standardized questionnaires, physical examinations, and laboratory assays were used to assess demographic and cardiovascular risk factors at ARIC visit 5. After the participants had rested for at least 5 min, sitting blood pressure was measured using a random-zero sphygmomanometer and the average of the 2nd and 3rd blood pressure readings were used. The body mass index was weight in kilograms divided by the height squared in meters. Total cholesterol and triglycerides were determined by enzymatic methods, and high-density lipoprotein cholesterol was measured after dextran-magnesium precipitation. Low-density lipoprotein cholesterol was calculated, using the Friedewald's formula [21]. Hypertension was a systolic blood pressure $\geq$140 mmHg, or diastolic blood pressure $\geq$90 mmHg, or the use of antihypertensive medication. Diabetes mellitus was a fasting blood glucose $\geq$126 mg/dL or non-fasting blood glucose $\geq$200 mg/dL, or use of antidiabetic agents, or a self-reported physician diagnosis of diabetes mellitus. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation based on serum creatinine levels [22].

2.3. Measurement of cardiac biomarkers

Standardized assay procedures for hs-cTnT and NT-proBNP measurements have been described previously [20,23]. The hs-cTnT and NT-proBNP concentrations were measured using the Elecsys Troponin T high sensitivity assay and proBNP II assay on an automated Cobas e411 analyzer (Roche Diagnostics, Indianapolis, Indiana) at visit 5 [20]. The concentrations of hs-cTnT were quantified across a range of 3–100,000 ng/L with undetectable values imputed as half the limit of blank (1.5 ng/L) [20], while the concentrations of NT-proBNP spanned a range of 5–70,000 ng/L with undetectable values imputed as half the limit of blank (2.5 ng/L) [20,23].

2.4. Cognitive impairment

The observer-administered MMSE was used to measure cognitive performance in several domains, including memory, orientation, and language. The MMSE has been utilized as a screening tool for the detection of cognitive impairment in institutionalized and community-dwelling individuals and as an instrument for tracking cognitive changes over time [24]. The technicians in the ARIC field centers were fully trained and certified and maintained a standardized interview protocol throughout the whole data collection phase. The 30 MMSE test items were each scored by one point if successfully completed, so that higher values reflect better cognitive performance. In the current study, the cognitive change over time was analyzed as continuously distributed outcome by subtracting the baseline from the follow-up score and as categorical outcome by a decline in the baseline score from $\geq$24 to $<$24 at follow-up [24].

2.5. Statistical analysis

For database management and statistical analysis, we used SAS software, version 9.4 (SAS Institute Inc, Cary, NC), maintenance level 5. We applied the Kolmogorov-Smirnov test for assessing the normality of distributions. Mean $\pm$ SD and median (interquartile range, [IQR]) were used for normally and non-normally distributed data, respectively. Categorical variables were expressed as percentages. Analysis of variance was used for comparison of means, while the χ^2-statistic was used for comparison of proportions as appropriate. Because of the skewed distribution of cardiac biomarkers, we normalized the distribution of these variables by logarithmic transformations. The significance was a 2-sided α level of $\leq$0.05.

We employed the restricted cubic spline (RCS) modeling to explore the non-linear relationship between baseline cardiac biomarkers and longitudinal cognitive change defined as MMSE score at baseline $\geq$24 and MMSE score at follow-up $<$24. The Youden index was used to determine the optimal cutoff values for cardiac biomarkers in binary classification tests (Supplementary Fig. 2). The linear regression analyses were performed to examine the associations of baseline NT-proBNP and hs-cTnT with absolute cognitive change (|MMSE score at follow-up minus MMSE score at baseline|). In line with previous ARIC publication [25], we adjusted for sex, race, age, body mass index, current smoking, low density lipoprotein cholesterol, eGFR, hypertension, and diabetes mellitus in model 1. Model 2 adjusted for variables listed in model 1 plus educational attainment. Model 3 adjusted for variables listed in model 1 plus income. Model 4 adjusted for variables listed in model 1 plus educational attainment and income. For absolute MMSE score change, we additionally adjusted for baseline MMSE score. We performed subgroup analyses according to sex, race, median of age ($<$74 years versus $\geq$74 years), the status of hypertension and diabetes mellitus, and NT-proBNP and hs-cTnT categories, using the appropriate interaction terms.

3. Results

3.1. Clinical characteristics of participants

Among 2540 participants, baseline age ($\pm$SD) averaged 74.5 $\pm$ 4.56 years, and 1425 (56.1 %) individuals were women, and 2002 (78.8 %) were White, and 137 (5.39 %) had MMSE score $<$24 at baseline (Fig. 1). The median concentration of NT-proBNP was 107.4 ng/L (IQR, 57.0–203.6 ng/L) and the median concentration of hs-cTnT was 10 ng/L

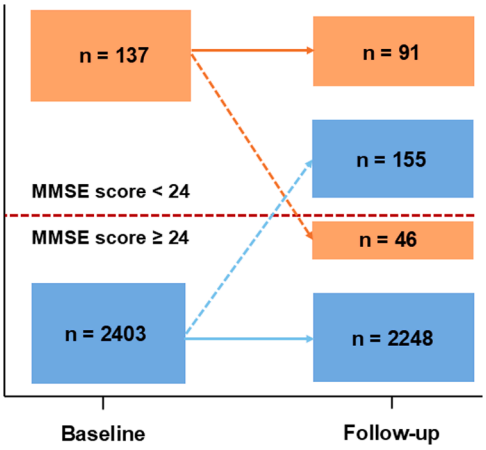

Fig. 1. Changes in distribution of MMSE score between baseline and follow-up. MMSE groups were categorized by cutoff of 24.

(IQR, 7–14 ng/L).

In Table 1, the baseline characteristics of the participants are stratified by the optimized thresholds generated by the Youden index (Supplementary Fig. 2). Individuals in the higher categories of hs-cTnT and NT-proBNP at baseline were more likely to be older and had a high prevalence of hypertension, but lower diastolic blood pressure and worse renal function (Table 1). Among participants with MMSE score available, participants and nonparticipants did not differ (Supplementary Table 1) in age, body mass index, blood pressure, low-density lipoprotein cholesterol and eGFR, or prevalence of hypertension and coronary heart disease, but participants excluded were more likely to be women (64.7 % vs 56.1 %; $P < 0.001$) and to have Diabetes (33.7 % vs 28.0 %; $P = 0.013$).

3.2. The longitudinal change in cognition

The MMSE sore averaged 27.9 ± 2.28 at baseline and 27.3 ± 3.47 at follow-up. Over a median follow-up of 6.6 years (IQR, 6.1 to 7.0 years) from visit 5 to 7, the MMSE score decreased by 0.57 (95 % CI, 0.46 to 0.67; $P < 0.001$) and the frequency of an MMSE score <24 increased from 5.39 % to 9.69 % ($P < 0.001$). The 246 patients with an MMSE score <24 at follow-up included 91 (3.58 %) with a low score both at baseline and follow-up and 155 (6.10 %) new cases at follow-up (Fig. 1). As shown in Table 2, the MMSE change over time (ΔMMSE) was computed as the follow-up minus the baseline score. Compared with Whites (Table 2), Blacks had a greater MMSE decrease over follow-up (ΔMMSE score: −1.09 vs. −0.43; $P < 0.001$). Compared with individuals with low NT-proBNP levels (Table 2), those with high levels had a larger MMSE decrease (ΔMMSE score: −0.79 vs. −0.42; $P < 0.001$). A similar trend was observed in relation to hs-cTnT, individuals with high levels showing more MMSE decrease (ΔMMSE score: −0.84 vs. −0.44; $P < 0.001$; Table 2). Compared with participants above age of 83 years, MMSE score decreased notably in participants with NT-proBNP ≥138.0 ng/L compared to those with NT-proBNP <138.0 ng/L (Supplementary Fig. 3). The individuals with high concentrations of cardiac biomarkers were more likely ($P < 0.001$) to progress to an MMSE score <24 at follow-up compared with those who had low concentrations of cardiac biomarkers (Supplementary Table 2).

3.3. Cognitive change related to cardiac biomarkers

We employed the RCS regression model to examine the relationship between cardiac biomarkers and cognitive changes captured by MMSE (Fig. 2). The RCS regression model reveals a linear relationship (Fig. 2) of cognitive change analyzed as categorical outcome with NT-proBNP (P for non-linearity: 0.83) and hs-cTnT (P for non-linearity: 0.34).

Table 1
Clinical characteristics of participants by cardiac biomarkers at baseline.

Characteristics	log-transformed NT-proBNP		log-transformed hs-cTnT	
	<2.14	≥2.14	<1.09	≥1.09
Number of participants (%)	1519 (59.8)	1021 (40.2)	1733 (68.2)	807 (31.8)
Women	776 (51.1)	649 (63.6)‡	1148 (66.2)	277 (34.3)‡
White race	1136 (74.8)	866 (84.8)‡	1391 (80.3)	611 (75.7)†
Current smokers	73 (4.80)	53 (5.19)	90 (5.19)	36 (4.46)
Education				
<High school	156 (10.3)	121 (11.9)	186 (10.7)	91 (11.3)
High school/vocational school	566 (37.3)	430 (42.1)	697 (40.2)	299 (37.1)
College, graduate, or professional school	797 (52.5)	470 (46.0)†	850 (49.0)	417 (51.7)
Annual household income (US$)				
<16 000	171 (11.3)	107 (10.5)	191 (11.0)	87 (10.8)
16 000 to <25 000	149 (9.81)	129 (12.6)	178 (10.3)	100 (12.4)
25 000 to <35 000	216 (14.2)	161 (15.8)	257 (14.8)	120 (14.9)
35 000 to <50 000	252 (16.6)	206 (20.2)	312 (18.0)	146 (18.1)
≥50 000	731 (48.1)	418 (40.9)†	795 (45.9)	354 (43.9)
Hypertension	1046 (68.9)	756 (74.0)†	1165 (67.2)	637 (78.9)‡
Diabetes mellitus	442 (29.1)	269 (26.3)	424 (24.5)	287 (35.6)‡
Coronary heart disease	143 (9.41)	210 (20.6)‡	190 (11.0)	163 (20.2)‡
Statin use	742 (49.0)	526 (51.5)	804 (46.5)	464 (57.6)‡
Antihypertensive drugs	1046 (68.9)	790 (77.4)‡	1162 (67.1)	674 (83.5)‡
Antidiabetic agent	262 (17.3)	167 (16.4)	236 (13.6)	192 (23.9)‡
Mean (SD) of characteristic				
Age (years)	73.6 ± 4.28	75.7 ± 4.68‡	73.8 ± 4.31	75.9 ± 4.74‡
Body mass index (kg/m^2)	29.2 ± 5.08	28.5 ± 5.89†	28.5 ± 5.16	29.9 ± 5.87‡
Brachial SBP (mm Hg)	127.4 ± 15.5	130.5 ± 18.4‡	128.6 ± 16.5	128.7 ± 17.3
Brachial DBP (mm Hg)	67.6 ± 9.94	65.4 ± 10.8‡	67.0 ± 10.1	66.1 ± 10.8*
Heart rate (beats per min)	61.8 ± 10.1	60.4 ± 9.61‡	61.3 ± 9.63	61.1 ± 10.5
HDL-c (mmol/L)	1.33 ±0.34	1.38 ±0.37‡	1.38 ±0.35	1.27 ±0.34‡
LDL-c (mmol/L)	2.73 ±0.85	2.67 ±0.89 *	2.78 ±0.86	2.56 ±0.85‡
eGFR (mL/min/1.73m^2)	73.9 ± 15.1	67.8 ± 16.5‡	73.9 ± 14.5	66.0 ± 17.4‡

The distribution of NT-proBNP and hs-cTnT were normalized by logarithmic transformations. Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; hs-cTnT, high-sensitivity cardiac troponin T; LDL-c, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and SBP, systolic blood pressure. Significance of the differences between groups: * $P \leq 0.05$, † $P \leq 0.01$, and ‡ $P \leq 0.001$.

In univariate analyses (Table 3), MMSE score at follow-up decreased with higher values of NT-proBNP (β=−0.64; 95 % CI, −0.95 to −0.34; $P < 0.001$) and hs-cTnT (β=−2.45; 95 % CI, −3.01 to −1.90; $P < 0.001$). With adjustments applied for potential confounders, these associations persisted ($P \leq 0.019$; Table 3). In fully adjusted analyses including educational attainment, income and MMSE score at baseline, the associations persisted for NT-proBNP (β=0.47; 95 % CI, 0.27 to 0.66; $P <$

Table 2
The MMSE score stratified by subgroups.

Characteristics	MMSE score at baseline	MMSE score at follow-up	ΔMMSE score	
			Difference	*P* value
Sex				
Men ($n = 1115$)	27.6 ± 2.31	27.0 ± 3.49	−0.57 ±2.82	0.95
Women ($n = 1425$)	28.1 ± 2.22	27.6 ± 3.44	−0.56 ±2.66	
Race				
White ($n = 2002$)	28.4 ± 1.75	27.9 ± 2.84	−0.43 ±2.57	<0.001
Black ($n = 538$)	26.2 ± 3.09	25.1 ± 4.54	−1.09 ±3.20	
Age, years				
<74 ($n = 1238$)	28.1 ± 2.06	27.9 ± 2.53	−0.22 ±2.04	<0.001
≥74 ($n = 1302$)	27.7 ± 2.45	26.8 ± 4.10	−0.89 ±3.22	
Hypertension				
No ($n = 738$)	28.3 ± 2.08	27.8 ± 3.08	−0.50 ±2.51	0.41
Yes ($n = 1802$)	27.8 ± 2.34	27.2 ± 3.60	−0.60 ±2.81	
Diabetes mellitus				
No ($n = 1829$)	28.1 ± 2.17	27.6 ± 3.28	−0.49 ±2.63	0.022
Yes ($n = 711$)	27.5 ± 2.49	26.7 ± 3.86	−0.77 ±2.95	
NT-proBNP				
<2.14 ($n = 1519$)	27.9 ± 2.23	27.5 ± 3.16	−0.42 ±2.45	<0.001
≥2.14 ($n = 1021$)	27.9 ± 2.35	27.1 ± 3.88	−0.79 ±3.08	
hs-cTnT				
<1.09 ($n = 1733$)	28.1 ± 2.16	27.7 ± 3.10	−0.44 ±2.48	<0.001
≥1.09 ($n = 807$)	27.5 ± 2.46	26.6 ± 4.07	−0.84 ±3.19	
NT-proBNP and hs-cTnT				
<2.14 and <1.09 ($n = 1105$)	28.1 ± 2.16	27.7 ± 2.95	−0.33 ±2.35	<0.001
<2.14 and ≥1.09 ($n = 414$)	27.5 ± 2.35	26.8 ± 3.57	−0.67 ±2.68	
≥2.14 and <1.09 ($n = 628$)	28.2 ± 2.16	27.5 ± 3.34	−0.64 ±2.67	
≥2.14 and ≥1.09 ($n = 393$)	27.4 ± 2.57	26.4 ± 4.53	−1.02 ±3.64	

The distribution of NT-proBNP and hs-cTnT were normalized by logarithmic transformations. The change in MMSE score that is ΔMMSE score refers to MMSE score at follow-up minus value at baseline. Participants were divided into age groups by 74 years (median). *P* values indicate the significance of the differences in the MMSE change between subgroups. Abbreviations: hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

0.001) and hs-cTnT (β=0.58; 95 % CI, 0.19 to 0.97; $P = 0.004$) related to the absolute cognitive changes captured by MMSE.

The results obtained by stratification by race, sex, median age, hypertension and diabetes are listed in Supplementary Table 3. For the absolute MMSE changes over time, the classification-by-cardiac biomarker interactions were significant for race, age group and diabetes in relation to NT-proBNP ($P \leq 0.031$) and for race, age group and hypertension in relation to hs-cTnT ($P \leq 0.041$). For both cardiac biomarkers, associations were stronger in Blacks than Whites and in older than younger individuals. For NT-proBNP, associations were closer in diabetic than non-diabetic participants and for hs-cTnT in normotensive compared with hypertensive participants.

4. Discussion

The key observations can be summarized as follows: (1) higher concentrations of baseline NT-proBNP and hs-cTnT were associated with lower MMSE score at follow-up; (2) higher concentrations of NT-proBNP and hs-cTnT were associated with greater MMSE decrease; and (3) the associations of cardiac biomarkers with cognitive changes over time varied by age and race.

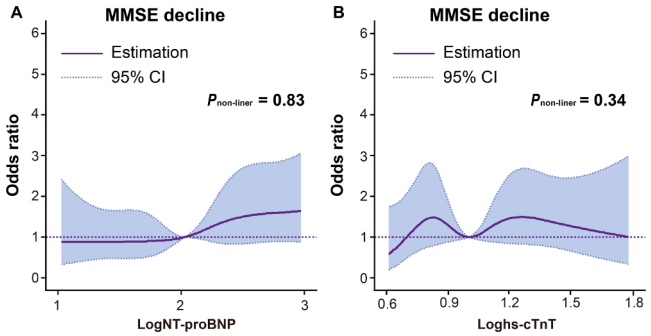

Fig. 2. Restricted cubic splines for the association of log-transformed NT-proBNP (A) and hs-cTnT (B) with cognitive change over time. The splines were modelled with four knots (5th, 35th, 65th and 95th percentiles). The red solid line in the figure represents odds ratio, and the red dashed represents the 95 % CI. The decrease in MMSE score was defined as MMSE score at baseline ≥24 and MMSE score at follow-up <24. The models were adjusted for sex, race, age, body mass index, current smoking, educational attainment, income, baseline MMSE score, lowdensity lipoprotein cholesterol, estimated glomerular filtration rate, hypertension, and diabetes mellitus.

Table 3
The MMSE score associated with cardiac biomarkers at baseline.

Cardiac biomarkers	MMSE score at follow-up		Absolute ΔMMSE score	
	Estimate (95 % CI)	*P* value	Estimate (95 % CI)	*P* value
Unadjusted				
NT-proBNP	−0.64 (−0.95 to −0.34)	<0.001	0.58 (0.38 to 0.77)	<0.001
hs-cTnT	−2.45 (−3.01 to −1.90)	<0.001	1.25 (0.89 to 1.62)	<0.001
Model 1				
NT-proBNP	−0.91 (−1.20 to −0.61)	<0.001	0.47 (0.27 to 0.67)	<0.001
hs-cTnT	−0.77 (−1.36 to −0.18)	0.010	0.59 (0.19 to 0.98)	0.003
Model 2				
NT-proBNP	−0.84 (−1.12 to −0.56)	<0.001	0.47 (0.27 to 0.67)	<0.001
hs-cTnT	−0.76 (−1.32 to −0.20)	0.008	0.58 (0.19 to 0.98)	0.004
Model 3				
NT-proBNP	−0.84 (−1.13 to −0.55)	<0.001	0.47 (0.27 to 0.67)	<0.001
hs-cTnT	−0.69 (−1.27 to −0.11)	0.019	0.59 (0.19 to 0.98)	0.004
Model 4				
NT-proBNP	−0.82 (−1.10 to −0.54)	<0.001	0.47 (0.27 to 0.66)	<0.001
hs-cTnT	−0.73 (−1.29 to −0.17)	0.011	0.58 (0.19 to 0.97)	0.004

Association sizes (95 % CI) express MMSE score at follow-up and the absolute changes in MMSE score over time associated with log-transformed NT-proBNP and hs-cTnT. Model 1: Adjusted models were adjusted for sex, race, age, body mass index, current smoking, low density lipoprotein cholesterol, estimated glomerular filtration rate, hypertension, and diabetes mellitus. Model 2: Adjusted for variables in model 1 plus educational attainment; Model 3: Adjusted for variables in model 1 plus income; Model 4: Adjusted for variables in model 1 plus educational attainment and income. For absolute MMSE score change, we additionally adjusted for baseline MMSE score. Abbreviations: hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Circulating cardiac biomarkers, such as hs-cTnT and NT-proBNP were not only associated with cardiac injury and cardiovascular disease but also correlated with cerebral small vessel disease and cognitive dysfunction in the general population [26], in patients with hypertension [27], cardiac disease [28] and stroke [29]. In 243 patients with clinically manifest cardiac disease (57 % women; mean age, 73 years), Hilal and colleagues reported that higher levels of hs-cTnT (RR, log-transformed hs-cTnT increment, 4.86; 95 % CI, 3.03–7.08) and NT-proBNP (RR, log-transformed NT-proBNP increment, 3.16; 95 % CI, 2.33–4.27) were significantly associated with higher risk of cortical cerebral microinfarcts after adjusting for potential confounders [28]. In another study that enrolled 434 patients without cognitive impairment or dementia (55 % women; mean age, 74 years), participants with higher baseline levels of hs-cTnT (β, −1.80; 95 % CI, −2.54 to −1.06) or NT-proBNP (β, −0.83; 95 % CI, −1.30 to −0.35) had greater memory decline during 3 years of follow-up [30]. In 278 hypertensive patients (41 % women; mean age, 63 years), Vilar-Bergua and coworkers reported that NT-proBNP was independently associated with silent brain infarcts (OR per 1-SD of log-transformed NT-proBNP increment, 2.11; 95 % CI,1.14–3.10), brain microbleeds (OR, 1.79; 95 % CI, 1.15–2.78) and WMH volume (β, 1.60; 95 % CI, 0.47–2.74) [27]. In 385 patients with acute stroke (32 % women; median age, 68 years), hs-cTnT was negatively associated with cognitive function (β, −0.27; 95 % CI, −0.44 to −0.11) [29]. However, these studies mentioned above mainly investigated the association of cardiac biomarkers with cognitive dysfunction and subclinical cerebral disease at a single time point. Few studies have reported the impact of cardiac biomarkers on cognitive performance trajectories over time.

Left ventricular injury and dysfunction as reflected by hs-cTnT and NT-proBNP [31,32], respectively, may be targeted as a modifiable factor to prevent cognitive decline [28]. However, association studies cannot prove causality, but plausible mechanisms include microvascular damage, cerebral hypoperfusion, blood-brain barrier dysfunction and microembolization [33,34]. In a previous ARIC publication [35], we demonstrated that the central systolic blood pressure measured by applanation tonometry was associated with the MMSE score and cerebral small vessel disease. The underlying mechanism may be that the pulsatile component of central blood pressure puts strain on the ventricular contractile performance and hence increases the circulating biomarkers reflecting myocardial stress (hs-cTnT) and decreased systolic and diastolic performance (NT-proBNP). In the cross-sectional population-based Hamburg City Health Study, NT-proBNP was associated with cognitive impairment mediated by neurodegeneration [36]. In the Systolic Blood Pressure Intervention Trial, the relative effect of intensive systolic blood pressure lowering on preventing cognitive impairment was stronger in patients with lower compared with higher circulating cardiac biomarker levels [37]. The difference in the prevalence of risk factors may affect the association of cardiac biomarkers with cognitive change over time. In keeping with our current findings (Supplementary Table 3), previous ARIC publications demonstrated higher dementia risk among Blacks (hazard ratio, 1.36; 95 % CI, 1.21–1.54) and among individuals aged 60–66 years compared with participants aged 44–49 years (hazard ratio, 8.06; 95 % CI, 6.69–9.72) [19].

To the best of our knowledge, our study is the first to explore the association of cardiac biomarkers with longitudinal cognitive change assessed by MMSE in the general population. Our present observations add to the literature by revealing that monitoring cardiac biomarkers may enhance the risk stratification for longitudinal cognitive change confirmed by multivariable-adjusted models and subgroup analyses by race. The current study showed that cardiac biomarkers are associated with MMSE decline over 6.6 years in the general population. A meta-regression analysis of 58,939 individuals (age range 18–108 years; 61.2 % women) recorded an annual MMSE decline by −0.04 (95 % CI, −0.05 to −0.03) at the age of 41 years, which in our study was −0.57 (95 % CI, −0.67 to −0.46) over a 6.6-year follow-up [38]. However, our findings must be interpreted within the context of potential limitations. First, concentrations of hs-cTnT and NT-proBNP were analyzed using Roche Diagnostics assays, thus results may not be extrapolated to other available biomarker assays. Second, the results may be affected by missing variables and residual confounding factors. Third, as in all long-lasting longitudinal studies attrition occurred in ARIC, because of mortality, participants leaving the catchment area, or for undocumented reasons. Non-attendance at visits 5 and 7 might have biased the current results to some extent. However, participants and non-participants had largely similar characteristics (Supplementary Table 1). Four, the MMSE test is a commonly used cognitive test in clinical practice and research, but does not cover executive function or attention, and has low sensitivity in detecting early cognitive changes. To prove true decline in cognitive function patients with an MMSE score <24 should undergo more elaborate tests [39], such as the Montreal Cognitive Assessment, examination of cerebrospinal fluid, and brain imaging studies. This information was not available in current study, so that the observed small changes of a 0.6-point decline in the MMSE score over a 6.6-year follow-up should be cautiously interpreted, as other factors such as learning effects or changes in living conditions may affect the MMSE score changes. Further studies conducted in populations at higher risk of cognitive decline with more sensitive cognitive measures should be warranted to better assess the clinical implications of these associations. Finally, genetic information, including the APOE genotype, could not be made available in the shared database used in the current analyses, so that we could not adjust for APOE genotype.

5. Perspectives

In a large community-based cohort with multiple adjustments applied, the cardiac biomarkers NT-proBNP and hs-cTnT were associated with significant cognitive trajectories over a 6.6-year follow-up, thereby expanding the evidence produced by previous cross-sectional studies. The clinical implication is that targeting the heart within the framework of a multifactorial prevention strategy might contribute to reducing the burden of cerebrovascular disease and cognitive decline. The perspective for future research on the heart-brain axis is how cardiac biomarkers in a multi-omics framework will contribute to unraveling the underlying mechanisms leading to cognitive decline as recently demonstrated in a seminal publication [13].

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Data sharing statement: The requests to access the dataset should be sent to the ARIC Data Coordinating Center.

Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in figures, images and artwork

During the preparation of this work, we did not use generative AI and AI-assisted technologies.

Supplementary materials: Supplementary data can be found online.

CRediT authorship contribution statement

Fang-Fei Wei: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Dubo Chen:** Writing – original draft, Validation. **Chaoxin Xu:** Writing – original draft, Visualization. **Zhongping Yu:** Writing – review & editing, Visualization, Formal analysis. **Zihao Chen:** Writing – review & editing, Visualization. **Chang Chen:** Writing – review & editing, Visualization, Formal analysis. **Xin He:** Writing – review & editing, Methodology, Conceptualization. **JingJing Zhao:** Writing – review & editing, Methodology, Investigation. **Wenqing Li:** Writing – review & editing, Methodology, Conceptualization. **Cuiping Zhao:** Writing – review & editing, Conceptualization. **Jiangui He:** Writing – review & editing, Methodology, Conceptualization. **Yugang Dong:** Writing – review & editing, Conceptualization. **Jan A. Staessen:** Writing – review & editing, Conceptualization. **Chen Liu:** Writing – review & editing, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100494.

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