Cross-sectional associations between cardiac biomarkers, cognitive performance, and structural brain changes are modified by age

Cross-Sectional Associations Between Cardiac Biomarkers, Cognitive Performance, and Structural Brain Changes Are Modified by Age

The Maastricht Study

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Objective—NT-proBNP (N-terminal pro-B-type natriuretic peptide) and cardiac troponin T (cTNT) are associated with cognitive performance. Whether this extends to individuals <60 years of age is unclear. We investigated whether age modified the associations between NT-proBNP and cTNT and cognitive performance and structural brain changes.

Approach and Results—In 3011 individuals (60±8 years; 49% women), NT-proBNP and cTNT, memory, information processing speed and executive functioning, grey matter (GM) and white matter, and white matter hyperintensity (WMH) volumes were determined. We used regression, adjusted for educational level, cardiovascular factors, and lifestyle factors, to test whether cross-sectional associations between biomarkers and cognitive performance and structural brain changes were modified by age (<60 versus ≥60 years). ≥60 years, higher NT-proBNP was associated with lower memory (β [SD] per 10-fold higher level [95% confidence interval (CI)], −0.11 [−0.22 to −0.00]), information processing speed (−0.12 [95% CI, −0.21 to −0.03]), executive functioning (−0.12 [95% CI, −0.22 to −0.03]), and smaller GM (β [mL] per 10-fold higher level, −6.89 [95% CI, −11.58 to −2.20]). Additionally, higher cTNT was associated with lower memory (−0.33 [95% CI, −0.53 to −0.12]) and information processing speed (−0.17 [95% CI, −0.3 to −0.01]); with smaller GM (−16.07 [95% CI, −24.90 to −7.24]) and greater WMH (10^{β} WMH per 10-fold higher level, 0.31 [95% CI, 0.10–0.52]). <60 years, NT-proBNP and cTNT were not associated with cognitive performance ($P_{interaction}$, <0.10). In contrast, higher NT-proBNP was associated with smaller GM (−7.43 [95% CI, −11.70 to −3.16]) and greater WMH (0.13 [95% CI, 0.01–0.25]; $P_{interaction}$, >0.10). Higher cTNT was associated with greater WMH (0.18 [95% CI, −0.01 to 0.37]; $P_{interaction}$, >0.10) but not with GM (0.07 [95% CI, −6.87 to 7.02]; $P_{interaction}$, <0.10).

Conclusions—Biomarkers of cardiac injury are continuously associated with structural brain changes in both older and younger individuals but with poorer cognitive performance only in older individuals. These findings stress the continuous nature of the heart-brain axis in the development of cognitive impairment.

Visual Overview—An online visual overview is available for this article. **(*Arterioscler Thromb Vasc Biol*. 2018;38:1948-1958. DOI: 10.1161/ATVBAHA.118.311082.)**

Key Words: brain ■ humans ■ natriuretic peptide, brain ■ troponin T ■ white matter

Clinical heart failure and ischemic heart disease are thought to contribute to impairment of cognitive performance in older individuals.[1–3] Even in the absence of clinical disease, biomarkers of cardiac injury, such as NT-proBNP (N-terminal pro-B-type natriuretic peptide) and cardiac troponin T (cTNT), have been shown, in older individuals (>60 years of age), to be associated with lower cognitive performance.[4–9] Indeed, such biomarker studies have suggested a continuous role of the heart-brain axis in the development and progression of cognitive decline and opportunities for identifying older individuals at risk of developing cognitive impairment before the appearance of clinical cardiac disease.[10,11]

Whether or not the link between biomarkers of cardiac injury and cognitive performance extends to younger

Received on: October 28, 2017; final version accepted on: June 11, 2018.

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The online-only Data Supplement is available with this article at https://www.ahajournals.org/journal/atvb/doi/suppl/10.1161/atvbaha.118.311082.

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Nonstandard Abbreviations and Acronyms	
CHD	coronary heart disease
cTNT	cardiac troponin T
CVD	cardiovascular disease
GM	grey matter
HbA1c	glycohemoglobin
HDL	high-density lipoprotein
IPS	information processing speed
LDL	low-density lipoprotein
MRI	magnetic resonance imaging
NT-proBNP	N-terminal pro-B-type natriuretic peptide
T2D	type 2 diabetes mellitus
TB	total brain
WM	white matter
WMH	white matter hyperintensity

individuals is less clear.[12–14] On one hand, higher cognitive reserve capacity in younger individuals may protect against the deleterious effects of (sub)clinical cardiac disease on cognitive performance.[15] On the other hand, such (sub)clinical cardiac disease may still be associated with subtle structural brain changes, such as white matter (WM) hyperintensities (WMHs) and brain atrophy,[5,16–19] which can be detected by magnetic resonance imaging (MRI) and which are known to precede cognitive impairment.[10,20–24] Indeed, biomarkers of cardiac injury have been reported to be associated with WMHs and brain atrophy in older individuals,[5,16–19] but this issue has not been studied in younger individuals.[12–14]

In view of the above, we investigated, in a well-characterized population-based cohort, whether age (younger versus older) modified associations between biomarkers of cardiac injury (NT-proBNP, cTNT) and not only domains of cognitive performance but also structural brain changes. We thereby tested the hypothesis that the concept of the heart-brain axis is continuous in nature during the course of life (ie, alterations in levels of NT-proBNP and troponin T are associated proportionally with cognitive performance and structural brain changes independent of age).

Materials and Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population and Design

We used data from the Maastricht study—an observational prospective population-based cohort study. The rationale and methodology have been described previously.[25] Further (brief) details are described in Methods in the online-only Data Supplement. The present report includes cross-sectional data from the first 3451 participants, who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of 3 months. MRI measurements were implemented from December 2013 onward until February 2017 and were available in 2313 of 3451 participants. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Ministry of Health, Welfare and Sports of the Netherlands (Permit 131088-105234-PG) and has been preregistered within the institutional registry of the Maastricht study, which adheres to their disclosure requirements (no link available). All analyses were preregistered. All participants gave written informed consent. Data are unsuitable for public deposition because of ethical restriction and privacy of participant data according to the approved study protocol by the institutional medical ethical committee (Medisch-ethische toetsingscommissie azM/UM, NL31329.068.10) and the Ministry of Health, Welfare and Sports of the Netherlands (Permit 131088-105234-PG). Data are available from the Maastricht study for any interested researcher who meets the criteria for access to confidential data. The Maastricht Study Management Team (research.dms@mumc.nl) and the corresponding author (R.M.A.H.) may be contacted to request data. The present study was reported as per the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies.

Biomarkers of Cardiac Injury

Serum NT-proBNP and serum high-sensitive cTNT were used as biomarkers of cardiac injury. NT-proBNP and cTNT were determined in fasting venous blood samples by trained laboratory research assistants who were blinded for all clinical data regarding the participants, as described previously.[26] Further (brief) details are described in Methods in the online-only Data Supplement.

Cognitive Performance

Cognitive performance was assessed by a concise battery of neuropsychological tests by trained research assistants blinded for all clinical data regarding the participants, as described previously.[25,27] For concept clarity and to reduce the number of cognitive outcomes, test results were divided into composite scores for 3 cognitive domains (ie, memory, information processing speed [IPS], and executive functioning and attention), as described previously.[28] Further details on domains of cognitive performance are described in Methods in the online-only Data Supplement.

Brain MRI

Brain MRI was performed on a 3T MRI scanner (Magnetom Prismafit Syngo MR D13D; Siemens, Erlangen, Germany) by use of a 64-element head coil for parallel imaging. Further details on the MRI protocol and contraindications for MRI assessments are described in Methods in the online-only Data Supplement.

Measurement of Brain Volumes

T1 images and T2-weighted FLAIR images were analyzed by use of an ISO-13485:2012 certified, automated method (which included visual inspection)[24,29,30] by trained research assistants supervised by a neuroradiologist, which were for all clinical data regarding the participants. Overall, this method has an excellent repeatability with a true-positive fraction between 0.79 and 0.97.[30] T1 images were segmented into grey matter (GM), WM, and cerebrospinal fluid volumes (1 voxel=1.00 mm^3=0.001 mL).[29] Intracranial volume was calculated as the sum of GM, WM (including WMH volume), and cerebrospinal fluid volumes. Total brain (TB) volume was calculated as the sum of grey and WM volumes.

Measurement of WMHs

T2-weighted FLAIR and T1 images were used to identify WMHs.[24,30] WMHs identified were summed to assess total WMH burden in milliliters.

Covariates

We assessed fasting glucose, HbA1c (glycohemoglobin), glucose metabolism status, total cholesterol, HDL (high-density lipoprotein), LDL (low-density lipoprotein) cholesterol, total cholesterol-to-HDL cholesterol ratio, triglycerides, body mass index, office blood pressure, 24-hour ambulatory blood pressure, medication use (glucose lowering, antihypertensive, and lipid modifying), smoking status (never, former, and current), alcohol consumption, medical cardiovascular history, serum creatinine, serum cystatin C, 24-hour urinary albumin

excretion, educational level, occupational status (groups based on ISEI-08), income, current major depression (self-reported), physical activity, and difficulties falling asleep or experiencing breathing interruptions during sleep, as described previously.[25,31–33] Glucose metabolism status was classified as described previously.[25,34] Further details on covariates are described in Methods in the online-only Data Supplement.

Statistical Analyses

Because of the observational nature of our study, the post hoc sample size estimate based on the study by Field[35] was 160 to 240 for the analyses with domains of cognitive performance and 180 to 270 for the analyses with structural brain changes. Population characteristics between individuals <60 and ≥60 years of age, or between the total study population and individuals excluded from the analyses because of missing values in models 1 to 3, were compared by independent sample *t* test or χ^2 test as appropriate.

First, associations between biomarkers and domains of cognitive performance were investigated with multivariable linear regression analyses in the total cognitive performance study population and in this study population stratified according to younger and older age (<60 and ≥60 years). Given their skewed distribution, the log-transformed NT-proBNP or cTNT was used in the analyses. The analyses were adjusted for sex, age, educational level, and glucose metabolism status (model 1) and additionally adjusted for prior cardiovascular disease (CVD), body mass index, smoking status, alcohol consumption, total cholesterol/HDL-ratio, triglycerides, use of lipid-modifying medication, estimated glomerular filtration rate (model 2); and office systolic pressure, use of antihypertensive medication, and albuminuria (model 3). Because of their role as possible mediator or ascending proxy, office systolic pressure, the use of antihypertensive medication, and albuminuria were added in separate models because a model including these variables might be at risk of overadjustment.[36]

Second, associations between biomarkers and structural brain changes (TB, GM, WM, and WMH volumes) were investigated with multivariable linear regression analyses in the TB MRI study population and in this study population stratified according to age (<60 and ≥60 years). Given its skewed distribution, the log-transformed WMH volume was used in the analyses. The analyses were adjusted in the same way as the analyses with domains of cognitive performance and were additionally adjusted for intracranial volume and MRI lagtime in model 1.

Third, using model 2, we tested whether age either as dummy (ie, <60 versus ≥60 years of age) or as a continuous variable modified such associations ($P_{interaction}$ <0.10 was considered statistically significant).

Finally, we conducted several additional analyses to test the robustness of our results. First, we additionally adjusted model 2 for the presence of current major depression (Mini-International Neuropsychiatric Interview)[37] or moderate-to-vigorous physical activity,[2] difficulties falling asleep or experiencing breathing interruptions during sleep, occupational status (groups based on ISEI-08),[38] or income. Second, to restrict the analyses to subclinical disease, we repeated the analyses excluding individuals with prior coronary heart disease (CHD), stroke, or current atrial fibrillation or flutter.[39] Third, the analyses with structural brain changes were restricted to individuals with complete data on cognitive performance or to individuals with an MRI lagtime <1 or <2 years. Fourth, the analyses were repeated with the replacement of office systolic pressure in model 4 by office diastolic pressure or mean arterial pressure,[31] office pulse pressure,[40] their 24-hour ambulatory equivalents,[41] the presence of hypertension, and additionally, we repeated analyses stratified according to the presence of hypertension. Fifth, given the design of the Maastricht study, we used interaction terms added to model 2 (additionally adjusted for the interaction between NT-proBNP or cTNT and age in years) to examine whether the investigated associations were modified by type 2 diabetes mellitus (T2D). Sixth, we used interaction terms added to model 2 (additionally adjusted for the interaction between NT-proBNP or cTNT and age in years) to examine whether the investigated associations were modified by sex. Last, we performed mediation analyses to test whether structural brain changes mediated the association between biomarkers of cardiac injury and cognitive performance. The 95% confidence intervals (CIs) of the mediation effects were assessed according to Preacher and Hayes (5000 bootstrap iterations).[42]

All statistical analyses were performed using IBM SPSS Statistics, version 23 (IBM Corp, Armonk, NY). A 2-sided *P* value <0.05 was considered statistically significant. Because of the observational nature of our study, we made no corrections for multiple comparisons in our analyses.[43]

Results

Characteristics

Table 1 shows the characteristics of the study population for cognitive performance stratified according to age (Figure I in the online-only Data Supplement). The study population (60±8 years of age) was relatively highly educated (41.1% higher educational level) and consisted of 796 individuals with T2D. Levels of NT-proBNP and cTNT were below clinical cutoffs (125 pg/mL and 14 ng/L) in 85.9% and 95.1%, respectively (Figure II in the online-only Data Supplement). The study population in which brain MRIs were available overlapped for 97% with the above population and was comparable with regard to age, sex, and cardiometabolic risk (Figure I in the online-only Data Supplement; Table I in the online-only Data Supplement). The mean (±SD) lagtime of the MRI data was 838.6±474.3 days. Individuals ≥60 years of age were more often men and experienced T2D and CVD more often. In addition, they had higher levels of NT-proBNP and cTNT, lower educational levels, lower cognitive performance, smaller TB, grey, and WM volumes, and greater WMH and cerebrospinal fluid volumes (Table 1; Table I in the online-only Data Supplement). Individuals with missing values more often had T2D, CVD, hypertension, albuminuria, lower estimated glomerular filtration rate, lower educational level, and higher levels of NT-proBNP and cTNT (Tables II and III in the online-only Data Supplement).

Cardiac Biomarkers and Cognitive Performance

Table 2 shows the associations between biomarkers and memory, IPS, and executive function in the total study population.

After adjustment, higher levels of NT-proBNP were associated with worse executive function (regression coefficient [β] per 10-fold higher level, −0.08 [95% CI, −0.15 to −0.01]) and were borderline significantly associated with worse memory (−0.07 [95% CI, −0.14 to 0.01]) and IPS (−0.06 [95% CI, −0.12 to 0.01]). Higher levels of cTNT were significantly associated with worse memory (−0.16 [95% CI, −0.26 to −0.05]) and IPS (−0.16 [95% CI, −0.26 to −0.04]) but not with executive function (0.00 [95% CI, −0.11 to 0.12]; Table 2, models 2).

In individuals ≥60 years of age, after adjustment, higher levels of NT-proBNP were significantly associated with worse memory (−0.11 [95% CI, −0.22 to −0.00]), IPS (−0.12 [95% CI, −0.21 to −0.03]), and executive function (−0.12 [95% CI, −0.21 to −0.02; Table 2, models 2; Figure). These associations were somewhat attenuated after further adjustment for systolic pressure, antihypertensive medication, and albuminuria (Table 2, models 3). In individuals ≥60 years of age, after adjustment, higher levels of cTNT were significantly associated with worse memory (−0.33 [95% CI, −0.53 to −0.12]) and IPS (−0.17 [95% CI, −0.33 to −0.01])

Table 1. General Characteristics of the Cognitive Performance Study Population

	Total (N=3011)	<60 y (n=1381)	≥60 y (n=1630)	*P* Value
Demographics				
Men, n (%)	1542 (51)	610 (44)	932 (57)	<0.001
Age, y	60±8	52±5	66±4	<0.001
Educational level, low/middle/high, %	15.6/43.3/41.1	10.9/45.9/43.2	19.6/41.0/39.3	<0.001
Glucose metabolism status, NGM/prediabetes/T2D, %	58.0/15.5/26.4	69.0/12.0/19.0	48.7/18.5/32.8	<0.001
Prior CVD, %	16	10	21	<0.001
Prior CHD, %	7	5	9	<0.001
Prior stroke, %*	2	1	3	0.001
Current atrial fibrillation or flutter, %†	0.9	0.2	1.6	<0.001
Blood pressure				
Office systolic pressure, mm Hg	135±18	130±16	139±19	<0.001
Office diastolic pressure, mm Hg	76±10	77±10	76±10	<0.001
24-h systolic pressure, mm Hg‡	119±12	117±11	121±12	<0.001
24-h diastolic pressure, mm Hg‡	74±7	74±7	73±7	<0.001
Antihypertensive medication, %	39	27	49	<0.001
Hypertension, %	56	42	68	<0.001
Metabolic variables				
BMI, kg/m^2	27.0±4.5	26.9±4.7	27.2±4.3	0.056
Total cholesterol, mmol/L	5.3±1.2	5.3±1.1	5.2±1.2	0.011
HDL, mmol/L	1.53±0.48	1.53±0.48	1.52±0.48	0.533
LDL, mmol/L	3.11±1.03	3.17±1.01	3.06±1.05	0.003
Triglycerides, mmol/L	1.20 (0.88–1.72)	1.17 (0.84–1.71)	1.24 (0.93–1.73)	0.076
Total cholesterol-to-HDL cholesterol ratio	3.69±1.19	3.75±1.27	3.64±1.11	0.014
Lipid-modifying medication, %	35	22	45	<0.001
HbA1C, %§	5.9±0.9	5.7±0.9	6.0±0.9	<0.001
Fasting plasma glucose, mmol/L‖	6.0±1.6	5.8±1.7	6.2±1.6	<0.001
Oral antidiabetics or insulin use	21	15	25	<0.001
Kidney function				
eGFR, mL/min per 1.73 m2	88.4±14.6	94.6±13.1	83.1±13.7	<0.001
Albuminuria, %	8.0	5.5	10.2	<0.001
Lifestyle variables				
Smoking status: never/former/current, %	35.0/51.8/13.2	39.4/44.2/16.4	31.3/58.3/10.4	<0.001
Alcohol use: no/low/high, %	17.9/55.6/26.5	19.8/57.6/22.6	16.3/53.9/29.8	<0.001
Moderate-to-vigorous physical activity, h/wk¶	4.5 (2.3–8.0)	4.5 (2.5–7.8)	4.5 (2.3–8.0)	0.237
Biomarkers of cardiac injury				
NT-proBNP, pg/mL	50.57 (29.43–89.56)	41.19 (23.17–69.81)	59.96 (35.77–104.25)	<0.001
High-sensitivity cTNT, ng/L	5.35 (3.80–7.76)	4.28 (3.06–6.01)	6.45 (4.65–9.14)	<0.001
Cognitive performance and mental health				
Memory	0.03±0.95	0.31±0.89	−0.21±0.93	<0.001
IPS	0.04±0.77	0.35±0.70	−0.23±0.73	<0.001
Executive functioning and attention	0.02±0.81	0.30±0.74	−0.21±0.79	<0.001
Mini-mental state examination	29.0±1.2	29.2±1.0	28.9±1.3	<0.001
Current major depression (MINI), %#	3.6	4.4	3.0	0.050

(*Continued*)

Table 1. Continued

	Total (N=3011)	<60 y (n=1381)	≥60 y (n=1630)	*P* Value
Structural brain changes				
TB volume, mL**	1135.9±111.4	1153.5±112.1	1119.8±108.3	<0.001
GM volume, mL**	660.5±60.4	671.5±60.3	650.4±58.7	<0.001
WM volume, mL**	475.4±59.9	482.0±59.8	469.4±59.4	<0.001
WMH volume, mL**	0.225 (0.070–0.744)	0.105 (0.034–0.294)	0.447 (0.160–1.391)	<0.001
Cerebrospinal fluid volume, mL**	254.2±48.9	235.0±40.7	271.7±49.2	<0.001
Intracranial volume, mL**	1391.2±136.0	1388.9±136.5	1393.2±135.5	0.466

Data are presented as mean±SD, median (interquartile range), or frequencies (%) as appropriate. Data present the cognitive performance population for regression models 1 to 3. Significant difference between <60 and ≥60 y of age was tested by independent *t* test or χ^2 test as appropriate. For dichotomous variables, a χ^2 test was used. BMI indicates body mass index; CHD, coronary heart disease; cTNT, cardiac troponin T; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GM, grey matter; HbA1c, glycohemoglobin; HDL, high-density lipoprotein; IPS, information processing speed; LDL, low-density lipoprotein; MINI, mini-international neuropsychiatric interview; NGM, normal glucose metabolism; NT-proBNP, N-terminal pro-B-type natriuretic peptide; T2D, type 2 diabetes mellitus; TB, total brain; WM, white matter; and WMH, white matter hyperintensity.

n for specific variables (total, <60/≥60 y of age):

*prior stroke (n=3003, 1381/1622),

†current atrial fibrillation or flutter (n=2954, 1394/1605),

‡24-h blood pressure measurements (n=2666, 1196/1470),

§HbA1c (n=3004, 1377/1627),

‖fasting plasma glucose (n=3009, 1380/1629),

¶moderate-to-vigorous physical activity (n=2659, 1244/1415),

#current major depression (n=2990, 1371/1619),

**structural brain changes were available in a different subset of n=2104, 1003/1101 (Table I in the online-only Data Supplement).

but were not associated with executive function (0.01 [95% CI, −0.17 to 0.18]; Table 2, models 2). These associations were somewhat attenuated after further adjustment for systolic pressure, antihypertensive medication, and albuminuria (Table 2, models 3).

In individuals <60 years of age, no statistically significant associations were observed between NT-proBNP or cTNT and any of the cognitive performance domains after adjustment.

We thus found interactions with age, that is, the associations in individuals ≥60 years of age between NT-proBNP and memory, IPS, and executive function and between cTNT and memory, were statistically significantly stronger than the respective (not statistically significant) associations in individuals <60 years of age (Table 2, models 2, $P_{interaction}$ <0.03 for all).

Cardiac Biomarkers and Structural Brain Changes

Table 3 shows the associations between biomarkers and TB, GM, WM, and WMH volumes according to age.

After adjustment, higher levels of NT-proBNP were associated with smaller TB volume (−8.67 [95% CI, −12.25 to −5.09]), smaller GM volume (−8.21 [95% CI, −11.36 to −5.07]), and greater WMH volume (0.09 [95% CI, 0.01–0.17]) but were not associated with WM volume (−0.46 [95% CI, −3.69 to 2.76]). Higher levels of cTNT were significantly associated with smaller TB volume (−7.27 [95% CI, −13.63 to −0.92]), smaller GM volume (−7.15 [95% CI, −12.73 to −1.56]), and greater WMH volume (0.24 [95% CI, 0.10–0.36]) but were not associated with WM volume (−0.13 [95% CI, −5.82 to 5.57]; Table 3, models 2).

In individuals ≥60 years of age, after adjustment, higher levels of NT-proBNP were significantly associated with smaller GM volume (−6.89 [95% CI, −11.58 to −2.20]) but were not associated with WMH volume (0.06 [95% CI, −0.05 to 0.17]) or WM volume (−0.66 [95% CI, −5.29 to 3.97]; Table 3, models 2; Figure). The association with GM volume attenuated somewhat after further adjustment for systolic pressure, antihypertensive medication, and albuminuria (Table 3, models 3). In individuals ≥60 years of age, after adjustment, higher levels of cTNT were associated with smaller GM volume (−16.07 [95% CI, −24.90 to −7.24]) and greater WMH volume (0.31 [95% CI, 0.10–0.52]) but not with WM volume (−0.99 [95% CI, −9.73 to 7.74]; Table 3, models 2). The associations with GM and WMH volumes were attenuated somewhat after further adjustment for systolic pressure, antihypertensive medication, and albuminuria (Table 3, models 3).

In individuals <60 years of age, after adjustment, higher levels of NT-proBNP were associated with smaller GM volume (−7.43 [95% CI, −11.70 to −3.16]) and greater WMH volume (0.13 [95% CI, 0.01–0.25]) but were not associated with WM volume (−0.66 [95% CI, −5.29 to 3.97]; Table 3, models 2; Figure). Associations with GM and WMH volumes were attenuated somewhat after further adjustment for systolic pressure, antihypertensive medication, and albuminuria (Table 3, models 3). In individuals <60 years of age, after adjustment, higher levels of cTNT were borderline significantly associated with greater WMH volume (0.18 [95% CI, −0.01 to 0.37]) but were not associated with GM volume (0.07 [95% CI, −6.87 to 7.02]) or WM volume (0.22 [95% CI, −7.23 to 7.66]; Table 3, models 2). The association with WMH volume attenuated somewhat after further adjustment for systolic pressure, antihypertensive medication, and albuminuria (Table 3, models 3).

We found a single interaction with age, that is, the (statistically significant) association in individuals ≥60 years of age between cTNT and GM volume was statistically significantly

Table 2. Associations Between Biomarkers of Cardiac Injury and Domains of Cognitive Performance

		Total Cognitive Performance Study Population (N=3011)			<60 y (n=1381)			≥60 y (n=1630)		
	Model	B	95% CI	*P* Value	B	95% CI	*P* Value	B	95% CI	*P* Value
NT-proBNP, pg/mL										
Memory	1	−0.08	−0.16 to −0.00	0.04	0.01	−0.11 to 0.12	0.93	−0.13	−0.24 to −0.03	0.01
	2	−0.07	−0.14 to 0.01	0.10	0.00	−0.11 to 0.12	0.97	−0.11	−0.22 to −0.00	0.04*
	3	−0.06	−0.14 to 0.02	0.15	0.01	−0.11 to 0.13	0.89	−0.10	−0.22 to 0.01	0.07
IPS	1	−0.07	−0.13 to −0.01	0.03	0.03	−0.07 to 0.12	0.58	−0.14	−0.23 to −0.06	<0.005
	2	−0.06	−0.12 to 0.01	0.07	0.02	−0.07 to 0.11)	0.65	−0.12	−0.21 to −0.03	<0.01*
	3	−0.05	−0.11 to 0.02	0.14	0.02	−0.08 to 0.11	0.72	−0.10	−0.19 to −0.01	0.03
Executive functioning and attention	1	−0.08	−0.15 to −0.01	0.02	−0.02	−0.12 to 0.08	0.72	−0.13	−0.22 to −0.04	<0.01
	2	−0.08	−0.15 to −0.01	0.02	−0.03	−0.13 to 0.07	0.58	−0.12	−0.22 to −0.03	0.01*
	3	−0.08	−0.14 to −0.01	0.03	−0.02	−0.12 to 0.08	0.67	−0.11	−0.21 to −0.02	0.02
cTNT, ng/L										
Memory	1	−0.18	−0.32 to −0.05	<0.01	−0.01	−0.19 to 0.17	0.88	−0.36	−0.55 to −0.17	<0.001
	2	−0.14	−0.28 to 0.00	0.05	0.02	−0.16 to 0.21	0.81	−0.33	−0.53 to −0.12	<0.005*
	3	−0.13	−0.03 to 0.01	0.07	0.03	−0.16 to 0.22	0.77	−0.31	−0.52 to −0.11	<0.005
IPS	1	−0.17	−0.27 to −0.07	<0.005	−0.13	−0.27 to 0.01	0.07	−0.20	−0.35 to −0.05	<0.01
	2	−0.16	−0.26 to −0.05	<0.005	−0.13	−0.28 to 0.02	0.09	−0.17	−0.33 to −0.01	0.04
	3	−0.14	−0.25 to −0.04	<0.01	−0.14	−0.29 to 0.01	0.07	−0.14	−0.30 to 0.02	0.08
Executive functioning and attention	1	−0.02	−0.13 to 0.10	0.78	0.01	−0.15 to 0.16	0.95	−0.02	−0.18 to 0.15	0.83
	2	0.00	−0.11 to 0.12	0.94	0.02	−0.14 to 0.18	0.80	0.01	−0.17 to 0.18	0.94
	3	0.02	−0.10 to 0.14	0.80	0.03	−0.13 to 0.20	0.69	0.02	−0.16 to 0.20	0.81

The unstandardized regression coefficients (B) represent the difference in respective cognitive domain test score per 10-fold higher level of biomarker of cardiac injury. The biomarkers of cardiac injury were log-transformed. For example, in individuals ≥60 y of age, after adjustment for potential confounders, concentrations of 5 and 50 pg/mL NT-proBNP (ie, $10^{0.70}$ and $10^{1.70}$ and on a log scale, 0.70 and 1.70) correspond with 0.08 and 0.19 lower memory test scores, respectively. Model 1: sex, age, educational level, and glucose metabolism status; model 2: model 1 plus prior CVD, body mass index, smoking status, alcohol consumption, total cholesterol-to-HDL cholesterol ratio, triglycerides, use of lipid-modifying medication, and estimated glomerular filtration rate; and model 3: model 2 plus office systolic blood pressure, use of antihypertensive medication, and albuminuria. CI indicates confidence interval; cTNT, cardiac troponin T; CVD, cardiovascular disease; IPS, information processing speed; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*$P_{interaction}$ <0.03 represents the *P* value of the interaction effect between biomarkers of cardiac injury (per 10-fold higher level) and age ≥60 y as compared with <60 y in the association with the cognitive domain test score.

stronger than the respective (not statistically significant) association in individuals <60 years of age (Table 3, models 2; $P_{interaction}$, <0.04).

Cardiac Biomarkers and Cognitive Performance: Interaction Analyses

We found that associations between NT-proBNP or cTNT and the cognitive performance domains became statistically significantly stronger with age. The interaction terms indicated, per 1 year older age, a −0.02 to −0.01 worse performance score on tests of cognitive domains per 10-fold higher level of NT-proBNP or cTNT (Table IV in the online-only Data Supplement; $P_{interaction}$ <0.06 for all except for cTNT and IPS).

Cardiac Biomarkers and Structural Brain Changes: Interaction Analyses

We found that associations between biomarkers of cardiac injury and structural brain changes became stronger with age, although to a lesser extent than the associations between biomarkers and the cognitive performance domains. Only the associations between cTNT and GM, WM, and WMH volumes became statistically significantly stronger. The interaction terms indicated, per 1 year older age, a 1.38-mL smaller GM volume, a 1.02-mL smaller WM volume, or a 0.01 greater log WMH volume per 10-fold higher level of cTNT (Table IV in the online-only Data Supplement; $P_{interaction}$ <0.05 for all).

Additional Analyses

Further analyses showed that the associations were not materially altered after several additional adjustments (eg, for depression) or after excluding individuals with prior clinical disease (eg, CHD). There were few interactions with T2D (only between NT-proBNP and memory and WM volume [associations stronger in T2D]) and sex (only between NT-proBNP or cTNT and GM volume [associations stronger in men]). If we executed formal mediation analyses to determine whether structural brain changes mediated the association between

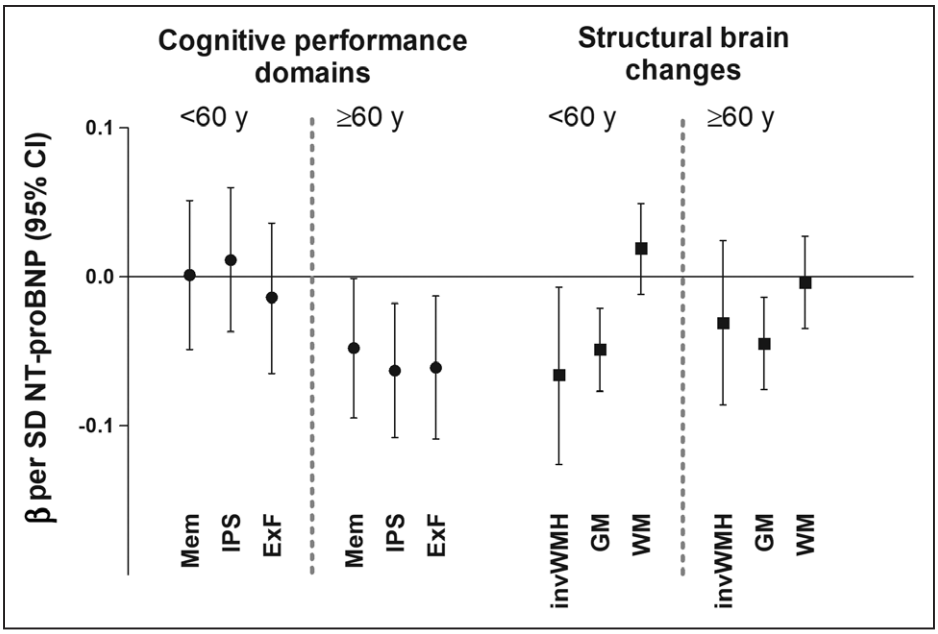

Figure. The association between NT-proBNP (N-terminal pro-B-type natriuretic peptide) and domains of cognitive performance and structural brain changes in individuals <60 and ≥60 y of age. The standardized regression coefficients represent the standardized difference in respective cognitive domain test score or structural brain change per SD 10-fold higher level of biomarker of cardiac injury in model 2*. The biomarkers of cardiac injury and white matter hyperintensity (WMH) volumes were log-transformed. WMH volumes were inverted so that lower volume indicated deteriorating WMH. CI indicates confidence interval; ExF, domain of executive functioning and attention; GM, grey matter; IPS, domain of information processing speed; invWMH, inverse of log white matter hyperintensity volume; Mem, domain of memory; and WM, white matter. *Model 2: adjusted for sex, age, educational level, glucose metabolism status, prior cardiovascular disease, body mass index, smoking status, alcohol consumption, total cholesterol-to-high-density lipoprotein cholesterol ratio, triglycerides, use of lipid-modifying medication, estimated glomerular filtration rate, and when structural brain changes used as outcome for intracranial volume and magnetic resonance imaging lagtime.

cardiac biomarkers and cognitive performance, the results showed that structural brain changes only mediated ≤17% of the association between cardiac biomarkers and cognitive performance. Further details on the additional analyses are given in Results in the online-only Data Supplement and Tables I through X in the online-only Data Supplement.

Discussion

This cross-sectional population-based study shows that biomarkers of cardiac injury were associated with domains of cognitive performance in older (≥60 years of age) but not in younger individuals, whereas such biomarkers were associated with structural brain changes in both younger and older individuals. In general, such associations were statistically significantly stronger with age both for domains of cognitive performance and—to a lesser extent—for structural brain changes. In addition, these associations were independent of educational level, cardiovascular risk factors, and lifestyle factors and remained after excluding individuals with prior CHD, atrial fibrillation, or stroke. Taken together, these data support the hypothesis that greater brain reserve capacity in younger individuals protects against the deleterious effects of subclinical CVD on cognitive performance. Nevertheless, this does not exclude structural brain changes. We found, in fact, that biomarkers of cardiac injury were associated with structural brain changes even in younger individuals. Therefore, these findings support the concept of a continuous nature of the causal connection between the pathophysiology of the heart and the brain (heart-brain axis) in development of cognitive impairment in not only older but also younger individuals.

This is, to the best of our knowledge, a large population-based study to show that age modifies the associations of biomarkers of cardiac injury with both cognitive performance and structural brain changes, in individuals without prior CHD, atrial fibrillation, or stroke. Previous studies have been performed in populations at high risk of CVD,[17,18,44–50] in older individuals only,[4–9,16–19] in populations that included younger individuals but did not evaluate these associations according to age,[12,13] or in a population that included younger individuals but was smaller and examined cognitive function less extensively.[14] Our study extends previous findings to a large population-based cohort of older and younger individuals.

NT-proBNP and cTNT represent biomarkers of impairment of cardiac hemodynamic function and perfusion, which has led to the hypothesis that the associations of these biomarkers with cognitive performance and structural brain changes may have a hemodynamic or (micro)vascular origin.[10,51] First, ischemic heart failure has been shown to be associated with impaired cerebral autoregulation, which, through hypoperfusion, may cause loss of integrity in a high metabolic demand organ, such as the brain[52]—a concept supported by the fact that NT-proBNP and cTNT were inversely associated with GM volume, which has the highest metabolic demand, but not with WM volume. Conceivably, a similar mechanism may also be operative in individuals with subclinical heart disease.[53] Second, these biomarkers may reflect systemic vascular dysfunction that affects large and small vessels of not only the heart but also the

Table 3. Associations Between Biomarkers of Cardiac Injury and Structural Brain Changes

		TB MRI Study Population (N=2104)			<60 y (n=1003)			≥60 y (n=1101)		
	Model	B	95% CI	*P* Value	B	95% CI	*P* Value	B	95% CI	*P* Value
NT-proBNP, pg/mL										
TB volume, mL	1	−9.68	−13.22 to −6.13	<0.001	−4.93	−9.72 to −0.14	0.04	−9.63	−14.82 to −4.43	<0.001
	2	−8.67	−12.25 to −5.09	<0.001	−4.62	−9.48 to 0.24	0.06	−7.55	−12.79 to −2.31	<0.01*
	3	−7.70	−11.30 to −4.10	<0.001	−4.03	−8.91 to 0.84	0.10	−6.46	−11.74 to −1.18	0.02
GM volume, mL	1	−8.91	−12.01 to −5.81	<0.001	−7.93	−12.14 to −3.73	<0.001	−8.30	−12.93 to −3.68	<0.001
	2	−8.21	−11.36 to −5.07	<0.001	−7.43	−11.70 to −3.16	<0.005	−6.89	−11.58 to −2.20	<0.005
	3	−7.14	−10.29 to −3.98	<0.001	−6.94	−11.22 to −2.66	<0.005	−5.52	−10.22 to −0.82	0.02
WM volume, mL	1	−0.77	−3.94 to 2.39	0.63	3.01	−1.51 to 7.52	0.19	−1.32	−5.85 to 3.21	0.57
	2	−0.46	−3.69 to 2.76	0.78	2.81	−1.79 to 7.41	0.23	−0.66	−5.29 to 3.97	0.78
	3	−0.56	−3.82 to 2.69	0.73	2.91	−1.75 to 7.56	0.22	−0.94	−5.61 to 3.74	0.69
WMH	1	0.11	0.03 to 0.19	0.01	0.14	0.03 to 0.26	0.02	0.09	−0.02 to 0.20	0.11
	2	0.09	0.01 to 0.17	0.02	0.13	0.01 to 0.25	0.03	0.06	−0.05 to 0.17	0.27
	3	0.07	−0.01 to 0.15	0.08	0.12	−0.00 to 0.24	0.06	0.04	−0.07 to 0.15	0.47
cTNT, ng/L										
TB volume, mL	1	−8.15	−14.26 to −2.04	<0.01	−1.02	−8.56 to 6.53	0.79	−17.14	−26.62 to −7.67	<0.001
	2	−7.27	−13.63 to −0.92	0.02	0.29	−7.58 to 8.16	0.94	−17.06	−26.94 to −7.18	<0.005*
	3	−5.78	−12.14 to 0.59	0.08	1.67	−6.20 to 9.53	0.68	−15.37	−25.29 to −5.45	<0.005
GM volume, mL	1	−7.09	−12.44 to −1.75	<0.01	−0.79	−7.45 to 5.86	0.82	−15.17	−23.59 to −6.74	<0.001
	2	−7.15	−12.73 to −1.56	0.01	0.07	−6.87 to 7.02	0.98	−16.07	−24.9 to −7.24	<0.001*
	3	−5.51	−11.09 to 0.06	0.05	1.35	−5.59 to 8.29	0.70	−14.16	−22.98 to −5.34	<0.005
WM volume, mL	1	−1.05	−6.48 to 4.37	0.70	−0.22	−7.32 to 6.88	0.95	−1.98	−10.23 to 6.28	0.64
	2	−0.13	−5.82 to 5.57	0.97	0.22	−7.23 to 7.66	0.95	−0.99	−9.73 to 7.74	0.82*
	3	−0.26	−5.99 to 5.47	0.93	0.32	−7.19 to 7.82	0.93	−1.21	−10.00 to 7.58	0.79
WMH	1	0.25	0.12 to 0.39	<0.001	0.20	0.02 to 0.39	0.03	0.31	0.12 to 0.51	<0.005
	2	0.24	0.10 to 0.38	<0.005	0.18	−0.01 to 0.37	0.07	0.31	0.10 to 0.52	<0.005
	3	0.21	0.07 to 0.35	<0.005	0.15	−0.05 to 0.34	0.14	0.28	0.07 to 0.48	<0.01

The unstandardized regression coefficients (B) represent the difference in respective structural brain change per 10-fold higher level of biomarker of cardiac injury. The biomarkers of cardiac injury were log-transformed. For example, in individuals ≥60 y of age, after adjustment for potential confounders, concentrations of 5 and 50 pg/mL NT-proBNP (ie, $10^{0.70}$ and $10^{1.70}$ and on a log scale, 0.70 and 1.70) correspond with 4.82 and 11.71 mL smaller GM volumes, respectively, and in individuals <60 y of age, after adjustment for potential confounders, concentrations of 5 and 50 pg/mL NT-proBNP correspond with 5.20 and 12.63 mL smaller GM volumes, respectively. In addition, WMH volume was log-transformed, for example, in individuals <60 y of age, a 10-fold higher level of NT-proBNP was associated with a ($10^{0.13}$=1.35) 1.35× (1.02–1.78) greater WMH volume. Model 1: sex, age, educational level, glucose metabolism status, intracranial volume, and MRI lagtime; model 2: model 1 plus prior CVD, body mass index, smoking status, alcohol consumption, total cholesterol-to-HDL cholesterol ratio, triglycerides, use of lipid-modifying medication, estimated glomerular filtration rate; and model 3: model 2 plus office systolic blood pressure, use of antihypertensive medication, and albuminuria. CI indicates confidence interval; cTNT, cardiac troponin T; CVD, cardiovascular disease; GM, grey matter; HDL, high-density lipoprotein; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TB, total brain; WM, white matter; and WMH, white matter hyperintensity.

*$P_{interaction}$ <0.04 represents the *P* value of the interaction effect between biomarkers of cardiac injury (per 10-fold higher level) and age ≥60 y as compared with <60 y in the association with structural brain changes.

brain.[2,51,54,55] Indeed, MRI-estimated WMHs and brain atrophy may be features of cerebral small vessel disease and have been shown to precede cognitive impairment.[21,22,24]

Alternatively or additionally, subclinical cardiac disease and cognitive performance and structural brain changes may share common risk factors, which over time produce damage in both heart and brain. However, we adjusted extensively for potential confounders, such as hypertension, diabetes mellitus, and other cardiovascular risk factors, which thus are unlikely explanations for the associations we observed. Still, we cannot exclude that other lifestyle factors (eg, dietary habits[2]), which were not included in these analyses, might play a role in the association between subclinical cardiac disease and cognitive performance and structural brain changes.[2,51]

The (inverse) associations of NT-proBNP and cTNT with cognitive performance were weak or absent in younger individuals, which may be explained by greater cognitive reserve in younger as compared with older individuals.[15] In contrast,

associations of these biomarkers with structural brain changes were apparent also in younger individuals. Thus, the absence, in younger individuals, of associations between these biomarkers and cognitive performance does not exclude biomarker-associated structural brain changes detectable with MRI. Nevertheless, associations between biomarkers and structural brain changes were also stronger in older than in younger individuals. A potential explanation may be the impaired effectiveness of cerebral autoregulation in older individuals[56] because this would increase sensitivity to hypoperfusion in older individuals at any given level of subclinical CVD.

The present study supports the hypothesis that subclinical cardiac disease contributes independently to impairment of cognitive performance and structural changes of the brain. First, we were able to accurately examine 3 domains of cognitive performance, structural brain changes, and biomarkers of cardiac injury through a concise battery of neuropsychological tests, an automated WMH detection, and brain segmentation[57] system with the use of a 3T MRI scanner[24] and the use of NT-proBNP and high-sensitivity cTNT,[58–60] respectively. In this population-based study, we established a continuous link between the full range of levels of biomarkers of cardiac injury and cognitive performance and structural brain changes, rather than categorizing these biomarkers by clinical cutoff values. The associations between these biomarkers of cardiac injury and mortality are also continuous in nature.[61,62] Second, we adjusted for an extensive series of potential confounders, including CVD risk factors, such as systolic blood pressure and use of antihypertensive medication and albuminuria. Risk of overadjustment bias[36] (in model 3) was small because associations were at the most slightly attenuated by adjustments. Moreover, associations remained after excluding individuals with prior CHD, atrial fibrillation, or stroke, indicating a role for subclinical cardiac disease in subclinical structural brain changes. Third, reverse causality is biologically unlikely. Fourth, formal mediation analyses showed that at most 17% of the association between cardiac biomarkers and cognitive performance was mediated by structural brain changes. This strongly suggests that other mechanism are operative; functional MRI scanning might provide further insights.

Strengths of our study include its population-based design with both younger and older individuals, which allowed us to accurately investigate whether the associations were modified by age; the use of deep phenotyping, which allowed us to adjust for an extensive series of CVD risk factors, including 24-hour ambulatory blood pressure; and the broad array of additional analyses, which all gave consistent results.

We tested for interactions with sex and T2D. However, we stress that we did not have strong a priori hypotheses with regard to why the associations investigated should differ according to sex or the presence of T2D. Therefore, the few interactions with T2D and sex that we did find are likely to be the play of chance.

Our study also had limitations. First, the cross-sectional design of the study does not allow us to draw strong causal inferences. However, it follows from the association between cardiac disease and cognitive decline[1–3] that there is a strong prior likelihood that cardiac injury contributes to impairment in cognitive performance and to structural brain changes. Second, a large number of individuals were excluded based on missing MRI data. However, included individuals with MRI data were relatively more healthy as compared with excluded individuals, and such selection may have caused us to underestimate any of the associations between biomarkers of cardiac injury and cognitive performance and structural brain changes. Third, the brain MRI scans were performed after the biomarkers of cardiac injury and cognitive performance assessments. However, associations remained after adjustment for the MRI lagtime, as one might expect given the slow progression of structural brain changes over time.[63,64] Fourth, our study population was intensively treated for cardiovascular risk factors, and such selection may have caused us to underestimate any of the associations between biomarkers of cardiac injury and cognitive performance and structural brain changes. Fifth, ApoE4 (apolipoprotein E4) status was not available in our study.[65] However, previously, ApoE4 allele did not influence the association between biomarkers of cardiac injury and cognitive impairment.[14] Sixth, cognitive performance may be negatively influenced by sleep disturbances. Because we currently do not have any information about sleep disturbances available, we cannot exclude that sleep disturbances may have influenced our results. However, if results were adjusted for difficulties falling asleep or experiencing breathing interruptions during sleep, they were not materially altered.

In conclusion, our cross-sectional population-based study shows that, independently of educational level, cardiovascular and lifestyle risk factors, and even after excluding individuals with prior CHD, atrial fibrillation, or stroke, biomarkers of cardiac injury are associated with domains of cognitive performance in older but not in younger individuals, whereas such biomarkers were associated with structural brain changes in both younger and older individuals. Our findings stress the significance of the role and the continuous nature of the heart-brain axis in the development of cognitive impairment. They also suggest biomarkers of cardiac injury as potential identifiers of a higher risk of developing cognitive impairment in not only older but also younger individuals. Future prospective studies need to unravel the exact cardiovascular mechanisms underlying these associations to better understand the usefulness of biomarkers of cardiac injury as potential targets in preventive and therapeutic strategies for cognitive impairment.

Sources of Funding

This work was supported by the European Regional Development Fund via OP-Zuid, the Province of Limburg, the Dutch Ministry of Economic Affairs (grant 31O.041); Stichting De Weijerhorst (Maastricht, the Netherlands); the Pearl String Initiative Diabetes (Amsterdam, the Netherlands); CARIM School for Cardiovascular Diseases (Maastricht, the Netherlands); Stichting Annadal (Maastricht, the Netherlands); Health Foundation Limburg (Maastricht, the Netherlands); and by unrestricted grants from Janssen-Cilag B.V. (Tilburg, the Netherlands), Novo Nordisk Farma B.V. (Alphen aan den Rijn, the Netherlands), and Sanofi-Aventis Netherlands B.V. (Gouda, the Netherlands). The sponsors of the study had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclosures

H.-P. Brunner-La Rocca reports unrestricted research grants from Roche Diagnostics and Novartis and serves as member of the advisory board of Roche Diagnostics, outside the submitted work. The other authors report no conflicts.

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Highlights

- In this cross-sectional population-based study, biomarkers of cardiac injury are independently and continuously associated with structural brain changes in both older and younger individuals but with poorer cognitive performance only in older individuals.
- These data support the hypothesis that greater brain reserve capacity in younger individuals protects against the deleterious effects of subclinical cardiovascular disease on cognitive performance.
- These findings stress the significance of the role and continuous nature of the heart-brain axis in the development of cognitive impairment in not only older but also younger individuals.
- Future prospective studies are needed to test the usefulness of biomarkers of cardiac injury as potential targets in preventive and therapeutic strategies for cognitive impairment in both older and younger individuals.