Received: 2 November 2022 | Accepted: 6 May 2023

DOI: 10.1111/ene.15859

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

NT-proBNP and changes in cognition and global brain structure: The Rotterdam Study

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Funding information
Delta plan Dementia from ZonMW Memorabel, Grant/Award Number: 73305095005; ZonMw; Alzheimer Nederland; Erasmus MC and Erasmus University Rotterdam; the Netherlands Organization for Scientific Research (NWO); Research Institute for Diseases in the Elderly (RIDE); the Netherlands Genomics Initiative; the Ministry of Education, Culture and Science; the Ministry of Health, Welfare and Sports; the European Commission (DG XII); the Municipality of Rotterdam; Stitching Erasmus Trustfonds, Grant/Award Number: 97030.2021.101.430/057/RB; the Netherlands Organization for Health Research and Development (ZonMW), Grant/Award Number: 73305095007; Health Holland, Grant/Award Number: LSHM20106

Abstract

Objective: To investigate the association between N-terminal pro-B-type natriuretic peptide (NT-proBNP) and changes in cognition and global brain structure.

Methods: In the Rotterdam Study, baseline NT-proBNP was assessed at baseline from 1997 to 2008. Between 1997 and 2016, participants without dementia or stroke at baseline ($n = 9566$) had repeated cognitive tests (every 3–6 years) for global cognitive function, executive cognitive function, fine manual dexterity, and memory. Magnetic resonance imaging of the brain was performed repeatedly at re-examination visits between 2005 and 2015 for 2607 participants to obtain brain volumes, focal brain lesions, and white matter microstructural integrity as measures of brain structure.

Results: Among 9566 participants (mean age 65.1 ± 9.8 years), 5444 (56.9%) were women, and repeated measures of cognition were performed during a median follow-up time of 5.5 (range 1.1–17.9) years, of whom 2607 participants completed at least one brain imaging scan. Higher levels of NT-proBNP were associated with a faster decline of scores in the global cognitive function (p value = 0.003) and the Word-Fluency test (p value = 0.003) but were not related to a steeper deterioration in brain volumes, global fractional anisotropy, and mean diffusivity, as indicators of white matter microstructural integrity, or focal brain lesions.

Conclusions: Higher baseline NT-proBNP levels were associated with a faster decline in cognition; however, no association with global brain structure was found.

KEYWORDS
brain structure, cognition, MRI, NT-proBNP, change, repeated measurements

Tian Xiao and Isabelle F. van der Velpen contributed equally as first authors.

INTRODUCTION

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is the inactive N-terminal fragment of proBNP, which is released by ventricular myocytes in response to increasing load in volume and pressure [1]. NT-proBNP is used in clinical settings as a well-established diagnostic marker of ventricular distention and cardiac dysfunction [2]. Recent evidence demonstrated that impaired cardiac function was associated with abnormal brain aging [3]. The heart–brain–axis hypothesis proposes possible mechanisms linking cardiac dysfunction to brain health, including reduced cardiac output, atherosclerotic changes, and perturbated cerebral perfusion, which may result in cognitive decline and brain atrophy [4–7]. Especially given that normal cerebral blood flow is essential for brain function maintenance, hemodynamic dysfunction of the heart–brain axis may play a role in vascular brain injury and impairment of cognition [5]. This is supported by a substantial proportion of patients with heart failure also experiencing cognitive impairment [8]. As a promising non-invasive biomarker of this axis [9], NT-proBNP clinically indicates left ventricular dysfunction and also relates to a higher risk of dementia [10]. Evidence from cross-sectional studies also showed that elevated NT-proBNP levels were associated with markers of abnormal brain aging, including decreased brain tissue volumes and worse cognitive function [11]. A more comprehensive insight into cerebral pathophysiology that links cardiac dysfunction to abnormal brain aging would benefit from clarifying the direction of the associations and assisting in unraveling the underlying mechanisms.

However, in previous studies, proposed associations between NT-proBNP and brain structure or cognition were based on single time-point measures of structural brain markers or cognitive tests at baseline, precluding any inferences on a temporal link between NT-proBNP and markers of brain aging or cognition. Also, although few studies reported an association between higher NT-proBNP levels and a faster decline in global cognitive function, using Mini-Mental State Examination [12, 13], the application of limited cognitive tests in previous studies might impede an investigation of individual cognitive domains, such as memory and executive function. Analyses of a comprehensive test battery of cognition could unravel the effect of NT-proBNP on both global and specific functions of multiple cognitive domains, which could contribute to a better overview of the association between cardiac function and cognition.

In this study, we determined the longitudinal associations between NT-proBNP levels and changes in cognition and global brain structure with multiple measures in community-dwelling older adults.

METHODS

The current study was embedded within the population-based Rotterdam Study, a prospective cohort study of which details have been described previously [14].

NT-proBNP was assessed during the study center visits at baseline in 9946 participants between 1997 and 2008. These cohorts formed the baseline of this current study. Of these 9946 participants, 380 persons with prevalent stroke ($n=223$) or dementia ($n=157$) were excluded. We used a standardized test battery for multiple cognitive domains to determine both longitudinal and cross-sectional associations between NT-proBNP levels and cognition. These cognitive tests were administered every 3 to 6 years at re-examination visits from 1997 to 2016. The cognitive test battery [15], including the Word-Fluency test (WFT), the Letter-Digit-Substitution task (LDST), the Stroop test, the Purdue Pegboard test (PPB test), and the 15-Word Learning test for delayed recall, immediate recall, and recognition (WLTdel, WLTimm, WLTrecog), is described in Table S1. A total of 9566 participants completed at least one of the following tests at baseline: the WFT ($n=9118$), the LDST ($n=9039$), the Stroop test 1 ($n=8862$), the Stroop test 2 ($n=8846$), the Stroop test 3 ($n=8821$), the PPB test ($n=3137$), the WLTdel ($n=3032$), the WLTimm ($n=3033$), and the WLTrecog ($n=3031$). Among 8667 participants at baseline, we also constructed a compound score for global cognitive function (G-factor) using only the WFT, the LDST, and the Stroop test 3 in principal component analysis, to prevent distortion by highly correlated tasks. The validity of the G-factor has been tested within the Rotterdam Study [16] and accounted for 64.1% of all variance in the cognitive tests, which is a typical proportion of variance that the G-factor can explain [17]. To guarantee the quality of the cognitive evaluation, cognitive tests of participants diagnosed with incident dementia ($n=110$) at a follow-up date of the cognitive test were excluded from their diagnosis onward.

Brain magnetic resonance imaging (MRI) scans were performed repeatedly at re-examination visits between 2005 and 2015 to obtain brain volumes, focal brain lesions, and white matter microstructural integrity as measures of brain structure. A total of 2775 participants had complete structural segmentation data of brain imaging at baseline. After the exclusion of 128 persons with prevalent stroke ($n=64$) or dementia ($n=64$) and 40 persons with cortical brain infarcts on MRI, 2607 participants were included in the analyses. The number of cognitive tests or brain MRI scans during the follow-up are presented in Table S2.

Assessment of NT-pro-BNP

Serum NT-proBNP levels were determined using electrochemiluminescence immunoassay at baseline (Elecsys proBNP, F Hoffman-La Roche Ltd) on an Elecsys 2010 analyzer, which measures concentrations ranging from 0.6 to 4130 pmol/L. Values below the detection limit are reported as <0.6 pmol. Values above the measuring range are reported as >4130 pmol/L or up to 8277 pmol/L for two-fold diluted samples. Detailed information on NT-proBNP measurement has been reported elsewhere [18].

Brain structure

Brain MRI scanning was performed on a single 1.5T MRI unit (General Electric Healthcare) with an eight-channel head coil. There were no software or hardware changes within the study period. The scans protocol included T1-weighted, proton density-weighted, fluid-attenuated inversion recovery, and T2*-weighted gradient recalled echo sequences. Detailed information about brain MRI is presented in the Appendix S1. The distribution of brain volumes and white matter microstructure was transformed into a normal standardized distribution. Normalized scores (z-scores) for each scan were calculated by the individual raw score minus the mean value of the whole population, divided by the population standard deviation. White matter hyperintensity volumes were log-transformed. Lower fractional anisotropy and higher mean diffusivity indicate worse white matter microstructural integrity [19].

Cognition

Similarly, z-scores were calculated for values of all cognitive tests. Lower scores on the WFT, the LDST, the PPB test, the WLTdel, the WLTimm, and the WLTrecog, and higher Stroop test scores indicate worse cognitive functions. As a compound score extracted from the principal component analysis, a higher G-factor indicates a better global cognitive function.

Covariates

We included potential covariates based on literature knowledge reporting an association with NT-proBNP, cognitive impairment, brain atrophy, or all, including age, sex, education levels (primary education, lower education, intermediate education, higher education), smoking status (never, former, current), body mass index (BMI, kg/m^2, calculated by weight [kg] divided by height [m] squared), systolic and diastolic blood pressure (mmHg), total and high-density lipoprotein cholesterol level (mmol/L), apolipoprotein E (*APOE*) genotype, depressive symptoms, and chronic comorbid conditions (diabetes mellitus type 2 and stroke) [20]. The majority of these variables are also related to cardiac function [21] and therefore were adjusted for in models. Blood samples were collected at the research center and used to determine cholesterol levels and DNA genotypes. *APOE* genotype was determined using a polymerase chain reaction or a biallelic TaqMan assay (rs7412 and rs429358) on labeled DNA samples. *APOE* genotype was classified into two groups: non-carriership or carriership of the *APOE*-ε4 allele, as *APOE*-ε4 has been recognized as a major genetic risk factor for cognitive impairment, brain lesions, and Alzheimer's disease onset [22]. Depressive symptoms were assessed with a validated version of the Centre for Epidemiologic Studies Depression (CES-D) scale (range 0–60) [23]. Scores of 16 or greater were regarded as suggestive of clinically significant depressive symptoms [23]. Diabetes mellitus was defined as a fasting plasma glucose level ≥ 7 mmol/L, a non-fasting plasma glucose level ≥ 11.1 mmol/L, or the use of blood glucose-lowering medication [24]. Stroke was defined according to the World Health Organization criteria [25].

Statistical analysis

Data were expressed as mean ± standard deviation (SD) for normally distributed variables or as median (interquartile range [IQR]) for non-normally distributed variables among participants in tertiles of baseline NT-proBNP levels. Missing covariates were imputed with five-time imputation using a chained equation [26].

We used linear mixed-effect models to study associations between NT-proBNP and continuous outcomes and applied generalized estimating equations for dichotomous outcomes. NT-proBNP concentrations were first analyzed per one unit increase of log-transformed values to achieve normal distribution and then categorized into tertiles with the lowest tertile as the reference.

Based on linear curves of cognitive changes after the age of 65 years, as found in a previous study [27], the fixed-effect structure included NT-proBNP levels, age, quadratic age (age^2), time, quadratic follow-up time (time^2), sex, smoking status, education levels, BMI, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol levels, prevalent diabetes mellitus, depressive symptom, and *APOE* genotype. The parameter of NT-proBNP ($\beta_{\text{NT-proBNP}}$) denoted an average effect of an increase in NT-proBNP on cognition, while other variables remain unchanged. For longitudinal analyses, we also added an interaction term between baseline age and time, and an interaction term between NT-proBNP levels and time ($\beta_{\text{NT-proBNP*time}}$), which provides the average effect of NT-proBNP per unit increase on cognitive changes per year. In the random-effect structure, we used random intercepts and random linear slopes to incorporate individual response trajectories of cognition.

Regarding nonlinear trajectories of brain imaging markers with advancing age [28], the main difference from the above models of cognition was the different multiplicative terms in the fixed-effect structure. We included multiplicative terms between baseline age and time variables, including follow-up time and time^2, and interaction terms for the product of NT-proBNP levels and time variables (time and time^2), which together interpret the effect of NT-proBNP on the overall rate of changes in brain structure per year, along with the same random-effect structure as above. Analyses involving volumetric measures were additionally adjusted for intracranial volumes. Gray and white matter volumes were adjusted for each other. White matter microstructural measures (fractional anisotropy and mean diffusivity) were additionally adjusted for intracranial volumes and macrostructural white matter measures (normal-appearing white matter and white matter hyperintensity). The associations between baseline NT-proBNP levels and the presence of microbleeds and lacunar infarcts were tested using the generalized estimating equation. We applied the same fixed-effect structure as the above

linear mixed-effect model and used a first-order autoregressive correlation matrix.

In addition, we performed stratifications on sex, age (median), and *APOE*-ε4 allele carriership (carrier vs. non-carrier). These were selected as possible effect modifiers based on previous literature and biological plausibility [28–30].

Because cut-off values of NT-proBNP are commonly used in clinical practice for the diagnosis of heart failure (900 pg/mL [=106.2 pmol/L] for likely heart failure, among populations aged >50 years) [31], in sensitivity analyses, we repeated longitudinal analyses after excluding participants with NT-proBNP values >106.2 pmol/L and/or any of following (cardio)vascular diseases, including prevalent chronic kidney disease, coronary heart disease, and atrial fibrillation, and also excluding participants with missing information on heart disease at baseline, with regards to the confounding effect of these comorbidities on the associations [32].

Given that we included one determinant (NT-proBNP) and 18 outcomes (cognitive tests and brain MRI), which are partly interrelated, we ran permutation testing to ascertain the number of independent tests. For each outcome variable, 10,000 iterations of linear regressions using a random variable were performed. The minimum *p* value for each regression model (permutation) was extracted and these *p* values were sorted to define the significance threshold based on the 5% quantile (0.0038). We then calculated the number of independent tests by dividing 0.05 by this threshold, resulting in 13.1 independent tests. A multiple-testing adjusted *p* value threshold (0.0039) was created by calculating the new significance threshold using the Sidák correction, $\alpha_n = 1 - (1 - \alpha)^{(1/n)}$, where *n* is the number of independent tests [33]. Data analyses were performed using R version 4.1.1 (Foundation for Statistical Computing).

RESULTS

Characteristics of the study population

As shown in Table 1, among 9566 participants (mean age 65.1 ± 9.8 years), 5444 (56.9%) were women, and repeated measures of cognitive tests were performed during a median follow-up time of 5.5 (range 1.1–17.9) years, of whom 2607 participants completed at least one brain scan (Table S3).

NT-proBNP and cognitive changes

Participants with higher NT-proBNP levels had poorer performance on cognitive tests at baseline, including the G-factor, the LDST, the Stroop test, and the PPB test. (Figure 1a–c, Table S4) Higher levels of NT-proBNP were linearly associated with a steeper decline in the G-factor, WFT scores, and PPB scores during the follow-up, but not with other cognitive tests (G-factor, interaction terms of time × NT-proBNP: mean difference of −0.003 per year per 1 unit increase in log-transformed NT-proBNP, 95% confidence interval [CI]: [−0.005, −0.001], *p* value = 0.003; WFT, mean difference: −0.004 per year, 95%CI: [−0.006, −0.001], *p* value = 0.003; PPB test, mean difference: −0.006 per year, 95%CI: [−0.012, 0.000], *p* value = 0.038). The association between NT-proBNP and PPB test was not statistically significant after multiple testing corrections. Compared to participants in the lowest tertile of NT-proBNP, participants in the highest tertile showed a faster decline in the G-factor, the WFT, and the PPB test (G-factor, mean difference: −0.004 per year, 95%CI: [−0.009, 0.000], *p* value = 0.046; WFT, mean difference: −0.007 per year, 95%CI: [−0.012, −0.002], *p* value = 0.011; PPB test, mean difference: −0.015 per year, 95%CI: [−0.028, −0.002], *p* value = 0.026). After multiple testing corrections, these associations were not statistically significant (Figure 1a–c, Table S4).

NT-proBNP and structural brain changes

As presented in Figure 2a,b, higher levels of NT-proBNP were associated with overall smaller volumes of total brain tissue, gray matter, and white matter, larger volumes of white matter hyperintensity, lower fractional anisotropy, and higher mean diffusivity at baseline.

Baseline NT-proBNP was not associated with the steepness of changes in brain structure over time (interaction terms of time × NT-proBNP and time^2 × NT-proBNP; Figure 2a,b, Table S5). As presented in Table S6, baseline NT-proBNP was not related to the occurrence of microbleeds and lacunar infarcts.

Stratification

Stratification by sex, age, or *APOE*-ε4 allele carriership on structural brain change did not show any differences between subgroups of the stratified factors. In cognitive analyses, we found a steeper deterioration in the G-factor, the WFT, and the Stroop test 3 with a per unit increase in NT-proBNP among males, but not in female participants. Participants aged above 60 years, and *APOE*-ε4 non-carriers, also showed a steeper decline in the G-factor, WFT, and PPB scores compared to younger participants or *APOE*-ε4 carriers (Tables S7.1–S7.3).

NT-proBNP levels were not longitudinally associated with brain structure or the occurrence of focal brain lesions in any of the stratifications (Tables S8.1–S8.3, S9.1–S9.3).

Sensitivity analysis

After the exclusion of participants with any (cardio)vascular diseases and participants with missing information on heart disease at baseline, higher levels of NT-proBNP were still associated with a steeper decline for the WFT (*p* value = 0.007, not statistically significant after multiple testing correction), but not for the G-factor and PPB test.

TABLE 1 Baseline characteristics of the population for cognition set.

	Tertiles of NT-proBNP (pmol/L)			
	Total	Lowest tertile	Medium tertile	Highest tertile
	(*N* = 9566)	(*N* = 3191)	(*N* = 3187)	(*N* = 3188)
Characteristics				
Age, years	65.1 ± 9.8	59.9 ± 7.2	64.2 ± 8.6	71.0 ± 9.9
Follow-up time, years	5.5 ± 9.8	5.7 ± 9.5	5.6 ± 10.1	4.9 ± 1.6
Female (%)	5444 (56.9)	1364 (42.7)	2060 (64.6)	2020 (63.4)
NT-proBNP level, pmol/L	18.7 ± 51.5	3.3 ± 1.3	8.4 ± 2.0	44.4 ± 83.4
Diastolic blood pressure, mmHg	78.8 ± 11.5	80.4 ± 10.4	78.6 ± 11.4	77.4 ± 12.4
Systolic blood pressure, mmHg	139.6 ± 21.1	135.0 ± 17.8	138.5 ± 20.4	145.3 ± 23.4
Diabetes, (%)	921 (9.6)	296 (9.3)	277 (8.7)	348 (10.9)
Clinically relevant depressive symptoms, (%)	786 (8.4)	242 (7.7)	265 (8.4)	279 (9.0)
Cholesterol, mmol/L	5.7 ± 1.0	5.8 ± 1.0	5.8 ± 1.0	5.7 ± 1.0
High-density lipoprotein cholesterol, mmol/L	1.4 ± 0.4	1.3 ± 0.4	1.4 ± 0.4	1.4 ± 0.4
Body mass index, kg/m^2	27.3 ± 4.2	27.6 ± 4.1	27.1 ± 4.2	27.0 ± 4.2
Educational level (%)				
Primary	1166 (12.3)	236 (7.5)	380 (12.0)	550 (17.4)
Lower	3836 (40.5)	1174 (37.1)	1348 (42.6)	1314 (41.7)
Intermediate	2781 (29.3)	978 (30.9)	898 (28.4)	905 (28.7)
Higher	1699 (17.9)	777 (24.5)	538 (17.0)	384 (12.2)
Smoking (%)				
Never	3131 (33.0)	996 (31.3)	1050 (33.1)	1085 (34.7)
Former	4548 (48.0)	1541 (48.5)	1488 (46.9)	1519 (48.6)
Current	1797 (19.0)	641 (20.2)	632 (19.9)	524 (16.8)
APOE genotype (%)				
ε4 allele carrier	2584 (28.4)	858 (28.2)	879 (29.0)	847 (27.9)
ε4 alleles non-carrier	6520 (71.6)	2188 (71.8)	2147 (71.0)	2185 (72.1)

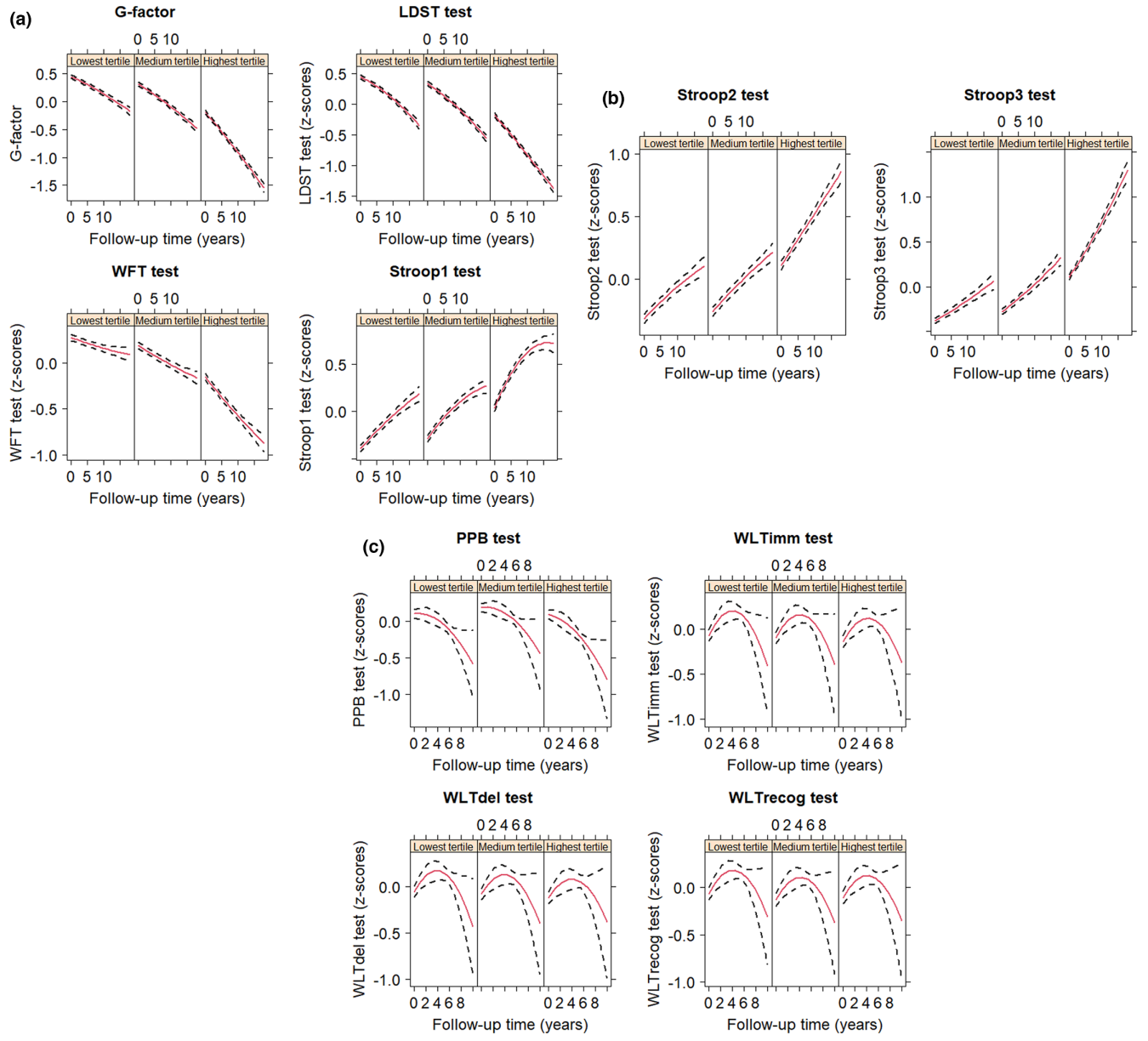
Note: Data represent original data without imputed values. The missing proportion for different variables is listed as follows: age (0.1%), body mass index (1.2%), cholesterol (0.6%), high-density lipoprotein cholesterol (1.2%), education (0.9%), smoking (0.9%), diabetes (0.6%), diastolic blood pressure (0.5%), depressive symptom (1.9%), systolic blood pressure (0.5%), and *APOE* (4.8%).

Abbreviations: *APOE*, apolipoprotein E; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

DISCUSSION

In this study, we found that higher baseline NT-proBNP levels were associated with a steeper decline in cognitive function, in particular the G-factor and WFT, but were not related to a faster deterioration of brain structure over time.

In line with previous studies (including one study from our group [10]), we confirmed a significant cross-sectional association between higher levels of NT-proBNP and cognitive impairment [10, 34, 35]. In analyses of cognitive changes, the main finding that higher NT-proBNP levels were also associated with a steeper decline in cognition was by a prior study [36]. However, the difference between the two studies lies in finding associations with different cognitive domains. In this study, higher levels of NT-proBNP were associated with a steeper decline in global cognitive function, and verbal fluency, but not with processing speed and memory, while a faster decline in processing speed, memory, and reaction was observed in the prior study. Part of the difference between the two studies could be explained by a difference in mean age between the study populations, as older age is a widely acknowledged risk factor of neurodegeneration and affects cognitive performance via brain structural deterioration in specific regions. In the current study, our findings for change over time for the



PPB disappeared after multiple testing adjustments, but the associations for the G-factor and WFT remained. This could indicate that NT-proBNP mechanisms are more involved in global cognitive function than in specific cognitive domains or specific brain structures. Given that the WFT may measure both executive functioning and verbal fluency, the WFT may capture a more global cognitive function than other individual cognitive tests.

There are several potential pathophysiological mechanisms linking NT-proBNP to cognitive decline. First, this link could be partly explained by cerebral hypoperfusion driven by reduced cardiac output [37, 38]. Cerebral hypoperfusion might influence cerebral blood flow, which could further lead to dementia development [39, 40]. Moreover, cognitive improvement has been observed in patients after receiving cardiac transplantation, implying a close link between cardiac function and cognition [41]. Second, plasma natriuretic peptides have been involved in the regulation of blood–brain barrier integrity, synaptic transmission, and brain fluid homeostasis, and disruption in these functions has been suggested as a potential mechanism for cognitive decline [42, 43]. Third, structural brain alterations might play a role in mediating the association between NT-proBNP and cognitive function [11]. As reported in previous work of our group [44], a significant association was observed between increased NT-proBNP levels and subclinical brain damage.

The cross-sectional association between increased NT-proBNP levels and subclinical brain damage was also confirmed in this study, which was comparable to the previous finding reported by our group [44]. However, we did not observe any significant longitudinal association between the cardiac marker and structural brain changes, which contrasts with a prior study [45]. Sabayan et al. [45], found that higher NT-proBNP was associated with a 1% annual decline in the volumes of total brain and gray matter. These different findings might be explained by the older age of their study population. Older

FIGURE 1 (a) Longitudinal associations between tertiles of baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and changes in individual cognitive tests (global cognitive function and executive cognitive function) over time (to be continued). G-factor, principal component scores of global cognitive function; LDST, letter-digit substitution test; WFT, Word-Fluency test. Cognitive data are presented in tertiles of NT-proBNP level, using the linear mixed-effect model. All data in parentheses are 95% confidence intervals. Models were adjusted for age, age^2, time, time^2, sex, smoking status, education levels, body mass index, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol level, diabetes mellitus, depressive symptom, *APOE* genotype, and an interaction term of the product of follow-up time and baseline age. Red solid lines represent the marginal (group) changes in individual cognitive tests, and black dashed lines represent the 95% confidence intervals based on fully adjusted models. Lower scores on the G-factor, the WFT, the LDST, and higher Stroop test scores indicate worse cognitive functions. (b) Longitudinal associations between tertiles of baseline NT-proBNP levels and changes in individual cognitive tests (executive cognitive function) over time. Cognitive data are presented in tertiles of NT-proBNP level, using the linear mixed-effect model. All data in parentheses are 95% confidence intervals. Models were adjusted for age, age^2, time, time^2, sex, smoking status, education levels, body mass index, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol level, diabetes mellitus, depressive symptom, *APOE* genotype, and an interaction term of the product of follow-up time and baseline age. Red solid lines represent the marginal (group) changes in individual cognitive tests, and black dashed lines represent the 95% confidence intervals based on fully-adjusted models. Higher Stroop test scores indicate worse cognitive functions. (c) Longitudinal associations between tertiles of baseline NT-proBNP levels and changes in individual cognitive tests (fine manual dexterity and memory) over time. PPB test, Purdue Pegboard test; WLTdel, Word Learning test, delayed recall; WLTimm, Word Learning test, immediate recall; WLTrecog, Word Learning test, recognition. Cognitive data are presented in tertiles of NT-proBNP level, using the linear mixed-effect model. All data in parentheses are 95% confidence intervals. Models were adjusted for age, age^2, time, time^2, sex, smoking status, education levels, body mass index, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol level, diabetes mellitus, depressive symptom, *APOE* genotype, and an interaction term of the product of follow-up time and baseline age. Red solid lines represent the marginal (group) changes in individual cognitive tests, and black dashed lines represent the 95% confidence intervals based on fully adjusted models. Lower scores on the PPB test, the WLTdel, the WLTimm, and the WLTrecog indicate worse cognitive functions.

age was associated with a steeper decline in multiple brain imaging markers [28], which was also demonstrated by the significantly inverse interaction between age and follow-up time on structural brain changes in our models. However, our age stratification did not unravel the presence of the association between NT-proBNP and structural brain changes. More prospective studies are warranted to explore the cardiac function of structural brain alterations over time.

In stratification by age, a steeper decline in cognition was observed in older participants with higher NT-proBNP levels. Reduced cerebral perfusion in older age leading to cognitive damage might explain this difference between age groups [46]. Among male but not female participants, we observed inverse associations between NT-proBNP and changes in cognition, with steeper deterioration among males. Estrogen provides a beneficial effect on both neural cells and against cardiomyocyte apoptosis, by reducing inflammatory metabolic syndrome, acute-phase inflammatory processes, and oxidation, all modifying the effect of cardiac function on cognition [47–49]. However, evidence on a general population level is still lacking. More attention should focus on testing these hypotheses underlying sex differences.

Strengths and limitations

The major strength of this study was the large sample size of >9500 participants with cognitive tests and >2500 with brain MRI scans, and multiple repeated measures of cognition and brain structure over time. However, certain limitations need to be considered. One limitation was the weakness in determining the causality of associations concerning inherent restraints of observational studies, such as selection bias derived from missing data on repeated measurements due to inevitable dropout during the long period of follow-up. Second, our study only focused on general brain structure without regarding specific brain regions, which impedes establishing links between NT-proBNP, brain regions, and specific cognitive domains. In addition, the magnetic field of 1.5T has its limitations, as a higher magnetic field increases the sensitivity of detecting abnormalities of the brain or changes in the brain over time, due to potentially better visualizing structural changes and characterizing signal properties of individual lesions, driven by a gain in the signal-to-noise ratio [50]. However, 1.5T MRI is a commonly used imaging method in research and in a clinical setting. The limitation of this imaging method regarding the brain structures measured and used in this research is expected to be minimal, since we investigated the association between NT-pro-BNP and global brain structures, rather than small brain regions; and are likely balanced by the advantage of having standardized image acquisition by keeping the hardware and software stable over time. Third, since this study mainly focused on global measures of brain structure, including global FA and MD, regional effects may have been missed, which is a limitation. Last, this cohort was almost entirely European, with a median age above 65 years at baseline, which might restrict the extrapolation of our findings to multiethnic and younger populations.

CONCLUSIONS

In conclusion, higher NT-proBNP levels were found to be associated with a faster decline in global cognition and the WFT but were not found with cognitive domains or global structural brain changes over time.

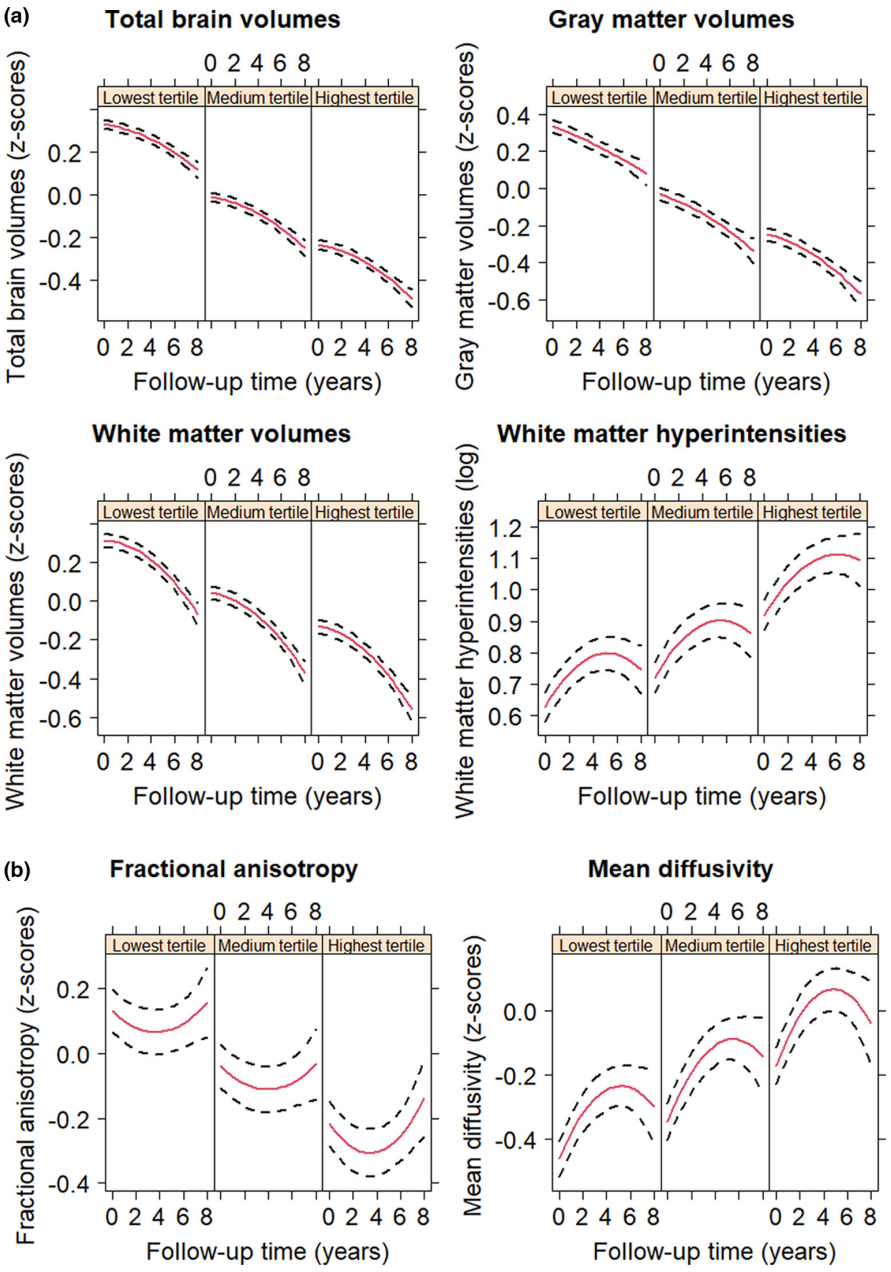


FIGURE 2 (a) Longitudinal associations between tertiles of baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and changes in brain volumes and white matter microstructure. MRI data are presented in tertiles of NT-proBNP level, using the linear mixed-effect model. All data in parentheses are 95% confidence intervals. Models were adjusted for age, age^2, time, time^2, sex, smoking status, education levels, body mass index, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol level, diabetes mellitus, *APOE* genotypes, and interaction terms of the product of follow-up time or time^2 and baseline age. Analyses involving volumetric measures were additionally adjusted for intracranial volumes. Gray and white matter volumes were adjusted for each other. Microstructural measures were additionally adjusted for phase encoding direction, intracranial volumes, and microstructural white matter measures (volumes of the normal-appearing white matter and white matter hyperintensity). Red solid lines represent the marginal (group) changes in brain structure, and black dashed lines represent the 95% confidence intervals based on fully-adjusted models. (b) Longitudinal associations between tertiles of baseline NT-proBNP levels and changes in white matter microstructure integrity. MRI data are presented in tertiles of NT-proBNP level, using the linear mixed-effect model. All data in parentheses are 95% confidence intervals. Models were adjusted for age, age^2, time, time^2, sex, smoking status, education levels, body mass index, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol level, diabetes mellitus, *APOE* genotypes, and interaction terms of the product of follow-up time or time^2 and baseline age. Microstructural measures were additionally adjusted for phase encoding direction, intracranial volumes, and microstructural white matter measures (volumes of the normal-appearing white matter and white matter hyperintensity). Red solid lines represent the marginal (group) changes in brain structure, and black dashed lines represent the 95% confidence intervals based on fully-adjusted models. Lower fractional anisotropy and higher mean diffusivity indicate worse white matter microstructural integrity.

AUTHOR CONTRIBUTIONS

Tian Xiao: Writing – original draft; formal analysis; conceptualization; visualization. **Wiro J. Niessen:** Resources. **Martijn J. Tilly:** Resources. **Maryam Kavousi:** Resources. **M. Arfan Ikram:** Funding acquisition; investigation; resources. **M. Kamran Ikram:** Conceptualization; supervision; investigation.

ACKNOWLEDGMENTS

This study was approved by the medical ethics committee of the Erasmus Medical Centre (Rotterdam, the Netherlands), and the review board of the Netherlands Ministry of Health, Welfare and Sports (1068889-159521-PG). All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians. All authors had access to the study data and take full responsibility for the data, analyses, and interpretation of results. The authors are grateful to the study participants, the staff from the Rotterdam Study, and the participating general practitioners and pharmacists.

FUNDING INFORMATION

This research was partly performed as part of the Netherlands Consortium of Dementia Cohorts (NCDC), which receives funding in the context of Delta plan Dementia from ZonMW Memorable (projector 73305095005) and Alzheimer Nederland. Further funding was obtained through the Stitching Erasmus Trustfonds (grant number 97030.2021.101.430/057/RB). The Rotterdam Study is supported by the Erasmus MC and Erasmus University Rotterdam; the Netherlands Organization for Scientific Research (NWO); the Netherlands Organization for Health Research and Development (ZonMW); the Research Institute for Diseases in the Elderly (RIDE); the Netherlands Genomics Initiative; the Ministry of Education, Culture and Science; the Ministry of Health, Welfare and Sports; the European Commission (DG XII); and the Municipality of Rotterdam. The funding sources had no involvement in the collection, analysis, writing, interpretation, or decision to submit the manuscript for publication.

CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data can be obtained upon request. Requests should be directed to the management team of the Rotterdam Study (datamanagement.ergo@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and the informed consent of the participants, data cannot be made freely available in a public repository.

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SUPPORTING INFORMATION

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

How to cite this article: Xiao T, van der Velpen IF, Niessen WJ, et al. NT-proBNP and changes in cognition and global brain structure: The Rotterdam Study. *Eur J Neurol*. 2023;00:1-10. doi:10.1111/ene.15859