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# High-Sensitivity Cardiac Troponin T and Cognitive Decline in Older Adults: Results of the Berlin Aging Study II

Regina von Rennenberg[a, b, c] Thomas Liman[a, b, d] Christian H. Nolte[a, b, c, d] Alexander H. Nave[a, b, d, e] Jan F. Scheitz[a, b, d] Sandra Düzel[f] Vera Regitz-Zagrosek[d, g] Denis Gerstorf[h] Elisabeth Steinhagen-Thiessen[i] Ilja Demuth[i, j] Matthias Endres[a, b, c, d, e]

[a]Department of Neurology, Charité – Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [b]Center for Stroke Research Berlin (CSB), Charité – Universitätsmedizin Berlin, Berlin, Germany; [c]German Center for Neurodegenerative Diseases (Deutsches Zentrum für Neurodegenerative Erkrankungen), Berlin, Germany; [d]German Center for Cardiovascular Research (Deutsches Zentrum für Herz-Kreislaufforschung), Charité-Universitätsmedizin Berlin, Berlin, Germany; [e]Berlin Institute of Health (BIH), Berlin, Germany; [f]Max Planck Institute for Human Development, Berlin, Germany; [g]Gender in Medicine (Institut für Geschlechterforschung in der Medizin, GiM), Charite-Universitätsmedizin, Berlin, Germany; [h]Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany; [i]Biology of Aging working group, Department of Endocrinology and Metabolic Diseases (including Division of Lipid Metabolism), Charité – Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [j]Berlin Institute of Health at Charité – Universitätsmedizin Berlin, BCRT – Berlin Institute of Health Center for Regenerative Therapies, Berlin, Germany

**Keywords**
Cardiac troponin · Cognitive decline · Heart-brain axis

**Abstract**
***Introduction:*** There is evidence of an association between markers of cardiac injury and cognition in patients with cardiovascular disease. We hypothesized that levels of high-sensitivity cardiac troponin T (hs-cTnT) are associated with cognitive performance and cognitive decline in a population of predominantly healthy older adults. ***Methods:*** We included 1,226 predominantly healthy adults ≥60 years from the Berlin Aging Study II. Participants were recruited from the general population of the Berlin metropolitan area from 2009 to 2014. At baseline, participants underwent measurement of hs-cTnT and cognitive testing using the extended Consortium to Establish a Registry for Alzheimer's Disease (CERAD-Plus) battery. In addition, the Digit Symbol Substitution Test (DSST) was performed at baseline and at follow-up (7.3 ± 1.4 years after the baseline visit). The CERAD test results were summarized into four cognitive domains (processing speed, executive function, visuo-construction, and memory). After summing-up the respective raw scores, we calculated standardized *z* scores. We performed unadjusted and adjusted linear regression models to assess links between hs-cTnT and cognitive domains. We used linear mixed models to analyze associations between hs-cTnT and cognitive decline according to changes in DSST scores over time.

Ilja Demuth and Matthias Endres contributed equally to this work.

Karger@karger.com
www.karger.com/ger



Correspondence to:
Regina von Rennenberg, regina-irene.freiin-von-rennenberg@charite.de

***Results:*** The mean age of study participants at baseline was 68.5 (±3.6) years, 49% were female, and median hs-cTnT levels were 6 ng/L (IQR 4–8 ng/L). We detected no significant association between hs-cTnT and different cognitive domains at baseline after adjustment for age, sex, education, and cardiovascular risk factors. Hs-cTnT was associated with cognitive decline, which remained statistically significant after full adjustment (adjusted beta-coefficient −0.82 (−1.28 to −0.36), $p = 0.001$). After stratification for sex, the association with hs-cTnT remained statistically significant in men but not in women. ***Conclusion:*** Higher hs-cTnT levels in older men are associated with cognitive decline measured with the DSST.


## Introduction

The increasing prevalence of dementia and cognitive impairment is a major public health concern worldwide [1]. An association of cardiovascular diseases with of cognitive impairment and dementia has long been demonstrated in many epidemiological studies [2–4]. Moreover, data suggest that treatment of heart diseases may lead to an improvement of cognitive function [5].

Furthermore, there is evidence of an association of subclinical markers of cardiac injury, such as higher levels of cardiac biomarkers or pathological findings on echocardiography, with cognitive impairment as well as cognitive decline [6–9]. The link between higher levels of natriuretic peptides (i.e., BNP and NT-proBNP) and cognitive impairment as well as incident dementia has been described previously by several studies conducted in the general population [8, 10]. Another well-established and routinely used biomarker that is both sensitive and specific for myocardial injury is cardiac troponin [11]. Different assays enable clinicians to measure the cardiac-specific subunits troponin T and troponin I [12]. With the introduction of highly sensitive assays (hs-cTn) in recent years, myocardial injury may now be detected and quantified more accurately and at lower thresholds [13]. However, data concerning the association between cardiac troponin and cognitive performance are still scarce, and studies examining the link between troponin and cognitive performance have so far reported inconsistent results. Among older adults with cardiovascular disease, there is an association between higher levels of cardiac troponin T and worse cognitive performance as well as cognitive decline [14, 15], with a possible limitation to certain cognitive domains [16]. Longitudinal studies in the general population found an association between cardiac troponin and incident dementia but not with decline in cognitive test performance in the general population of older adults [17, 18]. Taken together, the association between elevated levels of troponin as markers of subclinical myocardial injury and cognition is still not fully understood.

Moreover, there is uncertainty concerning sex-specific differences in the link between cardiovascular risk and cognitive impairment: while one study in individuals with mild cognitive impairment shows that a history of stroke and diabetes is more common in men [19] and the ARIC study found a stronger association between heart failure and subclinical cerebral infarcts in men [20], other studies found that a history of cardiovascular disease is more strongly associated with cognitive impairment in women [21, 22]. We hypothesized that in a large population of healthy older adults, higher levels of cardiac troponin T might be associated with worse cognitive performance at baseline as well as subsequent cognitive decline over a period of several years. In addition, we examined whether the association between cardiac troponin T and cognitive performance differed between men and women.

## Materials and Methods

*Study Population*

The Berlin Aging Study II (BASE-II) is a prospective, multidisciplinary, interinstitutional, and community-based longitudinal study with the primary goal of identifying risk factors for "healthy" and "unhealthy" aging. The BASE-II study has been described in detail previously [23]. BASE-II participants were recruited from the general population of the greater Berlin metropolitan area via advertisements placed in local newspapers and the Berlin public transport system. Baseline medical assessments took place between 2009 and 2014. The study population consisted of both a large group of older adults (60–85 years) and younger adults (22–37 years). Since participants of the younger age group did not undergo repeated cognitive testing, we only evaluated participants of the older age group for this substudy. At baseline, a thorough medical history was taken and patients provided blood samples for laboratory measurements. All older participants were invited to a follow-up visit, which was part of the GendAge study [24]. The aim of the GendAge study was to identify risk factors for cardiovascular disease and unfavorable outcomes in older adults in the context of biological "sex" and sociocultural "gender" [24]. The average follow-up period was 7.3 years (SD ± 1.4 years). At follow-up, participants were interviewed concerning adverse cardiovascular events and the diagnosis of incident dementia. Information on mortality was obtained from local registration offices. In order to assess the sociocultural dimension of "gender," nine gender-related psycho-social and socioeconomic variables were identified and used to construct a gender score in a subset of the participants included in BASE-II, resulting in a gender score from 0 to 100 [25].

**Table 1.** Participants' characteristics and cognitive function at baseline and follow-up

| At baseline | Total population (*n* = 1,226) | Male individuals (*n* = 621) | Female individuals (*n* = 605) |
|---|---|---|---|
| Age, mean (SD) | 68.5 (±3.7) | 68.9 (±3.7) | 68.1 (±3.5) |
| Years of education, median (IQR) | 15 (13–17) | 16 (13–17) | 14 (12–16) |
| Hypertension, *n* (%) | 576 (47.0) | 311 (50.0) | 265 (43.8) |
| Diabetes mellitus, *n* (%) | 120 (9.8) | 81 (13.0) | 39 (6.4) |
| Heart failure, *n* (%) | 30 (2.4) | 14 (2.3) | 16 (2.6) |
| MMSE, median (IQR) | 29 (28–30) | 29 (28–29) | 29 (28–30) |
| MMSE <26 points, *n* (%) | 32 (2.6) | 22 (3.5) | 10 (1.7) |
| DSST, median (IQR) | 44 (39–50) | 44 (39–50) | 43 (38–49) |
| Cardiac troponin T, ng/L, median (IQR) | 6 (4–8) | 7 (5–10) | 5 (3–7) |
| Gender-score,* median (IQR) | 49.8 (29.6–74.0) | 34.5 (20.2–52.8) | 67.5 (46.3–82.9) |
| **At follow-up** | **Total population (*n* = 1,072)** | **Male individuals (*n* = 537)** | **Female individuals (*n* = 535)** |
| Age, mean (SD) | 75.7 (±3.7) | 75.5 (±3.9) | 75.8 (±3.5) |
| MACE, *n* (%) | 180 (16.8) | 111 (20.7) | 69 (12.9) |
| Death, *n* (%) | 121 (11.3) | 75 (14.0) | 46 (8.6) |
| Stroke, *n* (%) | 28 (2.9) | 16 (3.5) | 12 (2.5) |
| Myocardial infarction, *n* (%) | 31 (3.3) | 20 (4.3) | 11 (2.2) |
| MMSE, median (IQR) | 29 (28–30) | 29 (28–30) | 29 (28–30) |
| MMSE <26 points, *n* (%) | 47 (4.9) | 29 (6.3) | 18 (3.7) |
| DSST, median (IQR) | 41 (35–46) | 40 (34–45) | 42 (36–47) |

MMSE, mini mental status examination (0–30 points); MACE, major adverse cardiovascular events; DSST, digit symbol substitution test. * Gender score was available for *n* = 948 subjects (*n* = 452 male, *n* = 496 female).

Lower scores represent more masculine and higher scores more feminine traits, and the distribution of scores differs significantly according to biological sex [25]. All research procedures were performed in accordance with the World Medical Association Declaration of Helsinki.

*Neuropsychological Assessments*

Baseline cognitive functioning was assessed using the German version of the extended Consortium to Establish a Registry for Alzheimer's Disease (CERAD-Plus) battery [26]. The CERAD-Plus battery is a comprehensive neuropsychological assessment containing a variety of tasks to examine different cognitive abilities. We summarized the test scores for the respective CERAD items into four cognitive domains. After summing-up the respective raw scores within each cognitive domain, we calculated standardized *z* scores for each domain. We assessed executive function by combining the item scores for semantic fluency and phonematic fluency. Memory function was examined using the items word list learning, word list recall, constitutional praxis recall, and word list discriminability. We assessed visuo-construction using the items constitutional praxis copy and constitutional praxis recall. Finally, processing speed was calculated using the Trail Making Test B. Global cognitive function was assessed using the Mini Mental Status Examination (MMSE), which was performed both at baseline and during follow-up [27].

Moreover, cognitive testing included the Digit Symbol Substitution Test (DSST) of the Wechsler adult intelligence scale-revised [28] both at baseline and during follow-up. The DSST tests mainly processing speed. Participants are asked to translate numbers into symbols using a key. The test score equals the number of correct translations from numbers to symbols within 90 s [28]. The diagnosis of incident dementia was based on participants' reported information.

*Measurement of High-Sensitivity Cardiac Troponin T Concentrations*

Cardiac troponin T concentrations were available for all individuals from the older age group (age range 60–85 years) who had undergone cognitive testing. High-sensitivity cardiac troponin T (hs-cTnT) was measured from the blood samples collected during the baseline visit using the Elecsys assay (Roche Elecsys Troponin Ths, Mannheim, Germany). This assay has a limit of detection of 3 ng/L and the upper reference limit (based on the 99th percentile of a healthy population) is at set 14 ng/L [29].

*Statistical Analysis*

Associations between Hs-cTnT and Cognition at Baseline

To assess the relationship between hs-cTnT and cognitive performance at baseline, we conducted unadjusted and adjusted linear regression models. Adjustment was made based on clinical relevance using two different models. In the first model (model 1), we adjusted for age (continuous), sex (dichotomous), years of education (as assessed in the context of CERAD-Plus testing, continuous), history of hypertension (dichotomous), history of diabetes

(dichotomous), and history of heart failure (dichotomous). In the second model (model 2), we adjusted for age (continuous), gender score (continuous), history of hypertension (dichotomous), history of diabetes (dichotomous), and history of heart failure (dichotomous). Since biological "sex" and the gender score were closely correlated in the GendAge study [25], we did not include sex in the second adjustment model. Moreover, since education was one of the contributing variables for the calculation of the gender score [25], we did not adjust for education as a separate variable in the second adjustment model.

Associations between Hs-cTnT and Change in Cognition

In order to assess the association between hs-cTnT and cognitive change over time, we used the repeated measure of the DSST, which was performed both at baseline and during follow-up, in linear mixed models with a random intercept for each individual and hs-cTnT as a fixed effect. We used years since the baseline visit as the time scale and the adjustment was made using the same two adjustments as described for the analysis of baseline cognitive function.

In the first approach, we included hs-cTnT as a continuous variable (continuous model). Since hs-cTnT levels were not normally distributed in our study population, we used log-transformed values. In a second approach, we categorized the study population into four groups according to hs-cTnT values. Participants with hs-cTnT values below the upper reference limit were split into tertiles, while the fourth group consisted of participants with hs-cTnT levels above the upper reference limit (categorical model).

Since there is evidence that performance in various cognitive domains may be different in men and women [30] and that the association between cardiovascular risk factors and cognitive function may also be sex-specific [22], we reran all our analyses after stratifying for sex. In addition, we conducted unadjusted and adjusted logistic regression analyses to examine the association between hs-cTnT and the frequency of all-cause mortality, stroke, and myocardial infarction), as well as the composite endpoint of these major adverse cardiovascular events during follow-up.

All statistical analyses were performed using SPSS Statistics 27.0 (IBM, Armonk, NY). Statistical procedures were conducted at a 0.05 significance level.

## Results

*Baseline Characteristics*

In total, 1,226 participants ≥60 years of age were included in our analyses. Baseline characteristics are shown in Table 1. On average, participants were 68.5 (SD ± 3.6) years of age, and 49.3% were female. Median years of education was 16 (IQR 13–17) in men and 14 (IQR 12–16) in women. Median hs-cTnT levels in our study population were 6 ng/L (IQR 4–8 ng/L) and 7.4% had hs-cTnT values above the upper reference limit of 14 ng/L. Follow-up DSST scores were available for 951 participants alive (86%). Of our analysis sample, 121 participants (11.3%) had died. The mean age at follow-up was 75.7 (±3.7) years.

**Table 2.** Association between cardiac troponin T and baseline cognitive function

| | Processing speed | Executive function | Visuo-construction | Memory | DSST |
|---|---|---|---|---|---|
| Unadjusted model | | | | | |
| Troponin log transformed continuous | −0.13 (−0.29 to 0.03), $p = 0.100$ | −0.20 (−0.35 to −0.05), $p = 0.011$ | 0.16 (0.00–0.31), $p = 0.076$ | −0.12 (−0.26 to 0.03), $p = 0.163$ | −2.72 (−4.00 to −1.43), $p < 0.001$ |
| Troponin categorical | 0.07 (0.01 – 0.13), $p = 0.017$ | −0.09 (−0.15 to −0.03), $p = 0.002$ | 0.06 (−0.00 to 0.12), $p = 0.066$ | −0.06 (−0.12 to −0.00), $p = 0.042$ | −1.40 (−1.88 to −0.91), $p < 0.001$ |
| Adjusted model 1 | | | | | |
| Troponin log transformed continuous | 0.03 (−0.13 to 0.19), $p = 0.708$ | −0.08 (−0.24 to 0.08), $p = 0.328$ | 0.14 (−0.02 to 0.30), $p = 0.085$ | 0.08 (−0.07 to 0.24), $p = 0.295$ | −1.4 (−2.78 to −0.06), $p = 0.040$ |
| Troponin categorical | 0.03 (−0.04 to 0.09), $p = 0.441$ | −0.04 (−0.10 to 0.02), $p = 0.195$ | 0.05 (−0.01 to 0.11), $p = 0.127$ | 0.03 (−0.03 to 0.09), $p = 0.341$ | −0.85 (−1.38 to −0.32), $p = 0.002$ |
| Adjusted model 2 | | | | | |
| Troponin log transformed continuous | 0.04 (−0.14 to 0.22), $p = 0.682$ | −0.18 (−0.38 to 0.01), $p = 0.064$ | 0.19 (−0.01 to 0.40), $p = 0.062$ | −0.05 (−0.24 to 0.14), $p = 0.629$ | −2.68 (−4.34 to −1.02), $p = 0.002$ |
| Troponin categorical | 0.04 (−0.04 to 0.11), $p = 0.340$ | −0.09 (−0.17 to −0.02), $p = 0.018$ | 0.06 (−0.03 to 0.14), $p = 0.178$ | −0.06 (−0.13 to 0.02), $p = 0.140$ | −1.526 (−2.17 to −0.88), $p < 0.001$ |

Coefficients and 95% confidence intervals of linear regression analyses. Adjusted model 1: adjustment for age, sex, years of education, history of hypertension, history of diabetes, and history of heart failure. Adjusted model 2: adjustment for age, gender score, history of hypertension, history of diabetes, and history of heart failure. DSST, digit symbol substitution test.

**Table 3.** Association between cardiac troponin T and cognitive function during follow-up according to DSST

| | Total population ($n$ = 951) | Male subjects ($n$ = 462) | Female subjects ($n$ = 489) |
|---|---|---|---|
| Unadjusted model | | | |
| Troponin log transformed continuous | −2.48 (−4.02 to −0.94), $p$ = 0.002 | −2.51 (−5.22 to 0.21), $p$ = 0.070 | −1.26 (−3.25 to 0.73), $p$ = 0.212 |
| Troponin categorical | −1.14 (−1.79 to −0.49), $p$ = 0.001 | −1.29 (−2.20 to 0.37), $p$ = 0.006 | −0.69 (−1.55 to 0.18), $p$ = 0.120 |
| Adjusted model 1 | | | |
| Troponin log transformed continuous | −1.53 (−3.21 to 0.15), $p$ = 0.073 | −3.24 (−6.11 to −0.37), $p$ = 0.027 | −0.50 (−2.52 to 1.52), $p$ = 0.628 |
| Troponin categorical | −0.73 (−1.41 to −0.05), $p$ = 0.036 | −1.35 (−2.35 to −0.35), $p$ = 0.008 | −0.09 (−1.03 to 0.85), $p$ = 0.856 |
| Adjusted model 2 | | | |
| Troponin log transformed continuous | −1.68 (−3.54 to 0.18), $p$ = 0.077 | −3.15 (−6.43 to 0.12), $p$ = 0.059 | 0.09 (−2.29 to 2.47), $p$ = 0.940 |
| Troponin categorical | −0.90 (−1.65 to −0.16), $p$ = 0.018 | −1.46 (−2.59 to −0.34), $p$ = 0.011 | 0.03 (−1.04 to 1.11), $p$ = 0.950 |

Coefficients and 95% confidence intervals of linear regression analyses. Adjusted model 1: adjustment for age, sex, years of education, history of hypertension, history of diabetes, and history of heart failure. Adjusted model 2: adjustment for age, gender score, history of hypertension, history of diabetes, and history of heart failure. DSST, digit symbol substitution test.

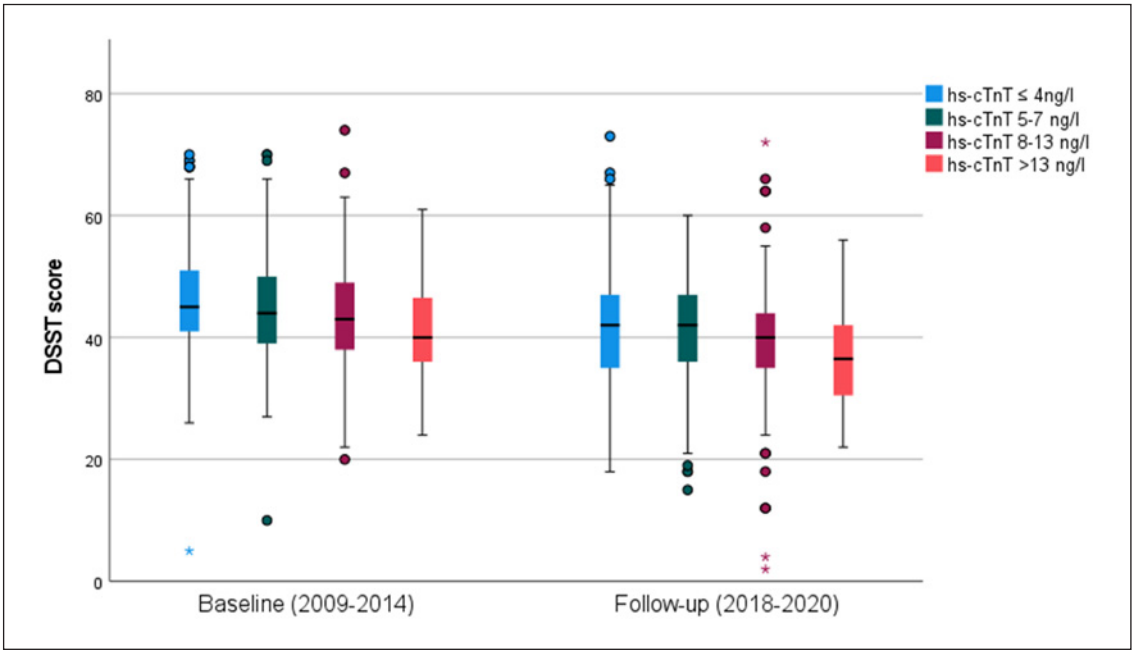


**Fig. 1.** DSST scores according to hs-cTnT category. DSST scores at baseline and at follow-up according to hs-cTnT in the categorical model. The average follow-up period was 7.3 (±1.4) years. hs-cTnT, high-sensitivity cardiac troponin T; DSST, digit symbol substitution test.

At follow up, 28 participants (2.9%) reported having suffered a stroke and 31 (3.3%) reported having suffered a myocardial infarction. Five participants reported a diagnosis of incident dementia at the follow-up visit.

*Associations of Cardiac Troponin T with Cognitive Performance and Decline*

Participants in our study had good to excellent global cognitive performance both at baseline (median MMSE 29 points [IQR 28–30]) and during follow-up (median MMSE 29 points [IQR 28–30]). There was no significant association between hs-cTnT and MMSE both at baseline and during follow-up (data not shown). In unadjusted analyses, hs-cTnT levels were associated with poorer performance regarding processing speed (β 0.071 [95% CI: 0.013–0.132], $p$ = 0.017) and executive function of the CERAD battery (β −0.092 [95% CI: −0.152 to −0.033], $p$ = 0.002) at baseline in the categorical model (see Table 2).

**Table 4.** Troponin and cognitive decline

| | Unadjusted | Adjusted model 1 | Adjusted model 2 |
|---|---|---|---|
| Troponin log-transformed continuous | | | |
| Group effect | −2.59 (−3.70 to −1.49), $p < 0.001$ | −1.50 (−2.69 to −0.31), $p = 0.013$ | −2.11 (−3.45 to −0.77), $p = 0.002$ |
| Time effect | −0.55 (−0.65 to −0.45), $p < 0.001$ | −0.57 (−0.67 to −0.47), $p < 0.001$ | −0.59 (0.70–0.47), $p < 0.001$ |
| Troponin categorical | | | |
| Group effect | −1.27 (−1.69 to −0.84), $p < 0.001$ | −0.82 (−1.28 to −0.36), $p = 0.001$ | −1.15 (−1.68 to −0.62), $p < 0.001$ |
| Time effect | −0.55 (−0.65 to −0.45), $p < 0.001$ | −0.57 (−0.67 to −0.47), $p < 0.001$ | −0.59 (−0.70 to −0.47), $p < 0.001$ |

Coefficients and 95% confidence intervals of linear mixed models. Adjusted model 1: adjustment for age, sex, years of education, history of hypertension, history of diabetes, and history of heart failure. Adjusted model 2: adjustment for age, gender score, history of hypertension, history of diabetes, and history of heart failure.



However, the association was no longer significant after adjustment according to both adjustment models (see Table 2). Our results remained unchanged when rerunning the analyses after stratifying for sex (see online suppl. Tables S1, S2; for all online suppl. material, see www.karger.com/doi/10.1159/000523845).

Higher hs-cTnT levels were significantly associated with poorer performance in the DSST both at baseline (see Table 2) and during follow-up (see Table 3; Fig. 1). Overall, cognitive performance according to the DSST decreased over time (see Table 4). We found an association between hs-cTnT and cognitive decline according to change in the DSST, which remained significant after adjustment for age, sex, education, and vascular risk factors (β −0.82 [95% CI −1.28 to −0.36, $p = 0.001$] in adjustment model 1) as well as after adjustment for gender (β −1.15 [95% CI: −1.68 to −0.62, $p < 0.001$] in adjustment model 2, see Table 4).

When rerunning the analyses after stratifying for sex, the association remained significant for men but not for women (see online suppl. Tables. S3, S4). This effect remained significant after adjustment for age and vascular risk factors as well as after additional adjustment for gender (see online suppl. Tables S3, S4). Both in the linear and in the categorical model, higher levels of hs-cTnT were significantly associated with major adverse cardiovascular events (death, stroke, and myocardial infarction, see online suppl. Table S5).

## Discussion/Conclusion

In this study, we analyzed whether levels of hs-cTnT were associated with cognitive performance at baseline and follow-up in a population of predominantly healthy older adults with good global cognitive function. We found that in a cross-sectional approach, hs-cTnT was not associated with the performance in specific cognitive domains using a comprehensive cognitive test battery (CERAD). However, higher hs-cTnT levels were associated with poorer performance in the DSST cross-sectionally and a steeper decline in DSST scores longitudinally.

Our findings are in line with other studies observing an association between higher hs-cTnT values and cognitive decline in different populations at high vascular risk [14, 15, 31]. Similar to our results, the ARIC study found that hs-cTnT was associated with lower DSST scores when analyzed cross-sectionally in a community-based approach [32]. A study by Veugen et al. [16] examining the link between hs-cTnT and individual cognitive domains in the general population found an association with both memory and processing speed, while we were unable to find such an association with specific cognitive domains. However, this study used a different cognitive test battery, which may explain different results from ours.

Interestingly, there was no significant association between hs-cTnT or NT-proBNP and changes in cognitive scores over time in the ARIC study [18]. After stratifying for sex, the investigators found a trend for cognitive decline in association with higher hs-cTnT in men only. This, however, did not reach statistical significance [18]. To our knowledge, our study is therefore the first to find such an association between hs-cTnT levels and faster cognitive decline in perceptual speed among predominantly healthy older adults with good global cognitive function at baseline. However, it should be pointed out that the effect of hs-cTnT on cognitive decline we were able to detect in our analyses was rather small. Our results show that cognitive decline in perceptual speed is pre-

dicted by hs-cTnT in men but not in women. Thus, the association between myocardial injury and cognitive change might vary according to sex.

Most studies examining cognitive performance according to sex found similar overall rates of cognitive impairment and cognitive decline in men and women [33–35]. However, cardiovascular disease manifests earlier in life in men [36, 37]. Since the average age in our study population was similar in men and women, the differences we observed in the association between hs-cTnT levels and cognitive change between men and women might merely result from different durations of cardiovascular risk exposure.

Data specifically concerning sex differences in the association between cardiovascular diseases and cognition are scarce and have reported conflicting results [19, 20, 22]. In our study, the difference in the association between hs-cTnT and cognitive decline after stratification for sex remained unchanged after additional adjustment for the sociocultural dimension of "gender" as assessed by the previously published gender score [25]. This suggests that in the context of cardiovascular disease, cognitive outcomes might vary more according to biological "sex" rather than sociocultural "gender."

Since study participants did not repeat the CERAD battery during follow-up, we were not able to analyze cognitive decline for the separate domains of this test battery. The DSST, which was used both at baseline and during follow-up, measures mostly executive function and processing speed. Performance in those domains is particularly associated with subcortical brain function, which is typically affected by vascular cognitive impairment. The ARIC study, which also used the DSST, similarly found that lower DSST scores were associated with higher cross-sectional hs-cTnT levels but could not make a similar observation for a test of memory function [32]. Therefore, the authors concluded that hs-cTnT may be more indicative of vascular cognitive impairment than other forms of dementia, which is well in line with our results.

The pathogenetic mechanisms involved in the association between cardiac biomarkers and cognitive function are not yet fully elucidated [38]. A possible explanation is that both myocardial injury and cognitive impairment represent different forms of end organ damage caused by systemic vascular disease such as arteriosclerosis [39]. In the brain, this may particularly involve small vessel disease affecting the white matter. Of note, elevated hs-cTnT is indeed associated with more severe white matter disease [40, 41]. Apart from that, elevated troponin may be associated with lower cardiac output due to structural heart disease, which in turn may lead to cerebral hypoperfusion [42]. Moreover, cognitive impairment may also be the consequence of cardioembolism [43]. Lastly, there is also evidence that, depending on the localization, cerebral injury may also cause myocardial damage [44, 45].

Besides being associated with cognition, hs-cTnT is also associated with incident adverse cardiovascular events, incident stroke, and mortality, as numerous studies have shown in the past [46, 47]. We were able to corroborate these findings in our study population as well. This suggests that our study population represents the older general population adequately.

Strengths of the study include the large and relatively homogeneous sample (all participants were ≥60 years of age and from the general population) as well as the standardized and prospective data collection. Moreover, all participants underwent a comprehensive neuropsychological assessment, including the examination of different cognitive domains. Patients were followed up systematically for several years and underwent cognitive reassessment.

Nevertheless, certain limitations have to be considered. First, selection bias applies since people with higher level of education, better cognitive function, and lower comorbidity may have been more likely to respond to the advertisement for study enrollment and are overrepresented in BASE-II [23]. Moreover, participants with greater cognitive decline and adverse cardiovascular events might have been less likely to attend the follow-up visit. In addition, patients with cognitive impairment have a higher mortality rate [48]. Therefore, there may have been a bias toward better cognitive outcomes among the surviving participants that could be reevaluated cognitively during follow-up. This may also have influenced our results concerning the association between hs-cTnT and cognitive decline. Although the effect of hs-cTnT on cognitive decline that we found in our analyses remained statistically significant after adjustment for potential confounders, it was indeed small. Another factor that might have somewhat attenuated the association between cardiac troponin and cognitive performance in our study is that our study population had excellent global cognitive function both at baseline and during follow-up and there was a low number of participants with incident dementia.

## Conclusion

In our study of healthy older adults with good global cognitive function at inclusion, we found that cardiac troponin T levels are associated with cognitive decline as

measured by change in the DSST. Our results thus provide further evidence of an association between myocardial injury and cognitive decline, which may be caused by common underlying risk factors. Measuring cardiac troponin T may be useful to identify subjects at risk of developing vascular cognitive impairment. Cardiovascular risk may play a greater role in the development of cognitive impairment in men than in women.

Future studies should focus on better understanding the underlying pathophysiological mechanisms leading to cognitive decline in older adults with myocardial injury and whether hs-cTnT could be a useful parameter to monitor treatment effects for the prevention of cognitive decline. Moreover, future studies may examine whether the association between hs-cTnT and cognitive decline is more pronounced in certain cognitive domains and elucidate sex-specific differences in the relationship between cognitive decline and cardiovascular risk.

## Statement of Ethics

Study approval statement: Both BASE-II and GendAge were approved by the Ethics Committee of Charité-Universitätsmedizin Berlin (EA2/029/09 and EA2/144/16). Consent to participate statement: all participants included in BASE-II and GendAge gave written informed consent.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


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## Author Contributions

V.R.-Z., D.G., E.S.-T., and I.D. conceived and designed the study and acquired the data. R.R., T.L., C.H.N., I.D., and M.E. conducted the analysis and interpretation of the data. All the authors participated in drafting the paper or revising it critically and provided final approval.

## Data Availability Statement

Due to concerns for participant privacy, data supporting the findings of this study are available only upon reasonable request. External scientists can contact Ludmila Müller, scientific coordinator, for more information: lmueller@mpib-berlin.mpg.de.

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