

# High-sensitivity cardiac troponin T and cognitive function and dementia risk: the atherosclerosis risk in communities study

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## Aim

Clinical cardiovascular disease is a major risk factor for cognitive impairment and dementia. However, less is known about the association of subclinical myocardial damage with cognition and dementia. We sought to examine the associations of high-sensitivity cardiac troponin T (hs-cTnT) with cognition and dementia.

## Methods and results

Cross-sectional analysis of cognition (baseline 1996–98) and prospective analysis of dementia (follow-up through 2010) in 9472 participants in the Atherosclerosis Risk in Communities study. High-sensitivity cardiac troponin T was measured using a novel highly sensitive assay with a lower limit of the blank of 3 ng/L. Cognitive function was assessed by three tests: the delayed word recall test (DWRT), the digit symbol substitution test (DSST), and the word fluency test (WFT). Dementia was defined using ICD-9 codes. Linear regression and Cox models were adjusted for traditional cardiovascular risk factors. The mean age of participants was 63 years, 59% were female, 21% were black, and 66% had hs-cTnT  $\geq 3$  ng/L. In cross-sectional analyses, higher hs-cTnT was associated with lower scores on the DSST ( $P$ -trend  $< 0.001$ ) and the WFT ( $P$ -trend = 0.002), but not on the DWRT ( $P$ -trend = 0.089). Over a median of 13 years, there were 455 incident dementia hospitalizations. In prospective analyses, higher baseline concentrations of hs-cTnT were associated with an increased risk for dementia hospitalizations overall ( $P$ -trend  $< 0.001$ ) and for vascular dementia ( $P$ -trend = 0.029), but not for Alzheimer's dementia ( $P$ -trend = 0.212).

## Conclusion

Elevations in baseline concentrations of hs-cTnT were associated with lower cognitive test scores at baseline and increased dementia hospitalization risk during the follow-up. Our results suggest that subclinical myocardial injury is associated with cognition and dementia.

## Keywords

High-sensitivity Troponin T • Cognition • Dementia

## Introduction

Cognitive impairment and dementia affect ~10 and 14% of elderly persons in the USA, respectively,<sup>1,2</sup> and the number of persons with cognitive impairment and dementia are expected to triple by the year 2030.<sup>3</sup> A history of clinical cardiovascular disease has been shown to be a major risk factor for cognitive impairment and

dementia,<sup>4–6</sup> but the association of subclinical myocardial injury with cognition and dementia has not been fully characterized.

Novel highly sensitive assays for cardiac troponin can detect troponin concentrations ~10 times lower than the standard cardiac troponin assays.<sup>7</sup> These novel highly sensitive assays are approved and recommended for clinical use in parts of Europe,<sup>8</sup> but are not yet approved for clinical use in the USA. These highly

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sensitive assays are also of increasing interest for risk stratification purposes. Troponin concentrations measured using highly sensitive assays have been shown to improve the prediction of coronary heart disease and mortality in community-based populations without clinically evident cardiovascular disease.<sup>9,10</sup> It has been hypothesized that hs-cTnT is a novel marker for subclinical myocardial injury,<sup>11,12</sup> but the full-clinical significance of minor elevations in circulating troponin is unclear. For example, it has also been suggested that minute elevations in hs-cTnT may be a marker for diffuse subclinical small vessel disease rather than specific for myocardial damage.<sup>13</sup> It is possible that subclinical small vessel disease in the brain may contribute to associations of hs-cTnT with cognition and dementia. Alternatively, elevations in hs-cTnT may reflect subclinical ischaemia due to atherosclerosis. Subclinical atherosclerosis (e.g. elevated carotid intima medial thickness) has previously been associated with cognitive impairment and dementia risk.<sup>14</sup> Recent studies have shown that hs-cTnT is positively associated with risk of incident stroke, especially cardioembolic stroke.<sup>15,16</sup> However, there are scant data on the possible association of hs-cTnT with cognitive function and risk of dementia.

We sought to characterize the relationship of hs-cTnT with cognitive function and future dementia risk in a community-based population. We hypothesized that higher concentrations of hs-cTnT would be associated cross-sectionally with lower cognitive test scores and prospectively with an increased risk of incident hospitalization with an ICD-9 code for dementia.

## Methods

### Study population

The Atherosclerosis Risk in Communities (ARIC) study is an ongoing, community-based prospective cohort of 15 792 middle-aged adults from four US communities: Washington County, MD; Forsyth County, NC; suburbs of Minneapolis, MN; and Jackson, MS. The ARIC study participants were initially seen at four in-person visits which occurred ~3 years apart, from 1987–89 for visit 1, to 1996–98 for visit 4. A fifth visit was conducted from 2011 to 2013. High-sensitivity cardiac troponin T was measured in blood samples from ARIC participants who attended visit 4 (baseline for the present study). Of the 11 625 black and white participants who attended visit 4, we excluded those with a history of coronary heart disease (1151), myocardial infarction ( $n = 134$ ), heart failure ( $n = 100$ ), or stroke ( $n = 100$ ) at or before visit 4, those with a hospitalization with an ICD-9 code for dementia before visit 4 ( $n = 25$ ), those missing cognitive test ( $n = 246$ ) or hs-cTnT data ( $n = 339$ ), and those missing covariates included in statistical models ( $n = 60$ ), leaving 9472 participants included in the present analysis.

The ARIC study has been approved by the Institutional Review Boards of all participating institutions, including the University of Minnesota, Johns Hopkins University, University of North Carolina, and University of Mississippi Medical Center. All the participants gave written informed consent at each study visit.

### Measurement of high-sensitivity cardiac troponin T

High-sensitivity cardiac troponin T was measured in 2010–11 from plasma samples that were stored at  $-70^{\circ}\text{C}$  since collection during visit 4 (1996–98). The Elecsys troponin T, a novel high-sensitivity assay, was performed using a Cobas e411 analyzer (Roche Diagnostics, Indianapolis,

IN). As reported by the manufacturer, this assay has a limit of blank of 3 ng/L and a limit of detection (LOD) of 5 ng/L.<sup>9,17</sup> The reliability coefficient was 0.99 and the inter-assay coefficient of variation was 15%.<sup>18</sup> Our samples were analysed using a reagent lot numbers that were not impacted by a calibration issue disclosed by Roche.

### Measures of cognitive function

Cognitive functioning was assessed at visit 4 (1996–98) using three standardized tests: the delayed word recall test (DWRT),<sup>19</sup> the digit symbol substitution test (DSST) of the Wechsler adult intelligence scale-revised (WAIS-R),<sup>20</sup> and the word fluency test (WFT), also known as the controlled oral word association test of the multilingual aphasia examination.<sup>21</sup> Protocols for the tests were standardized, and trained examiners administered the cognitive tests in a fixed order during one session in a quiet room. Examiner performance was monitored by audio tape recording, and recordings were reviewed locally and shared across centres to ensure consistency with testing procedures.

The DWRT is a test of verbal learning and recent memory. In this test, participants were given 10 common nouns that they were asked to learn by using each word in one or two sentences. After a 5-min delay, participants were given 60-s to recall the words. The score for the DWRT is the number of words correctly recalled.

The DSST is a test of executive function and processing speed, where participants were asked to translate numbers to symbols using a key. The score is the total number of numbers correctly translated to symbols within 90-s and the range of possible scores is 0–93.

The WFT is a test of executive function and language, and tests the ability to spontaneously generate words beginning with a particular letter, excluding proper names or places. Participants were given 60-s for each of three trials for the letters 'F', 'A', and 'S'. The word fluency score is the total number of words generated across the three trials.

In addition to the raw cognitive scores, we calculated standardized z-scores for each test by subtracting the test mean and dividing by its standard deviation; means and standard deviations were calculated separately by race. We then calculated a composite global score by calculating the mean of the individual z-scores. We standardized the global score by subtracting the average global mean and dividing by its standard deviation.

### Incident hospitalization with an ICD-9 code for dementia

The ARIC study obtains hospitalization information from annual telephone contact with study participants and through active surveillance of all hospitalizations in the study communities. For the present study, follow-up was available through 31 December 2010. We defined time to first hospitalization with an ICD-9 code for dementia using the following ICD-9 codes (listed anywhere in the hospital discharge record): Alzheimer's disease (331.0), vascular dementia (290.4), or dementia of other aetiology (290.0, 290.1, 290.2, 290.3, 290.9, 294.1, 294.2, 294.8, 294.9, 331.1, 331.2, 331.8, and 331.9). This definition for incident hospitalization with an ICD-9 code for dementia has been used previously,<sup>22,23</sup> and scores on the DWRT, DSST, and WFT have previously been shown to be associated with this definition.<sup>23</sup>

### Covariates

All covariates used in the regression models were assessed at visit 4 (1996–98), except education, which was assessed at visit 1 (1987–89). Covariates included age (years), gender, race/centre (Maryland whites; Minnesota whites; North Carolina whites; North Carolina blacks; and Mississippi blacks), education (<high school; high school or equivalent; college, graduate or professional school), income (<\$35 000/year;

$\geq$ \$35 000/year; not reported), body mass index ( $\text{kg}/\text{m}^2$ ), physical activity (score range 1–5, based on replies to questions on type, frequency, intensity, and duration of physical activity from a modified Baecke Physical Activity questionnaire<sup>24,25</sup>), alcohol consumption [current high ( $>7$  drinks/week for women;  $>14$  drinks/week for men); current low ( $\leq 7$  drinks/week for women;  $\leq 14$  drinks/week for men); former; never], cigarette smoking (current; former; never), total and HDL cholesterol ( $\text{mg}/\text{dL}$ ), diabetes (self-report, medication use, or fasting blood glucose  $\geq 126$   $\text{mg}/\text{dL}$ ), systolic and diastolic blood pressure ( $\text{mmHg}$ , defined as the mean of the second and third of three measurements), and use of hypertension medication.

## Statistical analysis

We analysed hs-cTnT both continuously and categorically. For the categorical analysis, our reference group was the 34% of the ARIC population with hs-cTnT concentrations  $<3$   $\text{ng}/\text{L}$ . The remaining population was divided into categories as follows (based on prior publications<sup>9,10</sup>): 3–5  $\text{ng}/\text{L}$ , 6–8  $\text{ng}/\text{L}$ , 9–13  $\text{ng}/\text{L}$ , and  $\geq 14$   $\text{ng}/\text{L}$ . In a sensitivity analysis, we repeated our analyses using  $<5$   $\text{ng}/\text{L}$  (LOD) as the reference group. Baseline characteristics of our population are shown by hs-cTnT category and are adjusted for age and sex due to the differences in hs-cTnT distribution by these factors.<sup>9,26</sup> We also consider two binary definitions of hs-cTnT:  $\geq 3$  vs.  $<3$   $\text{ng}/\text{L}$ , elevated ( $\geq 14$   $\text{ng}/\text{L}$ ) vs. non-elevated ( $<14$   $\text{ng}/\text{L}$ ).

Linear regression models were used to assess the cross-sectional association between hs-cTnT and cognitive test scores. For the prospective association between hs-cTnT and incident hospitalization with an ICD-9 code for dementia, we estimated hazard ratios (95% confidence intervals) using Cox proportional-hazard models. The proportional-hazards assumptions were checked with the use of Schoenfeld residuals and graphic methods. We tested for linear trend across the median of hs-cTnT concentration categories. We also modelled the association of hs-cTnT with incident dementia using a restricted cubic spline model with knots at the 10th, 50th, and 90th percentiles. We performed the spline analyses among those with hs-cTnT concentrations within the measuring range only ( $n = 6221$ ). Models were adjusted for demographic factors (age, race/ethnicity, sex, education level, and income), lifestyle/behavioural factors (body mass index, physical activity, alcohol consumption, and smoking), and cardiovascular risk factors (total cholesterol, HDL cholesterol, diabetes, systolic and diastolic blood pressure, and blood pressure-lowering medication). We formally tested for interaction by gender. We calculated Harrell's *C*-statistic to assess the discriminatory ability of our models.<sup>27</sup>

In exploratory analyses, we used Cox proportional-hazards models to examine the prospective association between hs-cTnT and two subcategories of incident hospitalization with an ICD-9 code for dementia: incident Alzheimer's dementia ( $n = 112$ ) and incident vascular dementia ( $n = 34$ ).

Associations between hs-cTnT and hospitalization with an ICD-9 diagnosis of dementia may reflect differences in dementia or may reflect differences in hospitalization rates, as persons without a hospitalization could not receive a diagnosis of dementia. Therefore, we performed a sensitivity analysis where we restricted our analysis to those individuals who had at least one hospitalization during the follow-up ( $n = 7395$ ).

We also examined the past trajectory of cognitive function by examining the association of hs-cTnT with the 6-year change in cognitive test scores from visit 2 (1990–92) to visit 4 (1996–98) among the subset of participants who had cognitive function measured at both visits ( $n = 9311$ ). This past trajectory of cognitive function change analysis is less likely to be biased by cultural confounding factors and less affected by measurement error compared with our main cross-sectional analysis.<sup>28</sup> Therefore, we performed this analysis to attempt to account for

potential residual confounding and measurement error that may be present in our cross-sectional analyses.

We also performed analyses excluding participants with atrial fibrillation or atrial flutter at or before visit 4 ( $n = 143$ ). Atrial fibrillation diagnoses were obtained from ECGs performed at all study visits and hospital discharge records (ICD-9 codes: 427.31, 427.32). In our prospective analysis, we conducted additional analyses censoring participants who had a diagnosis of atrial fibrillation or atrial flutter prior to a dementia diagnosis ( $n = 37$ ), stroke occurring prior to a dementia diagnosis ( $n = 47$ ), or heart failure occurring prior to a dementia diagnosis ( $n = 60$ ). We performed two additional analyses where we adjusted for left ventricular hypertrophy (defined using Cornell voltage criteria,<sup>29</sup>  $n = 9472$ ) and where we adjusted for carotid intima media thickness ( $n = 5498$ ) to assess for possible mediation.

All reported *P*-values are two-sided and  $P < 0.05$  was considered statistically significant. All analyses were performed using Stata Version 12 (StataCorp, College Station, TX, USA).

## Results

Baseline (1996–98) characteristics of the study population overall and by hs-cTnT categories ( $<3$ , 3–5, 6–8, 9–13, and  $\geq 14$   $\text{ng}/\text{L}$ ) are shown in *Table 1*. The mean age of participants was 63 years old, 59% of participants were female, 21% of participants were black, and 66% of participants had hs-cTnT concentrations within the measuring range. Compared with those with hs-cTnT  $\geq 14$   $\text{ng}/\text{L}$  (elevated), those with hs-cTnT  $<3$   $\text{ng}/\text{L}$  (below the measuring range) were younger (61 vs. 65 years,  $P < 0.001$ ) and were more likely to be female (79 vs. 25%,  $P < 0.001$ ). After adjustment for age and sex, those with hs-cTnT  $<3$   $\text{ng}/\text{L}$  (compared with those with hs-cTnT  $\geq 14$   $\text{ng}/\text{L}$ ) were less likely to be black (18 vs. 31%,  $P < 0.001$ ), were less likely to have less than high school education (16 vs. 21%,  $P = 0.002$ ), and were less likely have diabetes (9 vs. 35%,  $P < 0.001$ ). Characteristics of the study population using the categories of  $<5$ , 5–8, 9–13, and  $\geq 14$  are shown in Supplementary material online, *Table S1*.

*Table 2* shows  $\beta$ -coefficients (95% confidence intervals) for the cross-sectional association of hs-cTnT with cognitive test scores. Higher concentrations of hs-cTnT were associated with lower cognitive test scores on the DSST (*P*-trend  $< 0.001$ ) and WFT (*P*-trend = 0.002), but not on the DWRT (*P*-trend = 0.089). Compared with participants with hs-cTnT concentrations  $<3$   $\text{ng}/\text{L}$ , participants with hs-cTnT concentrations  $\geq 14$   $\text{ng}/\text{L}$  translated 1.83 (95% CI: 0.96, 2.71) fewer numbers to symbols on the DSST and generated 1.63 (95% CI: 0.62, 2.64) fewer words on the WFT. Higher concentrations of hs-cTnT were also associated with a lower global *z*-score (*P*-trend  $< 0.001$ ). Results of analyses using our binary definitions of hs-cTnT  $\geq 3$  vs.  $<3$   $\text{ng}/\text{L}$  and  $\geq 14$  vs.  $<14$   $\text{ng}/\text{L}$  were similar to our main categorical analyses. We found no evidence of interaction by gender for DWRT and DSST scores (*P*-for-interaction = 0.625 and 0.132, respectively). Associations of hs-cTnT with lower WFT score tended to be stronger for women than men (*P*-for-interaction = 0.007). Similar results were found when the analyses were repeated using  $<5$   $\text{ng}/\text{L}$  as the reference group (Supplementary material online, *Table S2*).

Among our population of 9472 persons without a history of cardiovascular disease at baseline, there were 455 incident hospitalizations with an ICD-9 code for dementia that occurred during a

**Table 1** Baseline characteristics (1996–98) by category of high-sensitivity cardiac troponin T adjusted for age and sex

	All participants (n = 9472)	<3 ng/L (n = 3251)	3–5 ng/L (n = 2452)	6–8 ng/L (n = 1926)	9–13 ng/L (n = 1207)	≥14 ng/L (elevated) (n = 636)	P-value <3 ng/L vs. ≥14 ng/L
Age (years), mean	62.5	60.7	62.3	63.5	64.9	65.2	<0.001
Female, %	59.3	79.4	62.4	47.4	36.5	24.7	<0.001
Black, %	20.8	17.5	18.0	22.9	26.6	31.3	<0.001
Education, %							
<High school	17.1	15.7	16.7	17.1	19.3	21.1	0.002
High school or vocational school	42.6	44.0	42.8	42.5	40.9	38.5	0.002
College, graduate, or professional school	40.3	40.3	40.5	40.4	39.7	40.4	0.951
Income, %							
<\$35 000/year	46.8	45.2	46.3	46.5	49.7	52.0	0.002
≥\$35 000/year	47.9	49.0	49.7	48.4	44.0	41.4	0.001
Not reported	5.3	5.8	4.0	5.1	6.3	6.6	0.448
Cigarette smoking status, %							
Current smoker	14.4	20.8	12.8	9.6	9.9	11.1	<0.001
Former smoker	42.0	41.3	42.1	42.5	43.1	41.8	0.794
Never smoker	43.6	37.9	45.1	47.8	47.0	47.1	<0.001
Alcohol use status, %							
Current alcohol use—high <sup>a</sup>	39.8	41.8	42.8	38.0	35.2	31.8	<0.001
Current alcohol use—low <sup>b</sup>	11.2	13.7	10.8	9.9	8.8	8.7	0.006
Former alcohol use	28.3	27.2	26.3	29.1	29.6	36.7	<0.001
Never alcohol use	20.7	17.3	20.0	23.1	26.4	22.8	0.002
Physical activity index, mean	2.5	2.5	2.5	2.5	2.4	2.3	<0.001
Body mass index (kg/m <sup>2</sup> ), mean	28.7	27.7	28.5	29.4	30.0	30.5	<0.001
Total cholesterol (mg/dL), mean	202	204	202	201	200	197	<0.001
HDL cholesterol (mg/dL), mean	50.9	51.7	51.1	50.4	49.7	49.1	0.002
Diabetes, %	14.6	9.00	11.8	16.8	21.4	34.8	<0.001
Systolic BP (mmHg), mean	127	125	126	128	131	132	<0.001
Diastolic BP (mmHg), mean	71.1	70.4	70.9	71.6	72.1	71.8	0.033
Hypertension medication, %	38.5	31.5	35.1	42.3	47.3	59.5	<0.001
Delayed word recall test (words), mean	6.6	6.7	6.7	6.6	6.6	6.4	<0.001
Digit symbol substitution test (points), mean	44.4	45.3	45.3	44.0	42.8	40.4	<0.001
Word fluency test (words), mean	38.9	34.9	34.0	33.3	33.1	31.5	<0.001
Global z-score, mean	0.00	0.05	0.03	−0.03	−0.05	−0.18	<0.001

<sup>a</sup>Current high alcohol consumption was defined as >7 drinks/week for women and >14 drinks/week for men.

<sup>b</sup>Current low alcohol consumption was defined as ≤7 drinks/week for women and ≤14 drinks/week for men.

median of 13 years of follow-up. Table 3 shows the hazard ratios (95% confidence intervals) for the association of hs-cTnT at baseline with risk for incident hospitalization with an ICD-9 code for dementia. Higher concentrations of hs-cTnT were associated with an increased risk for incident hospitalization with an ICD-9 code for dementia ( $P$ -trend < 0.001). Compared with participants with hs-cTnT concentrations <3 ng/L, participants with hs-cTnT concentrations between 6 and 8 ng/L had 1.43 (95% CI: 1.07, 1.91) times increased risk, participants with hs-cTnT concentrations between 9 and 13 ng/L had 1.82 (95% CI: 1.33, 2.48) times increased risk, and participants with hs-cTnT concentrations ≥14 ng/L had 2.69 (95% CI:

1.87, 3.84) times increased risk for hospitalization with an ICD-9 code for dementia during the follow-up. Results of analyses using our binary definitions of hs-cTnT ≥3 vs. 3 ng/L and ≥14 vs. <14 ng/L were similar to our main categorical analyses. We found no evidence of interaction by gender ( $P$ -for-interaction = 0.240). Results from our sensitivity analysis restricted to individuals who had at least one hospitalization over follow-up ( $n$  = 7395) were slightly attenuated, but remained statistically significant ( $P$ -trend < 0.001). Comparing models with and without hs-cTnT, Harrell's C-statistics were 0.798 and 0.790, respectively ( $P$ -for-difference = 0.004), indicating that the addition of hs-cTnT to our model improves

**Table 2** Adjusted  $\beta$ -coefficients (95% confidence intervals) for the cross-sectional associations of categories of high-sensitivity cardiac troponin T with cognitive test scores

Categories of hs-cTnT	Delayed word recall test	Digit symbol substitution test	Word fluency test	Global Z-score
hs-cTnT <3 ng/L	Reference	Reference	Reference	Reference
hs-cTnT 3–5 ng/L	0.03 (–0.05, 0.11)	–0.04 (–0.55, 0.47)	<b>–0.80 (–1.38, –0.21)</b>	–0.02 (–0.06, 0.02)
hs-cTnT 6–8 ng/L	–0.06 (–0.15, 0.02)	–0.50 (–1.06, 0.07)	<b>–1.10 (–1.76, –0.45)</b>	<b>–0.08 (–0.12, –0.03)</b>
hs-cTnT 9–13 ng/L	–0.02 (–0.12, 0.08)	–0.64 (–1.33, 0.04)	–0.59 (–1.38, 0.19)	–0.05 (–0.11, 0.01)
hs-cTnT $\geq$ 14 ng/L	–0.10 (–0.23, 0.04)	<b>–1.83 (–2.71, –0.96)</b>	<b>–1.63 (–2.64, –0.62)</b>	<b>–0.14 (–0.22, –0.07)</b>
P-value for trend	0.089	<b>&lt;0.001</b>	<b>0.002</b>	<b>&lt;0.001</b>

Model is adjusted for age (continuous), race/field centre (Washington County, Maryland whites; suburbs of Minneapolis, Minnesota whites; Forsyth County, North Carolina whites; Forsyth County, North Carolina blacks; Jackson, Mississippi blacks), sex (male; female), education level (<high school; high school or equivalent; college, graduate or professional school), income (<\$35 000/year;  $\geq$ \$35 000/year; not reported), body mass index (continuous), physical activity (continuous), alcohol consumption (current high; current low; former; never), smoking (current; former; never), total cholesterol (continuous), HDL cholesterol (continuous), diabetes (yes; no), systolic and diastolic blood pressure (continuous), and blood pressure-lowering medication (yes; no). Bolded data represent  $P < 0.05$ .

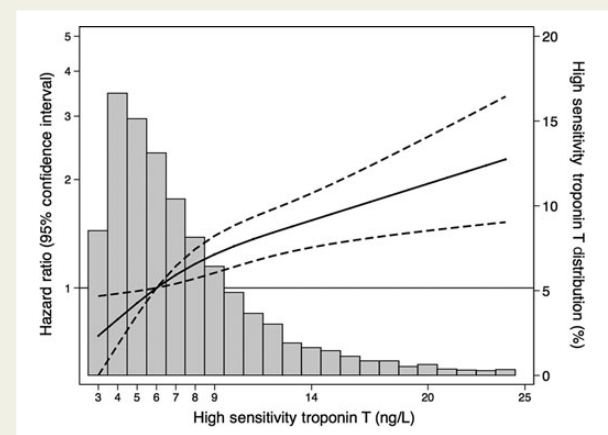
**Table 3** Adjusted hazard ratios (95% confidence intervals) for the prospective association between categories of baseline high-sensitivity cardiac troponin T and incident dementia hospitalization

Category of hs-cTnT	Hazard ratio (95% CI)
hs-cTnT <3 ng/L	1.00 (reference)
hs-cTnT 3–5 ng/L	1.09 (0.82, 1.45)
hs-cTnT 6–8 ng/L	<b>1.43 (1.07, 1.91)</b>
hs-cTnT 9–13 ng/L	<b>1.82 (1.33, 2.48)</b>
hs-cTnT $\geq$ 14 ng/L	<b>2.68 (1.87, 3.84)</b>
P-value for trend	<b>&lt;0.001</b>

Model is adjusted for age (continuous), race/field centre (Washington County, Maryland whites; suburbs of Minneapolis, Minnesota whites; Forsyth County, North Carolina whites; Forsyth County, North Carolina blacks; Jackson, Mississippi blacks), sex (male; female), education level (<high school; high school or equivalent; college, graduate or professional school), income (<\$35 000/year;  $\geq$ \$35 000/year; not reported), body mass index (continuous), physical activity index (continuous), alcohol consumption (current high; current low; former; never), smoking (current; former; never), total cholesterol (continuous), HDL cholesterol (continuous), diabetes (yes; no), systolic and diastolic blood pressure (continuous), and blood pressure-lowering medication (yes; no). Bolded data represent  $P < 0.05$ .

the discriminatory ability of our model. Similar results were found when the analysis was repeated using <5 ng/L as the reference group (Supplementary material online, Table S3). Figure 1 shows the continuous association of hs-cTnT with incident dementia-related hospitalization among the 6321 participants with hs-cTnT concentrations  $\geq$  3 ng/L using a restricted cubic spline model. Similar results were seen among the 4690 participants with hs-cTnT concentrations  $\geq$  5 ng/L (Supplementary material online, Figure S1).

In our exploratory analysis examining the association of hs-cTnT with two subcategories of incident hospitalization with an ICD-9 code for dementia, there were 112 incident cases of hospitalization with an ICD-9 code for Alzheimer's dementia and 34 incident cases of hospitalization with an ICD-9 code for vascular dementia.



**Figure 1** Adjusted restricted cubic spline model showing the hazard ratios (95% confidence intervals) for the association of high-sensitivity cardiac troponin T with incident dementia [among the 6321 participants with high-sensitivity cardiac troponin T concentrations within the measuring range ( $\geq$  3 ng/L)]. Knots at 4, 6, and 14 ng/L (10th, 50th, and 90th percentiles). Histogram shows the distribution of concentrations of high-sensitivity cardiac troponin T within the measuring range. Data truncated at 97.5 percentile of high-sensitivity cardiac troponin T. Model is adjusted for age (continuous), race/field centre (Washington County, Maryland whites; suburbs of Minneapolis, Minnesota whites; Forsyth County, North Carolina whites; Forsyth County, North Carolina blacks; Jackson, Mississippi blacks), sex (male; female), education level (<high school; high school or equivalent; college, graduate or professional school), income (<\$35 000/year;  $\geq$ \$35 000/year; not reported), body mass index (continuous), physical activity (continuous), alcohol consumption (current high; current low; former; never), smoking (current; former; never), total cholesterol (continuous), HDL cholesterol (continuous), diabetes (yes; no), systolic and diastolic blood pressure (continuous), and blood pressure-lowering medication (yes; no).

Three individuals who had ICD-9 codes for both Alzheimer's dementia and vascular dementia. High-sensitivity cardiac troponin T was not

associated with incident hospitalization with an ICD-9 code for Alzheimer's dementia ( $P$ -trend = 0.212), but higher concentrations of hs-cTnT were significantly associated with incident hospitalization with an ICD-9 code for vascular dementia ( $P$ -trend = 0.029).

In our analysis examining the past trajectory of cognitive function ( $n = 9311$ ), higher concentrations of hs-cTnT remained significantly associated with more cognitive decline over the prior 6 years on the DSST ( $P$ -trend = 0.001) and WFT ( $P$ -trend = 0.027), but not on the DWRT ( $P$ -trend = 0.753).

In the analyses excluding participants with atrial fibrillation or atrial flutter at or before visit 4 ( $n = 9331$  included in this analysis), higher concentrations of hs-cTnT remained significantly associated with lower DSST ( $P$ -trend < 0.001) and WFT ( $P$ -trend = 0.003) scores. In the analyses censoring participants who had a diagnosis of atrial fibrillation or atrial flutter, stroke, or heart failure occurring prior to a dementia diagnosis, the association of hs-cTnT with risk for dementia was slightly attenuated but remained statistically significant (Supplementary material online, Table S4). Similarly, when left ventricular hypertrophy ( $n = 9472$ ) and carotid intima media thickness ( $n = 5498$ ) were added to the model, the results were not appreciably altered.

## Discussion

In this large, community-based population without coronary heart disease, myocardial infarction, heart failure, or stroke at baseline, elevations in cardiac troponin T detected using a highly sensitive assay were cross-sectionally associated with lower scores on the DSST and the WFT, as well as with lower global z-scores, independent of traditional risk factors. High-sensitivity cardiac troponin T concentrations were not associated with DWRT scores. Elevations in cardiac troponin T were also significantly associated with an increased risk of incident hospitalization with an ICD-9 code for dementia, particularly incident hospitalization with an ICD-9 code for vascular dementia, independent of traditional risk factors.

Potential mechanisms whereby hs-cTnT could contribute to cognitive dysfunction and dementia include shared risk factors,<sup>30</sup> subclinical or clinical cardioembolic stroke,<sup>15,16</sup> hypoperfusion from inadequate left ventricular function,<sup>9,10,31,32</sup> or subclinical ischaemia due to atherosclerosis.<sup>14</sup> Although it remains unclear whether hs-cTnT is a marker of subclinical small vessel disease,<sup>13</sup> it has been hypothesized that the same persons with subclinical myocardial injury may also have subclinical small vessel disease in the brain as a result of shared risk factors.<sup>30</sup> Though we tried to account for many of these factors in our analyses, residual confounding remains a possibility. The subclinical small vessel disease in the brain may manifest as subtle impairment on standardized cognitive tests and may place the person at a higher risk for dementia later in life.

The association of baseline hs-cTnT concentration with risk of incident hospitalization with an ICD-9 code for dementia remained after accounting for the intervening occurrence (mediation effect) of incident atrial fibrillation or atrial flutter, stroke, or heart failure prior to the hospitalization. Previous reports have suggested that hs-cTnT may be a marker of atrial fibrillation resulting from subclinical myocardial injury,<sup>33</sup> which might lead to either clinical or subclinical cardioembolic stroke. Indeed, hs-cTnT been associated with cardioembolic stroke,<sup>15,16</sup> and stroke is a known cause of cognitive

impairment and dementia.<sup>34,35</sup> High-sensitivity cardiac troponin T may also be a marker for subclinical myocardial damage causing inadequate left ventricular function, which may lead to hypoperfusion in the brain.<sup>9,10,31,32</sup> Cerebral hypoperfusion has been noted to be associated with cognitive impairment and dementia.<sup>36,37</sup> Alternatively, elevations in hs-cTnT may reflect subclinical ischaemia due to atherosclerosis, which has been associated with cognitive function.<sup>14</sup> However, after adding left ventricular hypertrophy and carotid intima media thickness to our model to assess for possible mediation effects, our results remained significant, suggesting that these factors do not mediate the associations.

Our results suggest that hs-cTnT is more associated with vascular pathology in the brain than with Alzheimer's disease pathology. Higher concentrations of hs-cTnT were significantly associated with lower scores on the DSST and the WFT, but not on the DWRT. The DSST and WFT are tests of executive function that are more associated with vascular pathology and vascular dementia,<sup>34,38,39</sup> whereas the DWRT is a test of memory and is more associated with Alzheimer's dementia.<sup>19</sup> The results of our analyses of the subcategories of incident hospitalization with an ICD-9 code for subcategories of dementia also support this notion; higher concentrations of hs-cTnT were associated with an increased risk for incident hospitalization with an ICD-9 code for vascular dementia, but not for incident hospitalization with an ICD-9 code for Alzheimer's dementia.

Limitations of this study should be taken into consideration when interpreting the results. We used ICD-9 hospitalization codes to define incident dementia and we did not have information to determine whether dementia was the primary reason for hospitalization. Although hospitalization with an ICD-9 code for dementia is a relatively specific marker of dementia, it likely disproportionately occurs with the most severe cases of dementia and dementia in the presence of other diseases, suggesting that our results may be attenuated. A prior analysis of ARIC data<sup>22</sup> showed that age-specific incidence rates of hospitalization with an ICD-9 code for dementia were lower than age-specific incidence rates of dementia in other studies.<sup>40,41</sup> Additionally, in our main analysis, we had only single measurements of hs-cTnT and cognitive test performance, which have been shown to vary over time within individuals and can be subject to measurement error.<sup>42,43</sup> However, the results of our sensitivity analysis examining the association of hs-cTnT with the past trajectory of 6-year change in cognitive test scores remained significant, suggesting that the cross-sectional association of hs-cTnT with cognition is not due to residual confounding or measurement errors.<sup>28</sup> Our exploratory analysis of the subcategories of hospitalization with an ICD-9 code for dementia should be interpreted cautiously because we did not have the ability to validate the ICD-9 codes, leaving open the possibility of misclassification. The ability of ICD-9 codes to differentiate subtypes of dementia is limited; the majority of our dementia cases were identified by non-specific dementia ICD-9 codes, leaving small numbers of participants in these subcategory analyses.

Our study also had a number of important strengths, including the large sample size, a median of 13 years of follow-up, and comprehensive measurement of confounders. We also had data on three cognitive tests, which allowed us to investigate the association of hs-cTnT with different cognitive domains, as well as to investigate the association of hs-cTnT with a global cognitive assessment.

In conclusion, our study suggests that subclinical myocardial injury, as assessed by hs-cTnT, is associated with lower cognitive performance. Our results also suggest that higher concentrations of hs-cTnT are associated with an increased risk for incident hospitalization for dementia, particularly vascular dementia. These associations may be the result of shared risk factors for myocardial and cerebral injury or the result of subclinical small vessel disease affecting both the heart and the brain. Our results suggest that in addition to the prediction of hard cardiovascular events, minor elevations in cardiac troponin may provide risk information regarding dementia outcomes.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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## Corrigendum

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**Corrigendum to:** ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD [Eur Heart J (2013) 34:3035–3087; doi:10.1093/eurheartj/eh108].

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In the section 3.2 Epidemiology there are typographical errors. The printed text states:

A total of 281 million men and 317 million women worldwide died with DM in 2011,

This should read:

A total of 281 thousand men and 317 thousand women worldwide died with DM in 2011,

Table 5, which is linked to these data, is correct.