

High-sensitivity cardiac troponin I and risk of dementia: the 25-year longitudinal Whitehall II study

Yuntao Chen ^{1,2,*}, Martin Shipley¹, Atul Anand ³, Dorien M. Kimenai ³, Klaus P. Ebmeier ⁴, Severine Sabia ^{1,5}, Archana Singh-Manoux⁵, John Deanfield⁶, Mika Kivimaki ¹, Gill Livingston ¹, Nicholas L. Mills ^{3,7}, and Eric J. Brunner ²

¹Division of Psychiatry, University College London, W1T 7NF London, UK; ²Department of Epidemiology and Public Health, University College London, WC1E 6BT London, UK; ³British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh, EH16 4SA Edinburgh, UK; ⁴Department of Psychiatry and Wellcome Centre for Integrative Neuroimaging, University of Oxford, OX3 7JX Oxford, UK; ⁵Inserm U1153, Epidemiology of Ageing and Neurodegenerative Diseases, Université de Paris, 75010 Paris, France; ⁶Institute of Cardiovascular Science, University College London, WC1E 6BT London, UK; and ⁷Usher Institute, University of Edinburgh, EH16 4UX Edinburgh, UK

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See the editorial comment for this article ‘High-sensitivity troponin and incident dementia: more evidence of connected heart and brain health’, by E. Giannitsis *et al.*, <https://doi.org/10.1093/eurheartj/ehaf989>.

Abstract

Background and Aims This study hypothesizes that subclinical myocardial injury during midlife, indexed by increases in cardiac troponin I, is associated with accelerated cognitive decline, smaller structural brain volume, and higher risk of dementia.

Methods Overall, 5985 participants in the Whitehall II study, aged 45–69 who had cardiac troponin I measured by a high-sensitivity assay at baseline (1997–99), were followed until March 2023. The outcome measure was incident dementia; cognitive testing was performed at six waves; and neuroimaging metrics were obtained from magnetic resonance imaging scans in 2012–16. Cox model and linear mixed model were used to examine the association of cardiac troponin with incident dementia and cognitive trajectory. A nested case–control sample of 3475 participants (695 dementia cases and 2780 matched controls) was used for backward trajectory analysis for cardiac troponin, measured at three waves (1997–99, 2007–09, 2012–13).

Results A total of 606 (10.1%) cases of dementia were recorded over a median follow-up of 24.8 years. Doubling of cardiac troponin was associated with 10% (95% confidence interval 3%–17%) higher risk of dementia. Participants with increased cardiac troponin at baseline had a faster decline of cognitive function. Participants with dementia had increased cardiac troponin concentrations compared with those without dementia between 7 and 25 years before diagnosis. Compared with those with cardiac troponin levels < 2.5 ng/L at baseline, those with concentrations > 5.2 ng/L had lower grey matter volume and higher hippocampal atrophy 15 years later, equivalent to ageing effects of 2.7 and 3 years, respectively.

Conclusions Subclinical myocardial injury at midlife was associated with higher dementia risk in later life.

* Corresponding author. Email: yuntao.chen@ucl.ac.uk

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Structured Graphical Abstract

Key Question

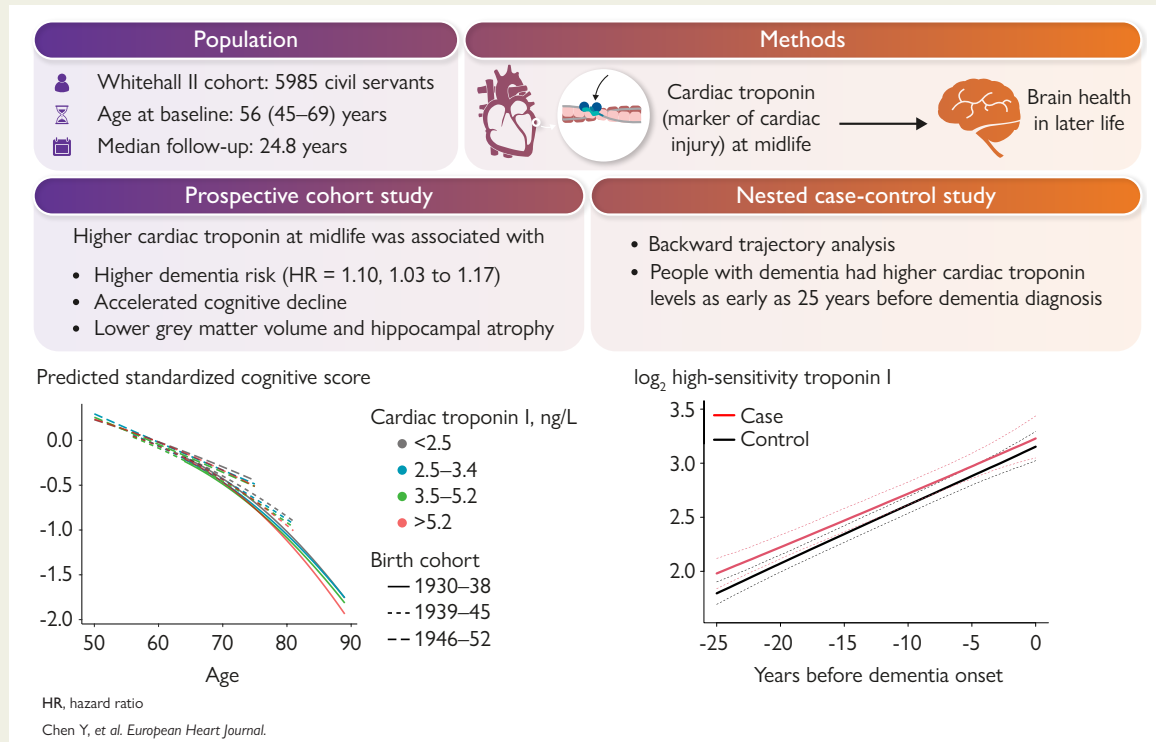
Is subclinical myocardial injury during midlife associated with accelerated cognitive decline, smaller structural brain volume, and higher risk of dementia?

Key Finding

Individuals with higher cardiac troponin I exhibited faster cognitive decline, higher risk of dementia, smaller grey matter volume, as well as greater hippocampal atrophy. Cardiac troponin I was consistently higher between 7 and 25 years before diagnosis in patients developing dementia vs controls.

Take Home Message

Measuring high sensitivity cardiac troponin I in midlife may be useful in the early identification of individuals at risk of cognitive decline and dementia.



Keywords Troponin • Dementia • Cognitive decline • Myocardial injury

Introduction

Emerging evidence suggests an intertwined relation between the health of the heart and brain.^{1–3} The 2024 Lancet Commission on dementia suggests 17% of dementia cases can be prevented or delayed by modifying cardiovascular risk factors including high cholesterol, physical inactivity, diabetes, hypertension, obesity, smoking, and excessive alcohol consumption.⁴ People with poor cardiovascular health, even in the absence of clinical coronary heart disease, have increased risk of dementia.^{5,6}

Cardiac troponin is a commonly used cardiac biomarker, and its utility has been extended with introduction of high-sensitivity assays.^{7–9} Modest elevation in cardiac troponin in apparently healthy populations is linked with increased risk of dementia, although existing studies have only assessed cardiac troponin once and had relatively short follow-ups.^{10–12} Consequently, it is unknown how long before dementia

diagnosis cardiac troponin levels become increased among cases relative to controls. Furthermore, few studies have prospectively examined whether cardiac troponin in midlife is a marker of potential preclinical changes in dementia-related measures such as cognition and brain volume. Consistent results from these different lines of research would strengthen the evidence on the role of subclinical myocardial injury in the aetiology of dementia. Previous research has hypothesized that structural brain changes are the link between impaired cardiac function and dementia.² While there is strong prospective evidence linking structural brain change to cognitive decline and increased dementia risk,^{13,14} few studies have examined the prospective association between midlife cardiac troponin level and later life structural brain changes.¹⁵

This study uses longitudinal data from the Whitehall II cohort study spanning 25 years and three measurements of cardiac troponin I based on a high-sensitivity assay. We examined (i) the long-term association of

cardiac troponin I at study baseline with cognitive trajectory and incident dementia in prospective analyses; (ii) how long before diagnosis of dementia the cardiac troponin I level has been elevated by modelling the backward trajectory of cardiac troponin I; and (iii) the association of cardiac troponin I with brain volume measures assessed 15 years later in a substudy of structural magnetic resonance imaging (MRI).

Methods

Study population

The Whitehall II study is an ongoing longitudinal study of 10 308 people recruited from the British Civil Service in 1985–88. Participants had clinical examinations of behavioural and biomedical factors in eight waves (1985–88, 1991–94, 1997–99, 2002–04, 2007–09, 2012–13, 2015–16, 2019–22). Written informed consent from participants was renewed at each contact. The baseline for this study is 1997–99 when cardiac troponin was first measured. We included six waves of clinical examination until 2022. Disease and death data up to March 2023 were obtained through linkage to electronic health records of the UK National Health Service.

Measures

High-sensitivity cardiac troponin I

Cardiac troponin I was measured using stored blood samples at three waves (1997–99, 2007–09, 2012–13).^{9,16} Blood samples for each wave were handled according to a standardized protocol. Fasting venous blood samples were collected and centrifuged, and serum was stored in aliquots at -80°C until batch analysis was performed. We performed all troponin measurements from all time points in a single batch to minimize any potential impact of variation in reagent lot or calibration between runs on the analyser. Cardiac troponin I concentrations were measured using the Siemens Atellica Immunoassay High Sensitivity Troponin I assay (Siemens Healthineers, Erlangen, Germany). This assay has a limit of blank of .5 ng/L, a limit of detection of 1.6 ng/L, and a limit of quantitation of 2.5 ng/L. In the analyses, we assigned .5 ng/L to those with cardiac troponin concentration below the limit of blank. The sex-specific 99th centile upper reference limits in the general population used for clinical referral are 34 ng/L and 53 ng/L in females and males, respectively.

Cognitive function

The cognitive test battery was introduced to the Whitehall II clinic in 1997–99 and repeated at all subsequent clinical assessments. We included all six waves of cognition data between 1997 (aged 45–69 years) and 2022 (aged 68–92 years). The tests have good test–retest reliability (range .6–.9), assessed in 556 participants and retested within 3 months in 1997–99. Three cognitive domains (memory, executive function, and fluency) were assessed. Memory was assessed using a 20-word free recall test. Executive function was assessed with the Alice Heim 4-I test. Fluency was assessed using measures of phonemic and semantic fluency. Participants were asked to recall in writing as many words beginning with ‘s’ (phonemic fluency) and as many animal names (semantic fluency) as they could. One minute was allowed for each test.

Based on three cognitive domains, we created a global cognitive score incorporating all tests described above by firstly using the distribution of the first wave of cognitive data (1997–99) to standardize the raw scores for each domain to z scores. We summed these z scores and re-standardized them to yield the global score, an approach that minimizes measurement error inherent individual tests.¹⁷

Dementia

We used three registers [the national hospital episode statistics (HES) database, the Mental Health Service Data Set, and the mortality register] to ascertain dementia using ICD-10 codes F00–F03, F05.1, G30, and G31. Record linkage was available up to 1 March 2023. Date of dementia was

set as the earliest record of a diagnostic code for dementia in any of the three ascertainment databases. As our outcome was incident dementia, participants with dementia at baseline were excluded.

Neuroimaging outcomes

A total of 771 participants, randomly selected from Whitehall II Phase 11 (2012–13), received multimodal brain MRI scans at the Oxford Centre for Functional MRI of the Brain, as part of the Whitehall II imaging substudy.¹⁸ Due to a scanner upgrade, two MRI scanners were used: a 3T Siemens Magnetom Verio scanner (Erlangen, Germany) with a 32-channel head coil (April 2012–December 2014) and a 3T Siemens Prisma Scanner (Erlangen, Germany) with a 64-channel head-neck coil in the same centre (July 2015–December 2016). The scan parameters were identical or closely matched between scanners. Analyses were adjusted for scanner type. Brain tissues were segmented using an automated segmentation tool, which extracts measures of total grey matter, white matter, and cerebrospinal fluid.¹⁸ Intracranial volume was calculated as the sum of total grey matter, white matter, and cerebrospinal fluid. All volumes were normalized by converting them to percentages of the intracranial volume. Burden of white matter hyperintensities was estimated using the Fazekas visual rating scale¹⁹ and FSL-BIANCA tool.²⁰ For the Fazekas visual rating scale, a score (range 0–3) was assigned for deep white matter and periventricular areas based on the size, location, and confluence of lesions. We used the sum of the two scores to estimate the total burden of white matter intensities. Hippocampal atrophy was estimated using the Scheltens score assessed by three clinicians independently.²¹ Diffusion tensor imaging metrics fractional anisotropy and mean diffusivity were generated using DTIFit (<http://fsl.fmrib.ox.ac.uk/fsl/fdt>).

Clinical characteristics

We included sociodemographic, health behaviours, and health status at baseline (1997–99) as covariates: age, sex, education (less than secondary school, secondary school, university), occupational position based on British Civil Service employment grade (administrative grades, professional or executive grades, clerical or support grades), birth cohort defined based on sociohistorical events²² (depression-era cohort born 1930–38, World War 2 cohort born 1939–45, post-war cohort born 1946–52), smoking status (never, former, current), alcohol consumption (non-drinker, moderate consumption: 1–14 units/week in women or 1–21 units/week in men, heavy consumption: >14 units/week in women or >21 units/week in men), physical activity (hours of moderate or vigorous exercise/week, categorized as low, <1 h; moderate, 1–2.4 h; high, ≥ 2.5 h), body mass index (BMI, kg/m^2), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), fast glucose (mmol/L), total cholesterol (mmol/L), triglycerides, HDL, anti-hypertensive drugs, diabetic medication, and lipid-lowering drugs. Cardiovascular disease was identified via linkage to national HES data, recording any diagnosis of coronary heart disease (ICD-9 codes 410–414 and 429; ICD-10 codes I20–I25) or stroke (ICD-10 codes I60–I64 and G45).

Statistical analysis

Association between cardiac troponin I at baseline and incidence of dementia

We included all participants free of dementia or cardiovascular disease, who had data on cardiac troponin I at baseline (1997–99). These participants were followed up to date of record of dementia, death, or 1 March 2023, whichever came first. Cox proportional hazards models were used to examine the association between cardiac troponin I and dementia incidence. We modelled cardiac troponin I both continuously and categorically. For the continuous analysis, we used log₂ transformation as the cardiac troponin levels were right skewed. For the categorical analysis, we used the following categories: <2.5 ng/L (below the limit of quantitation threshold, reference group), 2.5–3.4 ng/L, 3.5–5.2 ng/L, and >5.2 ng/L. The latter three groups were cut based on tertiles of troponin measurements above the limit of quantitation threshold. We also modelled cardiac troponin I

using natural cubic spline function with three knots (10th, 50th, and 90th percentile)²³ to visualize possible non-linear association with dementia incidence. In the above analyses, we used age as time scale and adjusted for sex, ethnicity, education level, occupational position, alcohol consumption, smoking status, physical activity, BMI, SBP, DBP, glucose, total cholesterol, triglycerides, HDL, anti-hypertensive drugs, diabetes medication, and lipid-lowering drugs at baseline. Proportional hazards assumptions were examined using Schoenfeld residual plots, and no violations were found. We conducted two sensitivity analyses. First, we further adjusted for APOE $\epsilon 4$ (0, 1, or 2) in a sub-sample of participants with data on Apolipoprotein E (APOE) genotype. Second, we further adjusted for estimated Glomerular Filtration Rate (eGFR) in a sub-sample of participants who were free of chronic kidney disease or end-stage renal disease at baseline and had serum creatinine measurements available from the 1997–99 examination.

Association between cardiac troponin I at baseline and cognitive trajectory

We included all participants that were free of dementia and cardiovascular disease at baseline, had data on cardiac troponin I at baseline, and had at least one measurement of cognitive function among six repeated measurements between 1997 and 2022. Random slope linear mixed models with age as the time scale were used to examine whether cardiac troponin I at baseline was associated with cognitive trajectories. The model included sex, ethnicity, education level, occupational position, birth cohort, cardiac troponin I (\log_2 transformed), age, age², and interactions of all the covariates with age and age². See the [Supplementary data](#) for a more detailed description for the model parameterization and diagnosis. A likelihood ratio test was conducted for the interaction of cardiac troponin I with age and age² to examine whether the cognitive trajectory differed in different cardiac troponin I levels at baseline. We replicated the analysis using categorized cardiac troponin I in four groups as above to relax the linear assumption and to visualize and present the results. We plotted the cognitive trajectory by different baseline cardiac troponin level and statistically compared cognitive scores for different troponin I groups at age 60, 70, 80, and 90. We repeated the analysis by further accounting for alcohol consumption, smoking status, physical activity, BMI, SBP, DBP, glucose, total cholesterol, triglycerides, HDL, anti-hypertensive drugs, diabetes medication, and lipid-lowering drugs at baseline.

Backward trajectory of cardiac troponin I before dementia

We included all participants who were free of dementia and cardiovascular disease at baseline and had at least one cardiac troponin measurement before the end of follow-up. We used a nested case–control design to compare the trajectory of cardiac troponin I in those who developed dementia and those who did not. Each dementia case was matched to four controls at the diagnostic date. We used random sampling with replacement (i.e. same control is possible to be matched with different cases). The eligibility of the control sample is (i) free of dementia at the diagnostic date (a control could later become a case), (ii) of similar sex and age (± 3 years), and (iii) of same education level. In the sensitivity analysis, we further matched with the same cardiovascular disease to see whether the association was attenuated.

We used retrospective time since the matching date as the time scale. Time 0 was the date of dementia diagnosis for each quintet (one case and four matched controls). A latent process mixed model²⁴ was used to model the trajectory of cardiac troponin I (\log_2 transformed). The model included time, time², index age (age at Time 0), sex, education level, case indicator (coded as 1 for cases and 0 for controls), and interactions of all the covariates (index age, sex, education level, and case indicator) with time and time². Wald test was used for the interaction of case indicator with time and time² to examine whether the trajectory of cardiac troponin I differed between cases and controls. We also used the Wald tests to compare the differences of predicted mean cardiac troponin I levels between cases and controls at different time points before dementia diagnosis. In the sensitivity analysis, we further incorporated time-dependent covariates

(SBP, fast glucose, BMI, total cholesterol, triglycerides, and HDL) at three waves (1997–99, 2007–09, 2012–13) to examine the robustness of the results.

Association between cardiac troponin I at baseline and brain volume

We included participants that were free of dementia and cardiovascular disease, did not have missing data for cardiac troponin I at Phase 5 (1997–99), and had MRI scans between 2012 and 2016. Linear regression models were used to examine the association between cardiac troponin I at baseline and whole brain volume (sum of grey and white matter), grey matter volume, white matter volume, white matter hyperintensities volume (FSL-BIANCA), fractional anisotropy, and mean diffusivity. Poisson regression models were used to examine the association of baseline cardiac troponin I with white matter hyperintensity burden (Fazekas visual rating scale) and hippocampal atrophy. We conducted overdispersion test, and the evidence for overdispersion was weak. We modelled cardiac troponin I both continuously and categorically aforementioned. The models were all adjusted for age at MRI assessment, sex, education, occupational position, smoking status, and alcohol consumption.

The proportion of missing data across covariates ranged from .1% to 13.6%. A total of 1685 (28.2%) participants had at least one missing covariate. Simple imputation using mice was applied for the missing covariate values using information from other covariates and the outcome. All analyses were performed using R statistical software, version 4.4.1.

Results

A total of 7299 participants had at least one measure of cardiac troponin I. They did not have dementia at baseline. After excluding participants with cardiovascular disease ($n = 62$) at baseline, 7237 participants were included. Among these participants, 5985 had cardiac troponin at baseline. A total of 606 (10.1%) cases of dementia and 1180 (19.7%) deaths were recorded over a median follow-up time of 24.8 (interquartile range 23.3–25.1) years. Baseline characteristics, as well as by cardiac troponin I levels and dementia status at follow-up, are presented in [Table 1](#). Participants with higher cardiac troponin I were older, more likely to be men, and from higher educational and occupational group. They had higher BMI, SBP, DBP, and glucose level. Compared with those who were dementia free at the end of follow-up, people with incident dementia were older, more likely to be women, and from lower education and occupational group. They had higher BMI, glucose, SBP, and total cholesterol level.

Association between cardiac troponin I at baseline and incidence of dementia

A total of 5985 participants free of diagnosed cardiovascular disease and dementia at baseline (age range 45–69) were included in the analyses. Every doubling of cardiac troponin I was associated with 10% higher hazard of dementia (Hazard ratio (HR) 1.10, 95% CI 1.03–1.17). The association did not differ between age group (≤ 60 vs > 60 years) ($P_{\text{interaction}} = .74$) or sex ($P_{\text{interaction}} = .57$). Compared with those with cardiac troponin I below quantification limit (< 2.5 ng/L), participants with cardiac troponin I > 5.2 ng/L had 38% higher hazard of dementia (HR 1.38, 95% CI 1.09–1.74) ([Table 2](#)). We also plotted the association between cardiac troponin I and dementia incidence using natural cubic splines (see [Supplementary data online, Figure S1](#)). The result was consistent with analysis with categorized cardiac troponin I group and showed continuously increased risk of dementia as cardiac troponin I increases. The increase in dementia risk tended to be smaller as troponin I level increased; however, this was not a statistically significant effect (P for

Table 1 Characteristics of the study sample

	High-sensitivity cardiac troponin I at baseline		Dementia status at the end of follow-up		Total population (n = 5985)
	≤3.4 ng/L (n = 3417)	>3.4 ng/L (n = 2568)	No dementia (n = 5379)	Dementia (n = 606)	
Age, years	55.3 (5.8)	57.5 (6.1)	55.7 (5.9)	61.1 (5.1)	56.2 (6.0)
Women	1351 (39.5)	398 (15.5)	1539 (28.6)	210 (34.7)	1749 (29.2)
Ethnicity, White	3142 (92.0)	2350 (91.5)	4960 (92.2)	532 (87.8)	5492 (91.8)
Education					
Less than secondary school	1277 (37.4)	852 (33.2)	1847 (34.3)	282 (46.5)	2129 (35.6)
Secondary school	890 (26.0)	701 (27.3)	1455 (27.0)	136 (22.4)	1591 (26.6)
University	1189 (34.8)	958 (37.3)	1971 (36.6)	176 (29.0)	2147 (35.9)
Occupation position					
Low	520 (15.2)	260 (10.1)	646 (12.0)	134 (22.1)	780 (13.0)
Intermediate	1506 (44.1)	1036 (40.3)	2308 (42.9)	234 (38.6)	2542 (42.5)
High	1347 (39.4)	1245 (48.5)	2361 (43.9)	231 (38.1)	2592 (43.3)
Alcohol consumption					
Non-drinkers	556 (16.3)	331 (12.9)	757 (14.1)	130 (21.5)	887 (14.8)
Moderate	1960 (57.4)	1539 (59.9)	3175 (59.0)	324 (53.5)	3499 (58.5)
Heavy	788 (23.1)	617 (24.0)	1271 (23.6)	134 (22.1)	1405 (23.5)
Smoking status					
Never	1679 (49.1)	1264 (49.2)	2644 (49.2)	299 (49.3)	2943 (49.2)
Former	1300 (38.0)	1079 (42.0)	2128 (39.6)	251 (41.4)	2379 (39.7)
Current	382 (11.2)	183 (7.1)	515 (9.6)	50 (8.3)	565 (9.4)
Physical activity, hours per week					
Low	1129 (33.0)	634 (24.7)	1564 (29.1)	199 (32.8)	1763 (29.5)
Moderate	588 (17.2)	379 (14.8)	878 (16.3)	89 (14.7)	967 (16.2)
High	1615 (47.3)	1484 (57.8)	2791 (51.9)	308 (50.8)	3099 (51.8)
BMI, kg/m ²	25.9 (4.0)	26.4 (3.8)	26.1 (3.9)	26.3 (4.1)	26.1 (3.9)
SBP, mmHg	121 (15.3)	127 (17.5)	123 (16.5)	126 (16.6)	123 (16.5)
DBP, mmHg	76.4 (9.9)	79.0 (11.2)	77.6 (10.5)	77.4 (10.4)	77.5 (10.5)
Glucose, mmol/L	5.2 (1.2)	5.3 (1.2)	5.2 (1.2)	5.4 (1.6)	5.2 (1.2)
Total cholesterol, mmol/L	5.9 (1.0)	5.9 (1.1)	5.9 (1.0)	6.1 (1.1)	5.9 (1.1)
HDL, mmol/L	1.5 (.4)	1.4 (.4)	1.5 (.4)	1.5 (.4)	1.5 (.4)
Triglycerides, mmol/L ^a	1.1 (.8–1.6)	1.1 (.8–1.6)	1.1 (.8–1.6)	1.1 (.8–1.6)	1.1 (.8–1.6)
Anti-hypertensive drugs	306 (9.0)	421 (16.4)	611 (11.4)	116 (19.1)	727 (12.1)
Diabetic medication	48 (1.4)	36 (1.4)	68 (1.3)	16 (2.6)	84 (1.4)
Lipid-lowering drugs	77 (2.3)	95 (3.7)	150 (2.8)	22 (3.6)	172 (2.9)

Values are means (Standard deviations) for continuous variables and numbers (percentages) for categorical variables. BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

^aTriglyceride values were skewed and were presented as median and interquartile range.

Table 2 Association between high-sensitivity cardiac troponin I at baseline (1997–99) and incident dementia during 25 years of follow-up

Cardiac troponin I, ng/L	No. of cases/total no.	HR (95% confidence interval)
<2.5	158/2135	1.00 (reference)
2.5–3.4	133/1282	1.21 (.95, 1.53)
3.5–5.2	150/1281	1.29 (1.02, 1.63)
>5.2	165/1287	1.38 (1.09, 1.74)

The model was adjusted for age, sex, ethnicity, education, occupational position, smoking status, alcohol consumption, physical activity, body mass index, systolic blood pressure, diastolic blood pressure, glucose, total cholesterol, triglycerides, HDL cholesterol, anti-hypertensive drugs, diabetes medication, and lipid-lowering drugs.

non-linearity = .32). Sensitivity analyses further adjusting for APOE genotype or eGFR showed consistent results (see [Supplementary data online, Tables S1 and S2](#)).

Association between cardiac troponin I at baseline and cognitive trajectory

A total of 5895 participants free of diagnosed cardiovascular disease and dementia at baseline with one or more measurements of cognitive data were included in the analyses (90 participants without any cognitive data were excluded). Of them, 2508 (42.5%) had cognitive data at all six waves, 1102 (18.7%) at five waves, 652 (11.1%) at four waves, 555 (9.4%) at three waves, 500 (8.5%) at two waves, and 578 (9.8%) at only one wave. Cognitive trajectory differed by cardiac troponin I after adjusting for sex, ethnicity, education level, occupational position, birth cohort (continuous values, $P_{\text{interaction}} = .07$; grouped values, interaction $P = .0012$). Participants with higher cardiac troponin I at baseline had a faster decline of cognitive function with age ([Figure 1](#)). Compared with participants with cardiac troponin I < 2.5 ng/L, those with cardiac troponin I > 5.2 ng/L had similar global cognitive z score at age 60, but had .10 (.02–.18) standard deviations lower global cognitive z score at age 80, and .19 (.03–.35) standard deviations lower score at age 90 ([Table 3](#)). The differences at age 80 and 90 correspond to an accelerated cognitive ageing equivalent to ~1.4 and 2 years, respectively. Results were similar after further adjusting for behavioural and biomedical risk factors at baseline (see [Supplementary data online, Figure S2 and Table S3](#)).

Backward trajectory of cardiac troponin I before dementia

Among the 695 incident dementia cases identified in the study sample, all were successfully matched to four controls, and this led to a nested case–control sample of 3475 individuals. Both case and control groups had an increasing predicted cardiac troponin I level over time, which were not significantly different, though they tended to converge ($P_{\text{interaction}} = .12$) ([Figure 2](#)). Compared with controls, cases had consistently higher mean cardiac troponin I levels from 25 to 7 years preceding dementia diagnosis (see [Supplementary data online, Table S4](#)). Further matching by cardiovascular disease status or adjusting for time-dependent covariates showed similar but attenuated results (see [Supplementary data online, Figures S3 and S4 and Tables S5 and S6](#)).

Association between cardiac troponin I at baseline and brain volume

Of the 771 participants in the substudy, we excluded those without a cardiac troponin I measurement ($n = 129$), or who had dementia or cardiovascular disease at baseline ($n = 1$), producing an analytical sample of 641. One year older age was associated with .32% (95% CI .28%–.35%) lower total brain volume, .23% (95% CI .20%–.26%) lower grey matter volume, and .09% (95% CI .06%–.11%) lower white matter volume. Higher cardiac troponin I level at baseline was associated with lower grey matter volume, but was not statistically associated with white matter volume. People with cardiac troponin I concentrations > 5.2 ng/L had .64% (95% CI .24%–1.05%) lower grey matter volume and 18% (95% CI 0%–40%) increased risk of hippocampal atrophy compared with those with cardiac troponin I < 2.5 ng/L, corresponding to an age effect of 2.7 and 3 years, respectively ([Table 4](#)). Cardiac troponin I concentration was not significantly associated with white matter hyperintensities. Cardiac troponin I concentration was associated with lower fractional anisotropy and higher mean diffusivity, though this is not statistically significant (see [Supplementary data online, Table S7](#)).

Discussion

Our longitudinal study suggests that subclinical myocardial injury in mid-life, indicated by elevated cardiac troponin I levels, is associated with higher dementia risk. We have three key findings. First, people with higher cardiac troponin I concentrations at baseline had faster decline of cognition and were more likely to be diagnosed with dementia over a median 25 years of follow-up. Second, backward trajectory analysis showed that cardiac troponin I level was consistently higher in those who developed dementia compared with those who did not between 7 and 25 years before diagnosis. The length of time suggests that higher cardiac troponin I is unlikely to be due to prodromal changes. Rather, elevated cardiac troponin may indicate underlying cardiac injury or dysfunction, which could influence cerebral perfusion or systemic vascular health, thereby contributing to cognitive decline and dementia. Third, in the MRI substudy, people with increased cardiac troponin I at the midlife baseline were more likely to have relatively low grey matter volume and hippocampal atrophy 15 years later. These three consistent findings involving repeated assessments with a high-sensitivity cardiac troponin I assay starting in midlife strengthen the evidence that myocardial injury may directly or indirectly contribute to the aetiology of dementia ([Structured Graphical Abstract](#)).

Comparison with previous studies

Two published studies have examined the prospective association of cardiac troponin with incident dementia.²⁵ The Atherosclerosis Risk in Communities (ARIC) study found that elevated levels of high-sensitivity cardiac troponin T measured at mean age of 62.5 years were associated with higher dementia incidence over 13 years of follow-up.¹⁰ The national FINRISK 1997 study reported that high-sensitivity cardiac troponin I measured at a mean age of 47.9 years was associated with incident dementia over 18 years of follow-up.²⁶ Our study had longer follow-up and larger effect size compared with FINRISK using high-sensitivity troponin I (Abbott Architect), but a smaller effect size compared with the ARIC study using high-sensitivity troponin T (Roche Elecsys). These previous studies were based on a single measurement of cardiac troponin.

Our novel contribution to the evidence is based on repeated measurements of cardiac troponin I over a 15-year period, which allowed

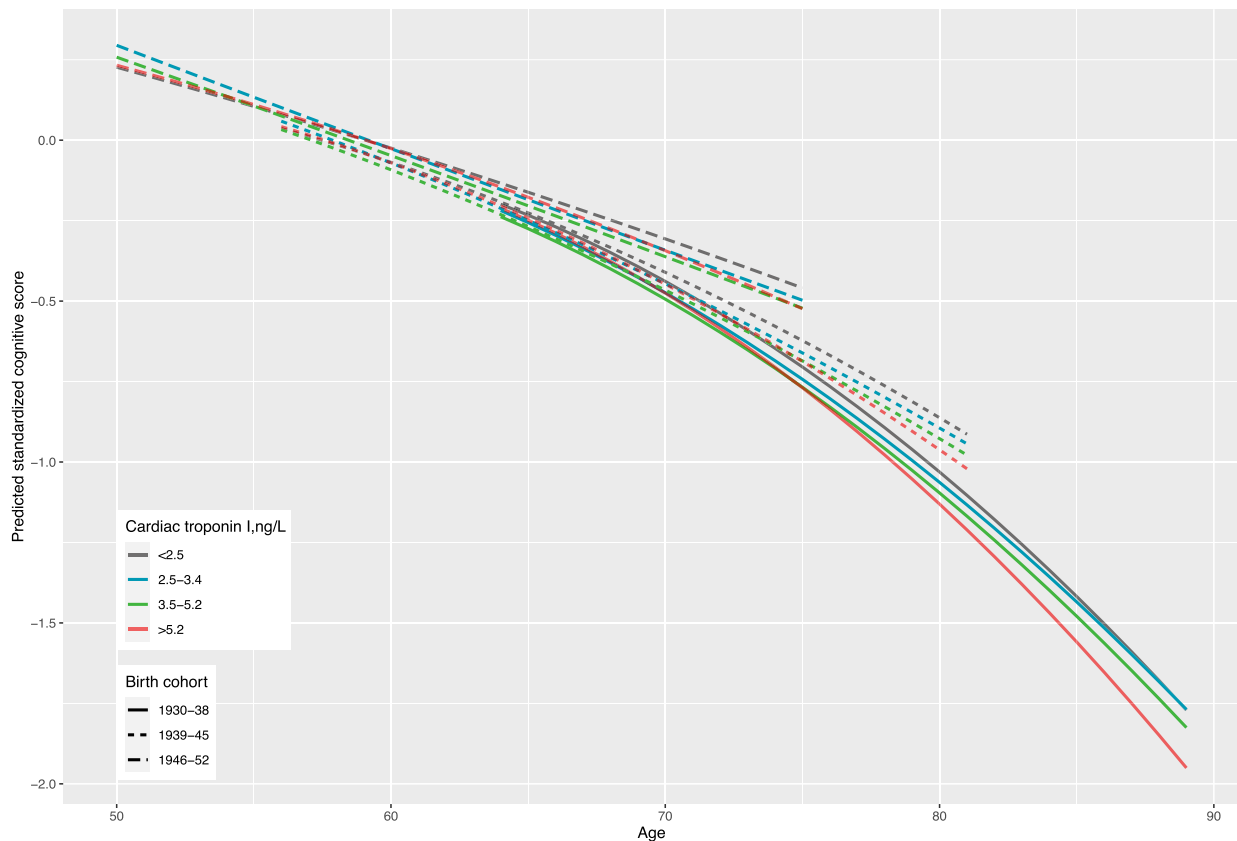


Figure 1 Cognitive trajectories from age 50 to 89 years by levels of high-sensitivity cardiac troponin I at baseline stratified by birth cohort. Predicted cognitive scores estimated from a random slope linear mixed model (model terms: sex, ethnicity, education level, occupational position, birth cohort, cardiac troponin I group, age, age², and interactions of all covariates with age and age²). *P* for difference in trajectory between different cardiac troponin levels = .0012

Table 3 Association of high-sensitivity cardiac troponin I with cognitive performance at age 60, 70, 80, and 90 years

Cardiac troponin I, ng/L	Difference in cognitive function			
	Age 60	Age 70	Age 80	Age 90
<2.5	Ref	Ref	Ref	Ref
2.5–3.4	0 (–.06, .05)	–.04 (–.09, .01)	–.03 (–.11, .04)	0 (–.15, .16)
3.5–5.2	–.03 (–.08, .03)	–.06 (–.11, –.01)	–.07 (–.15, .01)	–.06 (–.21, .10)
>5.2	0 (–.06, .05)	–.04 (–.09, .02)	–.10 (–.18, –.02)	–.19 (–.35, –.03)

The model term included sex, ethnicity, education level, occupational position, birth cohort, cardiac troponin I group, age, age², and interactions of all the covariates with age and age².

the backward trajectory before dementia diagnosis to be modelled. We observed an increased cardiac troponin level occurred as early as 25 years before dementia diagnosis. Furthermore, our characterization of cognitive decline, based on six assessments of cognitive function over 25 years, substantiates the interpretation that subclinical myocardial injury is associated with long-run processes in the midlife preclinical period.

A few prospective studies found higher cardiac troponin T concentration at baseline was associated with faster annual decline in global cognition. However, these studies either had cardiac troponin measured at older age (>65 years),^{11,12,27} or had few repeated measurements of cognitive function (<3 times),²⁸ or had a short follow-up time (<5 years).^{11,12} Consequently, no previous study investigated the association of the cardiac troponin at midlife on the subsequent

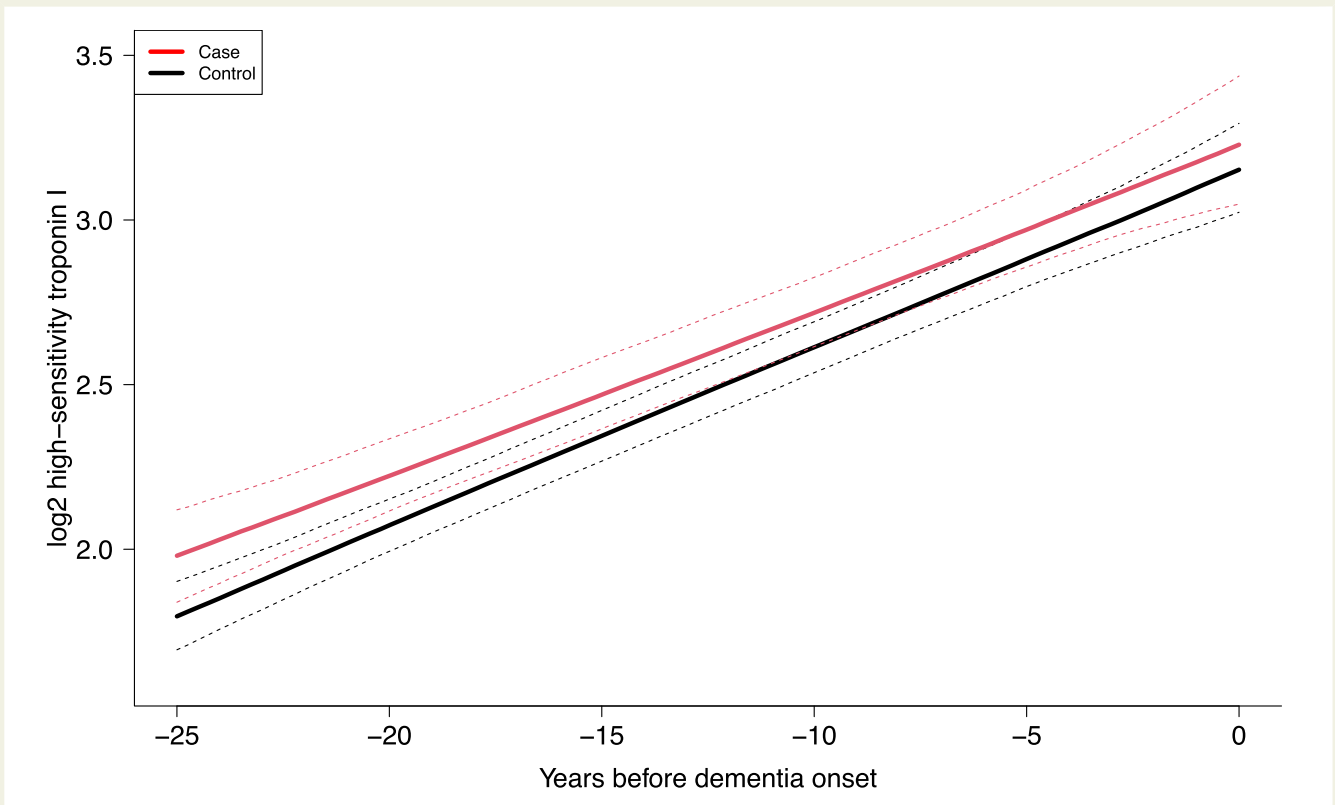


Figure 2 Averaged predicted trajectories of high-sensitivity cardiac troponin I (ng/L, log2 transformed) for 695 incident cases of dementia and 2780 matched controls over 25 years preceding diagnosis of dementia estimated from a latent process mixed model. Nested case-control design matching with age, sex and education level. Dashed lines represent 95% confidence intervals. *P* for difference in trajectory between cases and controls = .12

Table 4 Association between high-sensitivity cardiac troponin I at Phase 5 (1997–99) and structural brain volume 15 years later: Whitehall II imaging substudy (*n* = 641)

Cardiac troponin I, ng/L	No	Total brain volume (grey matter + white matter) (% total intracranial volume)	Grey matter volume (% total intracranial volume)	Hippocampal atrophy (Scheltens score summed across both sides, range 0–8)
		Difference (95% confidence interval)	Difference (95% confidence interval)	Ratio of the score (95% confidence interval)
<2.5	220	0 (ref)	0 (ref)	1 (ref)
2.5–3.4	144	–.34 (–.83, .14)	–.44 (–.84, –.05)	1.03 (.87, 1.23)
3.5–5.2	136	–.38 (–.88, .11)	–.63 (–1.04, –.22)	1.16 (.98, 1.38)
>5.2	141	–.65 (–1.14, –.15)	–.64 (–1.05, –.24)	1.18 (1, 1.40)
Every doubling in cardiac troponin I	641	–.10 (–.26, .06)	–.13 (–.26, .00)	1.03 (.98, 1.09)

For total brain volume, grey matter volume, and white matter volume, linear regression models were used adjusted for age, sex, ethnicity, education level, occupational position, smoking status, alcohol consumption, and magnetic resonance imaging scanner.

For total white matter hyperintensities and hippocampal atrophy, Poisson regressions were used adjusted for age, sex, ethnicity, education level, occupational position, smoking status, alcohol consumption, and magnetic resonance imaging scanner.

We did not find significant results for white matter volume and total white matter hyperintensities.

long-term cognitive trajectory until late life. Our study measured cardiac troponin I at a mean age of 56 years and had up to six repeated measurements of cognitive function across 25 years and found that

cognitive performance was not significantly different in the 60 and 70 s, but started to diverge around age 80. This is consistent with the finding from the ARIC study that cardiac troponin T measured at a

mean age of 63 years was not associated with 15-year change in cognitive function using only two repeated cognitive functions measured 15 years apart.²⁸

Few population-based studies have examined the association between cardiac troponin and structural brain changes, and cardiac troponin T assays were mostly used that have greater imprecision than high-sensitivity cardiac troponin I assays at the low concentrations observed in population studies.²⁹ A cross-sectional study using data from the Maastricht study found that a higher cardiac troponin T concentration was associated with smaller grey matter volume and greater white matter hyperintensity among participants aged 60 and above.³⁰ The ARIC study reported that individuals with higher cardiac troponin T were associated with MRI-defined silent brain infarcts and white matter lesions cross-sectionally and more white matter lesion progression on the follow-up MRI 11 years later.¹⁵ Our study used a high-sensitivity cardiac troponin I assay with consistent findings in regard to the smaller grey matter in those with higher cardiac troponin levels. A potential explanation is that grey matter is more susceptible to cerebral hypoperfusion caused by cardiac dysfunction as it has higher metabolic demand compared with white matter. Our study, however, did not find cardiac troponin to be associated with white matter hyperintensities. This is consistent with the previous evidence from the Whitehall II study that the Life's Simple 7 cardiovascular health score was not associated with white matter hyperintensities.⁵ A recent study using UK Biobank, however, found that higher Life's Essential 8 cardiovascular health score was associated with lower white matter hyperintensity volume.³¹ The small sample size and relatively healthier participants with lower vascular burden compared with the general UK population³² may have limited the power to estimate the association with white matter hyperintensities. Notably, we found that elevated cardiac troponin level tended to be associated with lower fractional anisotropy and higher mean diffusivity. These diffusion metrics may be more sensitive in detecting early microstructural alterations that occur before overt lesion formation in a healthy cohort.

Role of subclinical myocardial injury in dementia aetiology

Dementia and cardiovascular disease share risk factors such as hypertension and hyperlipidaemia.^{3,33–35} These risk factors may contribute to the heart–brain connection by causing damage to vessels in both organs. Importantly, our analysis shows that higher cardiac troponin was associated with higher dementia risk independent of hypertension and hyperlipidaemia. Higher cardiac troponin is associated with increased risk of stroke,³⁶ and stroke is known to double the risk of dementia.³⁷ Interestingly, the association was only slightly attenuated when adjusting for clinically diagnosed cardiovascular disease in our study, indicating other mechanisms beyond occlusion of major arteries, such as cerebral small vessel disease and cerebral hypoperfusion and hypoxia, may be involved.^{3,38} A previous review concluded that cardiac troponins are more consistently linked to vascular brain lesions than to neurodegenerative changes such as brain atrophy.² However, we found that cardiac troponin was prospectively associated with brain atrophy. It is possible that vascular and neurodegenerative brain damage may overlap and develop in parallel³⁹ and cardiac troponin may provide insights into both pathologic processes.

Strengths and limitations

Our study, with a median follow-up of 25 years, is less susceptible to reverse causation. The development of dementia involves a long

prodromal period, and neuropathological abnormality and change of biomarker levels can begin 15–20 years before clinical diagnosis of dementia. No other population-based studies have measured cardiac troponin level at midlife with a follow-up period of 20 years, which is critical to examine the association between subclinical myocardial injury in midlife and incident dementia.

Another novel strength is the incorporation of repeated measurements of high-sensitivity cardiac troponin I and modelling the backward trajectory of cardiac troponin before dementia diagnosis. Previous studies only focused cardiac troponin level at one time point, and its association with incident dementia depends on both when cardiac troponin was measured and the length of the follow-up period. This conventional study design cannot determine the length of time that cardiac troponin levels have been raised before dementia diagnosis.

Our study applied triangulation by using two different study designs: prospective cohort study and retrospective nested case–control study. In the prospective cohort study, we used baseline cardiac troponin only and did not consider the change in cardiac troponin over time because analysis using time-dependent cardiac troponin, e.g. time-dependent Cox model, tends to estimate short-term association with dementia rather than long-term risk.⁴⁰ In the backward trajectory analysis, informative dropouts due to death and other causes can truncate observation of cardiac troponin. This may lead to an underestimation of the true difference in troponin trajectory between dementia cases and controls as dementia cases are more likely to drop out early due to poor health and the observed troponin trajectory will be lower than the true underlying trajectory. We performed sensitivity analyses adjusting for key time-varying covariates that are likely predictors of missingness. Results remained consistent, supporting the robustness of our findings under the missing at random assumption.

Our results may underestimate the association as cardiac troponin is associated with mortality, although we would have picked up some of these people if dementia was recorded on the death certificate. Troponin I levels can be elevated due to non-cardiac causes such as intense exercise and renal impairment, but this would not be expected to increase the risk of dementia. We did a sensitivity analysis adjusting for eGFR and physical activity and found that the results remained consistent, reinforcing the robustness of our findings. The population in Whitehall II are predominantly white and comprises civil servants, and generalization of our results to other ethnicity groups or those with different socioeconomic profiles may be limited. Validation studies in other cohorts with more diverse populations are needed to confirm our results. All troponin measurements were performed in a single batch to minimize the batch effect. However, changes in dementia policy and diagnostic criteria over time may have influenced when and how dementia was diagnosed, potentially affecting the alignment of the backward troponin trajectories. We used one cardiac troponin I assay, and validation of our results using other cardiac troponin assays is needed if measurement were to be used in clinical practice to inform dementia risk. N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) and B-type Natriuretic Peptide (BNP) are important cardiac biomarkers that reflect haemodynamic stress and are found to be associated with incident dementia.⁴¹ However, these data are not available in the current study. Future research is needed to examine whether the findings remain consistent after further adjustment for NT-proBNP or BNP levels. The observational study design cannot establish causality. Although we comprehensively adjusted for potential confounders, residual confounding by unmeasured or uncontrolled shared risk factors or measurement error in the covariates may still influence the observed association. Furthermore, causal interpretation relies on key

assumptions related to competing risk of death, including its hypothetical elimination and the absence of unmeasured common causes of dementia and mortality, which may not always hold.⁴²

Conclusion

Subclinical myocardial injury at midlife is associated with higher dementia incidence in later life. Measurement of cardiac troponin I using a high-sensitivity assay in midlife may be useful in the early identification of a population at risk of cognitive decline and dementia.

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Supplementary data

Supplementary data are available at [European Heart Journal](https://academic.oup.com/eurheartj/article/47/3/359/8307234) online.

Declarations

Disclosure of Interest

D.M.K. reports honoraria from Roche Diagnostics. K.P.E. reports receiving consulting fees for being in the expert panel for the European Research Council, Flemish Science Foundation, and European Science Foundation and has been the Chair for Medical Science Division Interdivisional Research Ethics Committee (University of Oxford). J.D. reports consulting fees and honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk, and Bayer. G.L. serves as an unpaid Trustee of Nightingale Hammerson. N.L.M. reports honoraria from Abbott Diagnostics, Siemens Healthineers, and Roche Diagnostics.

Data Availability

Whitehall II data, protocols, and other metadata are available to the scientific community. Please refer to the Whitehall II data sharing policy at <https://www.ucl.ac.uk/epidemiology-health-care/research/epidemiology-and-public-health/research/whitehall-ii/data-sharing>.

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Ethical Approval

Written informed consent from participants and research ethics approvals were renewed at each contact. Ethical approval was from the University College London Hospital Committee on the Ethics of Human Research (reference number 85/0938).

Pre-registered Clinical Trial Number

Not applicable.

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