Longitudinal associations of cardiovascular health and vascular events with incident dementia

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ABSTRACT

Introduction Evidence supporting cardiovascular diseases could increase the risk of dementia remains fragmented. A comprehensive study to illuminate the distinctive associations across different dementia types is still lacking. This study is sought to: (1) determine the clinical validity of Framingham General Cardiovascular Risk Score (FGCRS) for dementia assessment and (2) examine the associations between cardiovascular diseases and the risk of dementia.

Methods A total of 432,079 dementia-free individuals at baseline from UK Biobank were included. Multivariable Cox proportional hazard models were used to investigate the prospective associations for FGCRS and a series of cardiovascular diseases with all-cause dementia (ACD) and its major components, Alzheimer’s disease (AD) and vascular dementia (VaD).

Results During a median follow-up of 110.1 months, 4711 individuals were diagnosed with dementia. FGCRS was associated with increased risks across the dementia spectrum. In stratification analysis, high-risk groups have demonstrated the greatest dementia burdens, particularly to VaD. Over 74 traits, 9 adverse associations, such as chronic ischaemic heart disease (ACD: HR=1.354; AD: HR=1.269; VaD: HR=1.768), atrioventricular block (ACD: HR=1.562; AD: HR=1.556; VaD: HR=2.069), heart failure (ACD: HR=1.639; AD: HR=1.543; VaD: HR=2.141) and hypotension (ACD: HR=2.912; AD: HR=2.361; VaD: HR=3.315) were observed. Several distinctions were also found, with atrial fibrillation, cerebral infarction, and haemorrhage only associated with greater risks of ACD and VaD.

Discussion By identifying distinctive associations between cardiovascular diseases and dementia, this study has established a comprehensive ‘mapping’ that may untangle the long-standing discrepancy. FGCRS has demonstrated its predictivity beyond cardiovascular diseases burdens, suggesting potential opportunities for implantation.

INTRODUCTION

Driven by an increasingly ageing population, dementia is one of the fastest-growing epidemics, with over 43 million affected individuals worldwide, and is anticipated to be tripled by 2050, posing immense social and economic burdens.¹ Given that disease-modifying therapy for dementia remains scarce, interventional management targeting identified risk factors is strongly advocated.

Compelling evidence has shown that cardiovascular risk factors, such as hypertension and diabetes mellitus, are major contributors to dementia’s development.²–⁴ These detrimental risk factors can trigger profound vascular alterations, cause cerebral blood reduction, blood–brain barrier destruction, immune dysregulation and trophic failure, and therefore, increase the vulnerability to cognitive impairment. Yet, the existing issue regarding therapeutic regimen is not about if, but to what degree it should be enforced. Based on this, previous literature has proposed the utilisation of Framingham

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiovascular health is considered as one of the critical factors in the pathogenesis of dementia, but extensive validation is required to pinpoint the effects of long-term cardiovascular risks and the underappreciated role of cardiovascular diseases.

WHAT THIS STUDY ADDS

⇒ Framingham General Cardiovascular Risk Score, a widely adopted tool for predicting 10-year cardiovascular event risks, was associated with greater risks of incident dementia, suggesting it might have clinical value to translate into dementia assessment.
⇒ Several previously established associations were reconfirmed in the analyses, in which primary hypertension, chronic ischaemic heart disease, cerebrovascular diseases and heart failure showed to be at-risk conditions predisposed to different dementia types.
⇒ Associations between the atrioventricular block and conduction disorders were also identified, indicating the existence of overlooked cardiovascular conditions.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings have reconfirmed and challenged the classic views on the heart–brain entanglement, providing insight into further investigations.
General Cardiovascular Risk Score (FGCRS), a model to estimate the 10-year risk of cardiovascular events, for dementia due to its potential predictive value and feasibility of formulating preventive strategies. The findings, however, were inconsistent, possibly due to confinement of overlapping diagnoses and restricted sample size.6

Thus, a further evaluation embedded with a large population may augment the clinical usefulness of FGCRS.

Cardiovascular diseases, on the other hand, share aetiological risk profiles that resemble dementia, and the entanglement of these diseases has been vigorously unveiled. For instance, atrial fibrillation (AF), heart failure...
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(HF) and ischaemic heart disease have been recognised as at-risk conditions predisposed to dementia via promoting cerebral hypoperfusion and proinflammatory state. Furthermore, recent data have pointed towards the existence of a nonexclusive biological process, where the underlying mechanisms of cardiovascular diseases can drive the formation of amyloid-β supporting its implication not only to vascular dementia (VaD) but also Alzheimer’s disease (AD). Still, the current evidence is believed to only capture partial aspects of heart-brain connections since many conditions are constantly overlooked. At a practical level, a well-characterised study can furtherly address the under-appreciated contributory role of cardiovascular diseases in different dementia types and serve as consolidation of established findings.

By using the UK Biobank’s magnitude sample size and articulated design, this study is sought to untangle the heart-brain connections with more particularity. First, we aimed to determine whether FGCRS is clinically valid for dementia prediction. Second, by examining the associations of a series of 74 cardiovascular disease traits with all-cause dementia (ACD), AD and VaD, we also aimed to uncover unrecognised factors and elucidate their distinctive relationships with dementia.

**METHODS**

**Study design**

The UK Biobank is a large population-based prospective cohort study that constitutes 502,493 individuals aged 40–69 years. Participants were invited to attend 1 of 22 centres across the UK between 2006 and 2010 for baseline assessment. A repeat assessment of 20,000 participants was carried out between August 2012 and June 2013 at the UK Biobank Co-ordinating Centre, Stockport, UK. Extensive information via questionnaires, interviews, health records, physical measures and blood samples was provided by participants. Repeat assessments are scheduled to be carried out every 2–3 years during follow-up. Written consents were provided electronically at first visits. This project was completed using application number 19542.

Data of individuals with pre-existing diagnosis of dementia at baseline were excluded, and a total of 432,079 individuals were eligible for analysis in our present study. Online supplemental materials 1 provides the workflow of this study.

**FGCRS and stratification**

Score points of FGCRS were assigned to corresponding risk factors, including age, sex, smoking status, blood pressure measurements, medication for hypertension, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol to compose a rating scale. After the obtainment by manual calculation, participants were further categorised into groups of low, intermediate and high in accordance with original prediction model for
general cardiovascular risk (online supplemental appendices 1 and 2).\(^5\)

Cardiovascular traits

The date and source of cardiovascular traits via self-report, primary care, hospital in-patient admission and death registry were collected under the circulatory system disorders category of the UK Biobank. The traits were defined based on the International Classification of diseases (ICD)-9 and ICD-10 codes. Initially, 77 traits were identified. After screening, three traits, including aneurysm and dissection, other aneurysms, and other peripheral vascular diseases, were excluded due to the absence of records after the removal of participants with dementia at baseline. In total, 74 traits were included in the present analysis (online supplemental appendix 3). The prevalence rate of cardiovascular diseases could be found in online supplemental materials 2.

Covariates

Sociodemographic variables and potential confounding variables associated with dementia and cardiovascular diseases in previous studies\(^6\) were included as the covariates (online supplemental appendix 4). Age and gender were obtained during initial study visits. Education was classified based on the attainment of college/university degree or professional certificate. Apolipoprotein E (ApoE) \(\varepsilon4\) status was categorised into 0, 1, 2 on account of carriers through the genetic database. Hypertension was defined based on the American Heart Association 2017 guidelines, in which systolic blood pressure \(\geq 140\) mm Hg and/or diastolic blood pressure \(\geq 90\) mm Hg were considered positive.\(^14\) Diabetes mellitus was determined by the self-reported doctor’s diagnosis and the usage of insulin. History of stroke was ascertained by either self-reported or hospital-inpatient records of stroke, not specified as haemorrhage or infarction. Smoking was categorised into three groups: current, former and never smoker. Alcohol intake was considered frequent if more than once a week frequency was reported. Body mass index (BMI) was calculated with the weight of the individual in kilograms divided by the square of the individual’s standing height in metres. Townsend Deprivation Index is a measurement of area deprivation, where it derived from the national census data of unemployment, ownership of vehicles, household overcrowding and occupation. We categorised the index into three levels using the national cut-off.
points (high ≤−2.08, middle −2.08–1.40 and low ≥1.40). Metabolic equivalent minutes per week (MET-min/week) were computed on the basis of the modified version of the international physical activity questionnaire. Medications, including blood pressure-lowering medication, cholesterol-lowering medication and insulin were self-reported; total cholesterol and high-density lipoprotein cholesterol were measured at baseline, and total cholesterol ≥6.2 mmol/L was used to define hypercholesterolemia.

**Outcomes of dementia**

The incident dementia (ACD, AD and VaD) was determined based on a combination of records from algorithmic adjudication, first occurrences of dementia onset, underlying/contributory death in the death registry and diagnoses from hospital inpatient or primary care data. All outcomes were defined in accordance with the ICD-9 codes, ICD-10 codes and Read codes V.2/3, with a follow-up period starting from March 2006 to April 2021. Poststroke dementia was defined by the occurrence of dementia among individuals with any stroke events based on ICD-10 codes: subarachnoid haemorrhage (I60), intracerebral haemorrhage (I61), other non-traumatic intracranial haemorrhages (I62), cerebral infarction (I63) and stroke not specified as haemorrhage or infarction (I64). Detailed UKB codes for dementia diagnosis and classification can be found in online supplemental appendix 5.

**Statistical analysis**

Baseline characteristics were presented as numbers (percentages) for categorical variables and as means (SD) or median (IQR) for continuous variables. In the

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**Ischemic heart disorders**

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR</th>
<th>95% CI</th>
<th>Age</th>
<th>Sex</th>
<th>Follow Up</th>
<th>Gray</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris</td>
<td>1.287</td>
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<td>Acute myocardial infarction</td>
<td>1.228</td>
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<tr>
<td>Other acute ischemic heart diseases</td>
<td>1.355</td>
<td>1.134-1.619</td>
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<tr>
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<td>1.263-1.452</td>
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<tr>
<td>Atherosclerosis</td>
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**Arithmetic and conduction disorders**

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<th>Condition</th>
<th>HR</th>
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<th>Follow Up</th>
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<tr>
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<td>1.403-1.739</td>
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<td>Conduction disorders</td>
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<td>1.452-1.893</td>
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<tr>
<td>Cardiac arrest</td>
<td>1.609</td>
<td>1.249-2.074</td>
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<td>Atrial fibrillation</td>
<td>1.479</td>
<td>1.275-1.591</td>
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<td>Other cardiac conduction disorders</td>
<td>1.275</td>
<td>1.120-1.453</td>
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**Blood flow-reduction disorders**

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<tr>
<td>Heart failure</td>
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<td>1.495-1.796</td>
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<tr>
<td>Hypertension</td>
<td>2.912</td>
<td>2.700-3.142</td>
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**Embolic and other cerebrovascular disorders**

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<th>HR</th>
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<th>Sex</th>
<th>Follow Up</th>
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<td>Pulmonary embolism</td>
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<td>1.461-1.894</td>
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<td>Intracerebral hemorrhage</td>
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<td>2.312-7.999</td>
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<tr>
<td>Nontraumatic intracranial hemorrhage</td>
<td>3.901</td>
<td>2.361-4.666</td>
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<tr>
<td>Cerebral infarction</td>
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<td>2.883-4.712</td>
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<tr>
<td>Stroke</td>
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<tr>
<td>Intracranial hemorrhages</td>
<td>2.138</td>
<td>1.893-2.416</td>
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<tr>
<td>Other cerebrovascular diseases</td>
<td>3.981</td>
<td>3.261-4.666</td>
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<tr>
<td>Cerebrovascular disorders, classified elsewhere</td>
<td>5.213</td>
<td>4.828-5.629</td>
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**Rheumatic and valvular disorders**

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<th>Follow Up</th>
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</thead>
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<td>Rheumatic chorea</td>
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<td>1.176-18.851</td>
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<tr>
<td>Multiple valve diseases</td>
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<td>1.023-1.382</td>
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<tr>
<td>Endocarditis, valve unspecified</td>
<td>1.172</td>
<td>1.019-1.348</td>
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**Other disorders**

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR</th>
<th>95% CI</th>
<th>Age</th>
<th>Sex</th>
<th>Follow Up</th>
<th>Gray</th>
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<tbody>
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<td>Primary hypertension</td>
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<td>1.314-1.509</td>
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<tr>
<td>Hypertensive heart disease</td>
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<td>1.288-3.257</td>
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<tr>
<td>Hypertensive renal disease</td>
<td>1.608</td>
<td>1.274-2.030</td>
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<td>**</td>
</tr>
<tr>
<td>Acute and subacute endocarditis</td>
<td>1.999</td>
<td>1.256-3.180</td>
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<tr>
<td>Complications of heart disease</td>
<td>1.398</td>
<td>1.264-1.545</td>
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<td>**</td>
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<tr>
<td>Phlebitis and thrombophlebitis</td>
<td>1.393</td>
<td>1.248-1.556</td>
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<tr>
<td>Other venous embolism</td>
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<td>1.064-2.417</td>
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<td>**</td>
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<td>**</td>
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<tr>
<td>Oesophageal varices</td>
<td>1.696</td>
<td>1.152-2.496</td>
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<tr>
<td>Other disorders of veins</td>
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<td>1.174-2.031</td>
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<td>Non-specific lymphadenitis</td>
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<td>Non-infective lymphatic disorders</td>
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<td>1.057-1.840</td>
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<td>Other disorders of circulatory system</td>
<td>2.698</td>
<td>1.737-4.193</td>
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**Figure 2** Associations between cardiovascular traits and all-cause dementia. Left: Illustration of significant traits in multivariate Cox regression model of all-cause dementia. Right (colored box): overview of sensitivity analysis. Gray box indicated null significance; one * indicated P value <0.05; two * indicated P value; <0.01 Three * indicated P value < 0.001. HR, Hazard ratio; 95% CI, 95% confidential interval.
case of missing covariates, imputation by predictive mean matching was performed using the MICE package in R.

Cox proportional hazards regression models were applied to examine the independent association between FGCRS, cardiovascular traits and the incidence of different dementia types. The results were presented in HR and 95% CIs. Proportional hazards were tested using scaled Schoenfeld’s residuals to avoid the violation of the assumption, in which p>0.05 in the global Schoenfeld test was considered satisfied.

The FGCRS analysis was initiated with an unadjusted model. The multiadjusted model was adjusted for education, alcohol intake, BMI, MET-min/week, ApoE ε4 status, Townsend Deprivation Index, pacemaker, cholesterol-lowering medication and insulin use (age and sex were excluded from this model since these factors were incorporated in the original calculation). Kaplan-Meier survival curves were used to assess the survival probability of dementia across different FGCRS risk groups.

The cardiovascular traits–dementia association analysis used the Cox regression model, starting with minimal adjustment for age, gender, ApoE ε4 status and BMI, followed by a completely adjusted model for all covariates mentioned above. To examine the robustness of our results, we performed several sensitivity analyses. First, we restricted the analysis among the population in age (≥65 and <65 years old), gender (male and female) to evaluate whether the associations remained significant, and the validity was determined when statistical consistency was reached in both groups. Second, in order to minimise potential reverse causation, any outcome events that occurred within the first 3 years and further 8 years of follow-up were excluded. Third, the Fine-Gray proportional subdistribution hazards models were performed, in which death was considered as a competing risk. Additionally, a model with complete adjustment on post-stroke dementia was performed to broaden the scope of observations.

All estimates would only be considered significant when a two-sided p<0.05 was observed. R software V.4.1.0 and GraphPad Prism V.8.00 (GraphPad Software, San Diego, California, USA) were used for all statistical analyses and figure preparation.

**RESULTS**

Baseline characteristics of participants

A total of 432,079 participants were assessed at baseline. Among these participants, 4,711 cases of ACD, 2,051 AD, and 1,073 VaD occurred during a median follow-up of 110.1 months (IQR: 85.63–129.10). We found that dementia groups were more likely to be constituted with elderly, white, men, lower educational levels, ApoE ε4 carriers and less frequent alcohol drinkers (all p<0.05).
Also, there were higher proportions of hypertension, diabetes mellitus, history of stroke, pacemaker instalment, medications usages and higher FGCRS scores (all p<0.05, except for ethnicity and MET min/week; table 1).

**Higher FGCRS was associated with increased risk of dementia**

FGCRS, treated both as continuous and categorical variables, was associated with increased risks of all types of dementia in the unadjusted and the multiajusted models, with slight differences in HRs (table 2 and online supplemental materials 3). In the multiajusted models, FGCRS was associated with increased risk of ACD (HR 1.589, 95% CI 1.550 to 1.627, p<0.001), AD (HR 1.630, 95% CI 1.581 to 1.680, p<0.001) and VaD (HR 1.680, 95% CI 1.630 to 1.733, p<0.001). Compared with low cardiovascular risk, we found a 3–7 folds excess risk of dementia in intermediate and high risk categories (ACD: intermediate vs low: HR 3.186, 95% CI 2.685 to 3.782, p<0.001, high vs low: HR 5.841, 95% CI 4.951 to 6.892, p<0.001; AD: intermediate vs low: HR 3.111, 95% CI 2.390 to 4.043, p<0.001, high vs low: HR 7.526, 95% CI 5.866 to 9.655, p<0.001; VaD: intermediate vs low: HR 3.111, 95% CI 2.390 to 4.043, p<0.001, high vs low: HR 7.526, 95% CI 5.866 to 9.655, p<0.001). **Figure 1** visually depicts the Kaplan-Meier curves of the three levels of vascular risk in relation to ACD (A), AD (B) and VaD (C).
Ischaemic heart disorders, including chronic ischaemic heart disease, acute myocardial infarction and angina pectoris were associated with higher risks of ACD. A vast majority of arrhythmias and conduction disorders also showed strong associations, including atrioventricular and left-bundle-branch block, other cardiac arrhythmias, other conduction disorder and AF. Disorders with blood flow-reduction potential, such as HF and hypotension, also exerted adverse effects on the risk of ACD. Nearly all cerebrovascular disorders tended to be associated with ACD, in which cerebrovascular disorders classified elsewhere, other cerebrovascular disorders, and sequelae of cerebrovascular disease presented with greatest risks, even after the inclusion of the history of stroke. Based on the manual, other cerebrovascular diseases contained a collective diagnosis of cerebral atherosclerosis, dissection/aneurysm, moyamoya disease, and nonpyrogenic thrombosis; other conduction disorders include the diagnosis of right fascicular/bundle-branch block, bifascicular/trifascicular block, and pre-excitation syndrome; Complications of heart diseases include the diagnosis of cardiac septal defect and intracardiac thrombosis, rupture of chordae tendineae/papillary muscle, myocarditis, and myocardial degeneration; other arrhythmias include the diagnosis of ventricular fibrillation and flutter, sick sinus syndrome, atrial/ventricular/junctional premature depolarization; other cardiovascular diseases include the diagnosis of cardiovascular disorders caused by syphilis, infection, and parasites; cerebrovascular diseases classified elsewhere include the diagnosis of cerebral amyloid angiopathy and arteritis. FGCRS, Framingham General Cardiovascular Risk Score.

**Figure 5** The ‘mapping’ of the associations between cardiovascular diseases and different types of dementia. Content Explanation: other cerebrovascular diseases include the diagnosis of cerebral atherosclerosis, dissection/aneurysm, progressive vascular leukoencephalopathy, progressive vascular leukoencephalopathy, hypertensive encephalopathy, Moyamoya disease, and nonpyrogenic thrombosis; other conduction disorders include the diagnosis of right fascicular/bundle-branch block, bifascicular/trifascicular block, and pre-excitation syndrome; Complications of heart diseases include the diagnosis of cardiac septal defect and intracardiac thrombosis, rupture of chordae tendineae/papillary muscle, myocarditis, and myocardial degeneration; other arrhythmias include the diagnosis of ventricular fibrillation and flutter, sick sinus syndrome, atrial/ventricular/junctional premature depolarization; other cardiovascular diseases include the diagnosis of cardiovascular disorders caused by syphilis, infection, and parasites; cerebrovascular diseases classified elsewhere include the diagnosis of cerebral amyloid angiopathy and arteritis. FGCRS, Framingham General Cardiovascular Risk Score.
and valvular disorders had the least statistical consistency across all models (figure 2 and online supplemental materials 5–8).

**Associations between cardiovascular traits and risk of AD**
The independent associations of AD attenuated drastically compared with ACD, with only 24 cardiovascular traits showing statistical significance (figure 3). Several traits were in-line with the established evidence, including angina pectoris, chronic ischemic heart disease, HF, hypotension and primary hypertension. Participants with different cardiac fascicular blockages, such as atrioventricular and left bundle-branch block and other conduction disorders, were also exposed to greater risk of AD. Strongest associations to the risk of AD were observed in other cerebrovascular disorders and cerebrovascular disorders classified elsewhere. However, the association for the latter was no longer valid in the sensitivity analysis. Interestingly, substantial number of cerebrovascular diseases and disorders with embolic potential, such as AF, failed to reach significance in the age-restricted and sex-restricted models (online supplemental materials 5–8).

**Associations between cardiovascular traits and risk of VaD**
The results had yielded similarity with ACD but with few distinctions (figure 4). Ischemic heart disorders such as angina pectoris, acute myocardial infarction and chronic ischemic heart disease remained robust. Also, arrhythmias and other conduction disorders, including atrioventricular and left bundle-branch block, other conduction disorders and AF significantly increased the risk of VaD. As expected, cerebrovascular disorders increased the risk of VaD with the highest HRs. However, the associations of three embolic traits, including pulmonary embolism, occlusion and stenosis of precerebral arteries, and arterial embolism were hampered by competing events. Lastly, primary hypertension was the only traits that satisfied statistical consistency in other disorders (online supplemental materials 5–8).

**Associations between cardiovascular traits and risk of poststroke dementia**
To further investigate the role of cardiovascular diseases in developing poststroke dementia, we repeated the analysis in individuals with documented stroke events. Of 15,849 participants, 783 ACD, 212 AD and 352 VaD developed during follow-up. Multiajusted models revealed certain differences in contrast to the initial analysis (online supplemental materials 9). We found that hypotension, other cerebrovascular diseases, sequelae of cerebrovascular disease were associated with greater risks of developing all types of dementia after stroke, whereas traits of ischemic heart disorders displayed a lack of statistical consistency.

**DISCUSSION**
By leveraging data of 432,079 individuals from the UK Biobank, this study has extensively illuminated the relationships between cardiovascular health and dementia risk. We found that FGCRS was associated with increased risks of dementia, and individuals carrying the highest vascular risk burdens were susceptible to the 3–7 folds greater risks of dementia, with VaD being the most hazardous. 9 cardiovascular traits showed robust associations for all dementia types. These pronounced associations did not just complement the existent evidence linking cardiovascular diseases and dementia but also supported the existence of overlooked conditions (figure 5). Distinctive and specific associations were also indicated, in which AF, phlebitis and thrombophlebitis, cerebral infarction and intracranial haemorrhage were associated with ACD and VaD, whereas the complications of heart disease, pulmonary embolism, other arrhythmias were associated with ACD solely.

Concerning cardiovascular traits analyses, we have verified several associations from the previous establishment. One of the coherent findings is primary hypertension, where its relationship with different dementia types has been well characterised, and the relevant treatments have shown to render overall benefits. Other consistent findings are angina pectoris and chronic ischemic heart diseases, where the prospective associations have been abundantly described. The complications of ill-defined diseases, coded for myocarditis and structural ruptures, can also be viewed as supported evidence since the occurrence of such events is not uncommon in infarcted heart tissue. Other findings such as cerebral infarction, intracranial haemorrhage and the corresponding sequelae still point to more compelling associations with VaD.

Several cardiovascular traits that are currently in the debate have shown to exert distinctive adverse effects on dementia risks. We found that HF has presented robust associations with all dementia types. The concept of HF in deteriorating cognitive function has grown in popularity in recent years. However, whether such associations extend to specific dementia types remains controversial, as evidence has shown HF may not necessarily be linked with AD. Nevertheless, one explanation is that long-term cerebral hypoperfusion due to low cardiac output can lead to persistent oxygen deficiency, which then exacerbates the vulnerability of neurons and drives the formation of pathological hallmarks of AD. On the other hand, AF has courted similar discrepancies, where its deleterious effects on dementia have not reach a consensus agreement. The gender differences and insignificances showed in the poststroke dementia models have precluded us from establishing associations between AF and AD, which is most in line with prior studies that failed to observe pathological differences of AD and establish causality using the Mendelian randomisation approach. The finding suggests, although indirectly, that AF relations to dementia still incline towards vascular origins.

With regard to overlooked conditions, few traits have been pinpointed. The atrioventricular block has been traditionally less of a focus since it is often considered...
benign, particularly first-degree block. Most dedicated evidence investigating its role has only converged on the risks and prognosis of cardiovascular-related events.\textsuperscript{25} Therefore, whether the atrioventricular and left-bundle block is merely a reflection of underlying structural heart disease or has a straightforward impact remains unclear. It is also not warranted whether other factors were mediated by atrioventricular block to different types of dementia. Even so, based on the consistent associations to increased risks of all dementia types, it is reasonable to suspect that the blockage may be intricately involved in both haemodynamic and systemic degenerative process. Another worth-mentioning trait is hypotension. Despite mixed findings from earlier studies, low diastolic blood pressure and orthostatic hypotension, even asymptomatic, has shown to be associated with elevated risks of dementia.\textsuperscript{17, 26} On this basis, we have furtherly advocated the hazardous effects of hypotension by examining associations with different dementia types.

FGCRS was initially designed as an aggregated measurement for predicting 10-year cardiovascular events,\textsuperscript{5} and the notion of invoking it for dementia wasn’t widely recognised until Song et al examined the relationship between FGCRS and brain pathologies through Rush Memory and Ageing Project.\textsuperscript{27, 28} Their findings have demonstrated that individuals with the highest vascular risk burdens are associated with a more significant decline in global cognition as well as episodic memory and working memory. Additionally, in the autopsies, participants with higher FGCRS have shown a greater tendency to develop vascular and AD-related lesions, such as chronic infarctions and atherosclerosis,\textsuperscript{28} suggesting brain can be reflected by FGCRS. One study further expanded the explorations, finding that cardiovascular diseases may partially mediate the association between FGCRS and the risk and progression of disability.\textsuperscript{20} Based on the close relationship between them, we think that cardiovascular risk factors (the components of FGCRS) could lead to the occurrence of cardiovascular diseases, and are associated with mixed brain lesions such as white matter hyperintensities and brain atrophy,\textsuperscript{30} which are known risk factors for dementia in older people.\textsuperscript{31, 32} A higher long-term cardiovascular risk may be indicative of dementia incidents, and the extensive implantation of FGCRS may be conceived for prevention practice.

Our study has several novelty and implications. Our study is the first to systematically and comprehensively utilize the UK Biobank’s magnitude sample size and articulated design to untangle the heart-brain connections. We found that FGCRS is clinically valid for dementia prediction, as well as the significant associations between a series of 74 cardiovascular diseases with dementia risk. Our findings highlight the importance of the control of cardiovascular risk for the prevention of both cardiovascular diseases and dementia, aiming at delaying the onset of dementia and slowing down its progression among elderly people. Our findings also have reconfirmed and challenged the classic views on the heart–brain entanglement, providing insight into further investigations.

There were several limitations we must acknowledge. First, some of the inclusion criteria for diagnosis were not specific. For example, HF was based on aetiology factors rather than left ventricular ejection fraction. We, therefore, could not furtherly distinguish subjects with reduced or preserved ejection fractions. This limitation might have precluded us from addressing associations with cardiovascular diseases in more clarity. Second, since the population has mainly derived from European ancestry, the current findings may not be compelling for other racial groups, especially since the prevalence rate of certain cardiovascular diseases has shown a degree across the different ethnic backgrounds. However, it has given us great advantages to ensure our results were less prone to bias as the groups were strictly controlled. Third, the observed effects could probably be attributed to residual confounding. Still, our study consisted of one of the most comprehensive adjustments. Last, the ascertainment of predictors might have been under-reported due to the nature of data collection. Luckily, we have included in-patients and hospital records to minimise the effects of this distortion.

**CONCLUSIONS**

In conclusion, FGCRS has been identified as a reliable tool to critically provide long-term risk estimates for dementia. By examining 74 cardiovascular traits, robust associations of 9 cardiovascular traits are found across all dementia types, where the pronounced associations have complimented not only the consistent evidence linking cardiovascular diseases and dementia but also supported the existence of overlooked conditions. Our findings have connected more dots, with potential implications for resolving discrepancies and orchestrating pertinent strategies of dementia treatments. However, the interpretation must be taken with caution, and further studies are warranted.

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**Contributors**

Y-NO and KK organised data, carried out the statistical analysis and participated in the first draft of the manuscript. Y-NO, KK and LY designed...
and drew the figures: Y-RZ, S-YH, S-DC, Y-TD, YG, R-QZ and B-SW organised data and participated in the revision of the manuscript. LT, QD, J-FF, WC and J-TY participated in the study design, reviewing and editing the manuscript. All authors read and approved the final manuscript. Guarantor: J-TY.

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