Longitudinal associations of cardiovascular health and vascular events with incident dementia

Ya-Nan Ou,1 Kevin Kuo,2 Liu Yang,2 Ya-Ru Zhang,2 Shu-Yi Huang,2 Shi-Dong Chen,2 Yue-Ting Deng,2 Yu Guo,2 Rui-Qi Zhang,2 Bang-Sheng Wu,2 Lan Tan,1 Qiang Dong,2,3,4 Jian-Feng Feng,3,4 Wei Cheng,2,3,4 Jin-Tai Yu2

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 hypertension (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 hemorrhage 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 45 million affected individuals worldwide, and is anticipated to be tripled by 2050, posing immense social and economic burdens. 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. 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 evidence 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...
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. 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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-dementia (n=427368)</th>
<th>Dementia (n=4711)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>56.90 (8.01)</td>
<td>64.40 (4.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>195 622 (45.8)</td>
<td>2455 (52.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>College/professional certificate (%)</td>
<td>8383 (2.0)</td>
<td>29 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White ethnicity (%)</td>
<td>402 970 (95.6)</td>
<td>4454 (96.0)</td>
<td>0.285</td>
</tr>
<tr>
<td>BMI (median, IQR)</td>
<td>26.86 (24.24–30.06)</td>
<td>27.18 (24.39–30.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MET min/wk (median, IQR)</td>
<td>1764.00 (792.00–3564.00)</td>
<td>1695.00 (742.00–3572.00)</td>
<td>0.039</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Never smoked</td>
<td>229 045 (53.9)</td>
<td>2174 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Previous smoked</td>
<td>149 774 (35.3)</td>
<td>1990 (42.8)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>46 036 (10.8)</td>
<td>487 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Alcohol intake more than once a week (%)</td>
<td>293 236 (68.8)</td>
<td>2836 (60.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Townsend Deprivation Index at recruitment (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>126 765 (29.7)</td>
<td>1331 (28.3)</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>84 833 (19.9)</td>
<td>1160 (24.6)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>215 770 (50.5)</td>
<td>2220 (47.1)</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>201 941 (47.3)</td>
<td>2721 (57.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mean, SD)</td>
<td>140.05 (19.71)</td>
<td>146.27 (20.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mean, SD)</td>
<td>82.28 (10.69)</td>
<td>81.73 (10.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>23 737 (5.6)</td>
<td>668 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>134 320 (31.4)</td>
<td>1359 (28.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.69 (1.15)</td>
<td>5.51 (1.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol</td>
<td>1.44 (0.38)</td>
<td>1.42 (0.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>1312 (0.3)</td>
<td>64 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol-lowering medication (%)</td>
<td>30987 (7.3)</td>
<td>712 (15.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure-lowering medication (%)</td>
<td>42 847 (10.0)</td>
<td>790 (16.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin use (%)</td>
<td>3047 (0.7)</td>
<td>115 (2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ApoE ε4 (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0</td>
<td>229 045 (53.9)</td>
<td>2174 (46.7)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>149 774 (35.3)</td>
<td>1990 (42.8)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>46 036 (10.8)</td>
<td>487 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Pacemaker (%)</td>
<td>1479 (0.3)</td>
<td>58 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FGCRS continuous</td>
<td>13.59 (4.31)</td>
<td>16.33 (3.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FGCRS categorical</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low risk</td>
<td>129 669 (30.3)</td>
<td>392 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>158 660 (37.1)</td>
<td>1559 (33.1)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>139 039 (32.5)</td>
<td>2760 (58.6)</td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; FGCRS, Framingham General Cardiovascular Risk Score; MET, metabolic equivalent of task; ApoE ε4, Apolipoprotein E.
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 underappreciated contributor role of cardiovascular diseases in different dementia types and serve as consolidation of established findings.

**METHODS**

**Study design**

The UK Biobank is a large population-based prospective cohort study that comprises 502,615 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 Coordinating 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 diagnoses of dementia at baseline were excluded, and a total of 432,079 individuals were eligible for analysis in our present study. Online supplemental material 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 risk in accordance with original prediction model 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.

### Table 2  Cox regression model of the association between Framingham General Cardiovascular Risk Score (FGCRS) and dementia

<table>
<thead>
<tr>
<th>Models</th>
<th>FGCRS</th>
<th>ACD</th>
<th>AD</th>
<th>VaD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continuous</td>
<td>HR and 95% CI</td>
<td>P value</td>
<td>HR and 95% CI</td>
</tr>
<tr>
<td></td>
<td>Unadjusted</td>
<td>1.167 (1.159 to 1.175)</td>
<td>&lt;0.001</td>
<td>1.173 (1.159 to 1.186)</td>
</tr>
<tr>
<td></td>
<td>Low risk</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Intermediate risk</td>
<td>2.966 (2.655 to 3.313)</td>
<td>&lt;0.001</td>
<td>3.220 (2.720 to 3.817)</td>
</tr>
<tr>
<td></td>
<td>High risk</td>
<td>5.672 (5.103 to 6.305)</td>
<td>&lt;0.001</td>
<td>5.810 (4.936 to 6.839)</td>
</tr>
<tr>
<td></td>
<td>Multiadjusted</td>
<td>Continuous</td>
<td>1.158 (1.150 to 1.167)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Low risk</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Intermediate risk</td>
<td>2.873 (2.569 to 3.214)</td>
<td>&lt;0.001</td>
<td>3.186 (2.685 to 3.782)</td>
</tr>
<tr>
<td></td>
<td>High risk</td>
<td>5.555 (4.990 to 6.183)</td>
<td>&lt;0.001</td>
<td>5.841 (4.951 to 6.892)</td>
</tr>
</tbody>
</table>

Multiajusted: adjusted for education, alcohol intake, BMI, MET-min/wk, ApoE ε4, Townsend Deprivation Index, pacemaker, cholesterol-lowering medication, and insulin use.

ACD, all-cause dementia; AD, Alzheimer’s disease; BMI, body mass index; CI, confidential interval; HR, Hazards ratio; MET, metabolic equivalent of task; VaD, vascular dementia.
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\(^4\) 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) \(\epsilon4\) 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 $\leq -2.08$, middle $-2.08$–$1.40$ and low $\geq 1.40$). 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 $\geq 6.2$ mmol/L was used to define hypercholesterolaemia.

### 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 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 Open access.

---

Figure 3  Associations between cardiovascular traits and Alzheimer’s disease.

Left: illustration of significant traits in multivariate Cox regression model of Alzheimer’s disease. 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.
RESULTS

Baseline characteristics of participants

A total of 432,079 participants were assessed at baseline. Among these participants, 4711 cases of ACD, 2051 AD, and 1073 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 implantation, 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 multiadjusted models, with slight differences in HRs (table 2 and online supplemental materials 3). In the multiadjusted models, FGCRS was associated with increased risk of ACD (HR 1.158, 95% CI 1.150 to 1.167, p<0.001), AD (HR 1.163, 95% CI 1.149 to 1.178, p<0.001), and VaD (HR 1.173, 95% CI 1.159 to 1.188, p<0.001).

GraphPad Prism V.8.00 (GraphPad Software, San Diego, California, USA) were used for all statistical analyses and figure preparation.

Figure 4  Associations between cardiovascular traits and vascular dementia.

Left: illustration of significant traits in multivariate Cox regression model of vascular 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.
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.

95% CI 1.150 to 1.177, p<0.001) and VaD (HR 1.188, 95% CI 1.169 to 1.208, 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). 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).

Associations between cardiovascular traits and risk of ACD
For ACD, statistical significances were observed in 39 cardiovascular traits in which substantial portions of the findings were concordant with the established
As expected, cerebrovascular disorders increased the risk of VaD. Among other conduction disorders, 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, dissections, aneurysm, encephalopathy and moyamoya disease. Primary hypertension and other disorders of circulatory system, classified by the diagnosis of cardiovascular diseases caused by syphilis, other infections and parasites, also demonstrated strong associations. In the sensitivity analysis, endocarditis, hypertensive, lymphatic, venous 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 ischaemic heart disease, HF, hypertension 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 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 15849 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 ischaemic heart disorders displayed a lack of statistical consistency.

**DISCUSSION**

By leveraging data of 432079 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 subsistent 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 ischaemic 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. 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 intricated 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. 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, 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. 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, 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. 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, which are known risk factors for dementia in older people. 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 been confirmed in the classic view 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 subsistent 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.

Author affiliations
1Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, Shandong, People’s Republic of China
2Department of Neurology and National Center for Neurological Disorders, Huashan Hospital, State Key Laboratory of Medical Neurobiology and MOE Frontiers Center for Brain Science, Shanghai Medical College, Fudan University, Shanghai, People’s Republic of China
3Institute of Science and Technology for Brain-inspired Intelligence, Fudan University, Shanghai, People’s Republic of China
4Key Laboratory of Computational Neuroscience and Brain-Inspired Intelligence, Fudan University, Ministry of Education, Shanghai, People’s Republic of China

Acknowledgements This study used the UK Biobank Resource under application number 19542. We would like to express our sincere gratitude to all associated researchers of UK Biobank. Medical arts of central illustration were drawn by Y. Ou YN, T. D., A. D. and D. Q. and medical arts of secondary illustration were drawn by D. F. and G. L. and drew the figures. Y- H. and S. C. and C. Y. and Y. H. and participated in the first draft of the manuscript. Y- H. and S. C. and C. Y. and Y. H. and drew the figures. Y. Ou YN, T. D., A. D. and D. Q. and medical arts of secondary illustration were drawn by D. F. and G. L. and drew the figures. Y- H. and S. C. and C. Y. and Y. H.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and all participants provided written consent, and the North West Multi-Centre Ethics Committee granted ethical approval to UKB (06/MRE08/65). This study was conducted under UKB project number 19542. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplemental information. According to European law (General Data Protection Regulation), data containing potentially identifying or sensitive patients’ information are restricted. However, for academic researchers, data could be available on request via the UK Biobank.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Qiang Dong http://orcid.org/0000-0002-3874-0130
Jin-Tai Yu http://orcid.org/0000-0002-7079-8041

REFERENCES


