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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.

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.

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.[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

Table 1 Baseline characteristics of participants by dementia status

Characteristics	Non-dementia (n=427 368)	Dementia (n=4711)	P value
Age (mean, SD)	56.90 (8.01)	64.40 (4.69)	<0.001
Male (%)	195 622 (45.8)	2455 (52.1)	<0.001
College/professional certificate (%)	8383 (2.0)	29 (0.6)	<0.001
White ethnicity (%)	402 970 (95.6)	4454 (96.0)	0.285
BMI (median, IQR)	26.86 (24.24–30.06)	27.18 (24.39–30.55)	<0.001
MET min/wk (median, IQR)	1764.00 (792.00–3564.00)	1695.00 (742.00–3572.00)	0.039
Smoking (%)			<0.001
Never smoked	229 045 (53.9)	2174 (46.7)	
Previous smoked	149 774 (35.3)	1990 (42.8)	
Current smoker	46 036 (10.8)	487 (10.5)	
Alcohol intake more than once a week (%)	293 236 (68.8)	2836 (60.6)	<0.001
Townsend Deprivation Index at recruitment (%)			<0.001
Low	126 765 (29.7)	1331 (28.3)	
Middle	84 833 (19.9)	1160 (24.6)	
High	215 770 (50.5)	2220 (47.1)	
Hypertension (%)	201 941 (47.3)	2721 (57.8)	<0.001
Systolic blood pressure (mean, SD)	140.05 (19.71)	146.27 (20.64)	<0.001
Diastolic blood pressure (mean, SD)	82.28 (10.69)	81.73 (10.88)	<0.001
Diabetes mellitus (%)	23 737 (5.6)	668 (14.3)	<0.001
Hypercholesterolaemia (%)	134 320 (31.4)	1359 (28.8)	<0.001
Total cholesterol	5.69 (1.15)	5.51 (1.29)	<0.001
High density lipoprotein cholesterol	1.44 (0.38)	1.42 (0.40)	<0.001
History of stroke (%)	1312 (0.3)	64 (1.4)	<0.001
Cholesterol-lowering medication (%)	30 987 (7.3)	712 (15.1)	<0.001
Blood pressure-lowering medication (%)	42 847 (10.0)	790 (16.8)	<0.001
Insulin use (%)	3047 (0.7)	115 (2.4)	<0.001
ApoE ε4 (%)			<0.001
0	229 045 (53.9)	2174 (46.7)	
1	149 774 (35.3)	1990 (42.8)	
2	46 036 (10.8)	487 (10.5)	
Pacemaker (%)	1479 (0.3)	58 (1.2)	<0.001
FGCRS continuous	13.59 (4.31)	16.33 (3.38)	<0.001
FGCRS categorical			<0.001
Low risk	129 669 (30.3)	392 (8.3)	
Intermediate risk	158 660 (37.1)	1559 (33.1)	
High risk	139 039 (32.5)	2760 (58.6)	

BMI, body mass index; FGCRS, Framingham General Cardiovascular Risk Score; MET, metabolic equivalent of task; *ApoE* ε4, Apolipoprotein E.

General Cardiovascular Risk Score (FGCRS),[5] 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

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

Models	FGCRS	ACD		AD		VaD	
		HR and 95% CI	P value	HR and 95% CI	P value	HR and 95% CI	P value
Unadjusted	Continuous	1.167 (1.159 to 1.175)	<0.001	1.173 (1.159 to 1.186)	<0.001	1.207 (1.187 to 1.226)	<0.001
	Low risk	Reference		Reference		Reference	
	Intermediate risk	2.966 (2.655 to 3.313)	<0.001	3.220 (2.720 to 3.817)	<0.001	3.390 (2.611 to 4.400)	<0.001
	High risk	5.672 (5.103 to 6.305)	<0.001	5.810 (4.936 to 6.839)	<0.001	8.272 (6.459 to 10.600)	<0.001
Multiadjusted	Continuous	1.158 (1.150 to 1.167)	<0.001	1.163 (1.150 to 1.177)	<0.001	1.188 (1.169 to 1.208)	<0.001
	Low risk	Reference		Reference		Reference	
	Intermediate risk	2.873 (2.569 to 3.214)	<0.001	3.186 (2.685 to 3.782)	<0.001	3.111 (2.39 to 4.043)	<0.001
	High risk	5.555 (4.990 to 6.183)	<0.001	5.841 (4.951 to 6.892)	<0.001	7.526 (5.866 to 9.655)	<0.001

Multiadjusted: 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.

(HF) and ischaemic heart disease have been recognised as at-risk conditions predisposed to dementia[7–10] via promoting cerebral hypoperfusion and proinflammatory state.[11 12] 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,[2–4] 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.[13] 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 19 542.

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

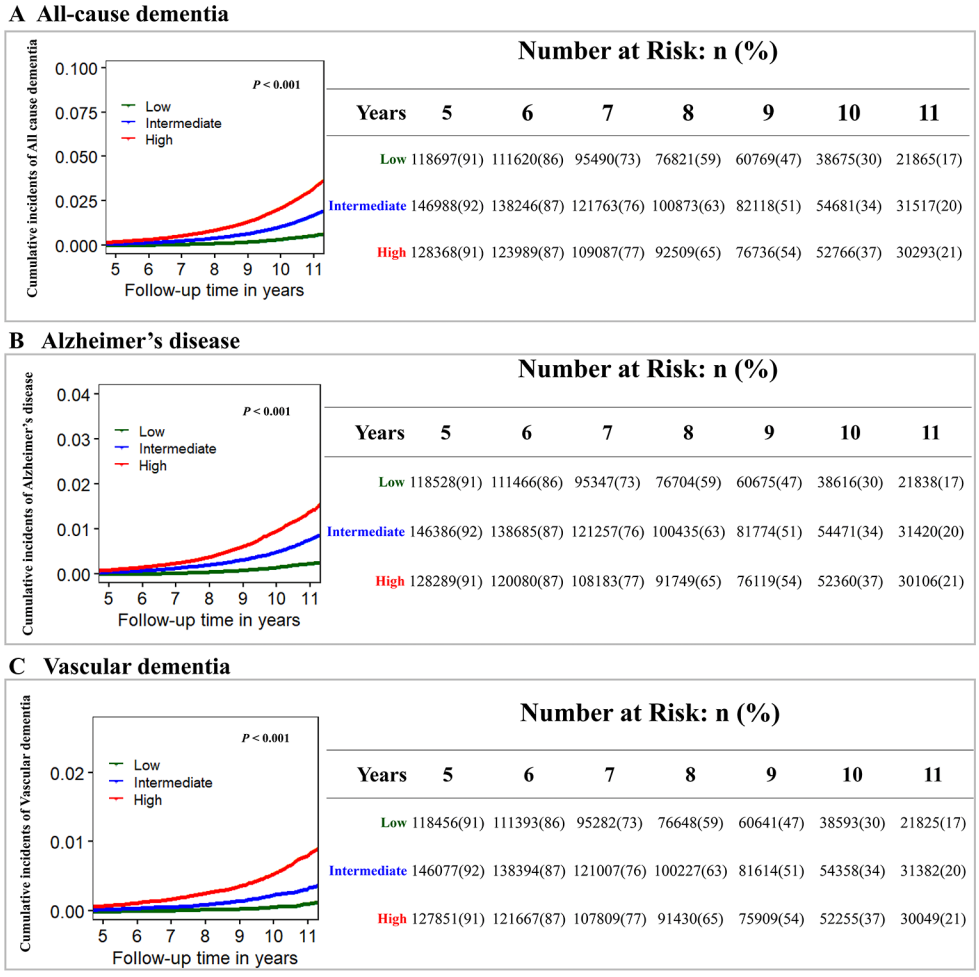

Figure 1 Kaplan-Meier survival analysis of FGCRS. (A) (B) (C) illustrate the overall survival of different risk groups based on the stratification of FGCRS. FGCRS, Framingham General Cardiovascular Risk Score.

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*) ε4 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 ≥140 mm Hg and/or diastolic blood pressure ≥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

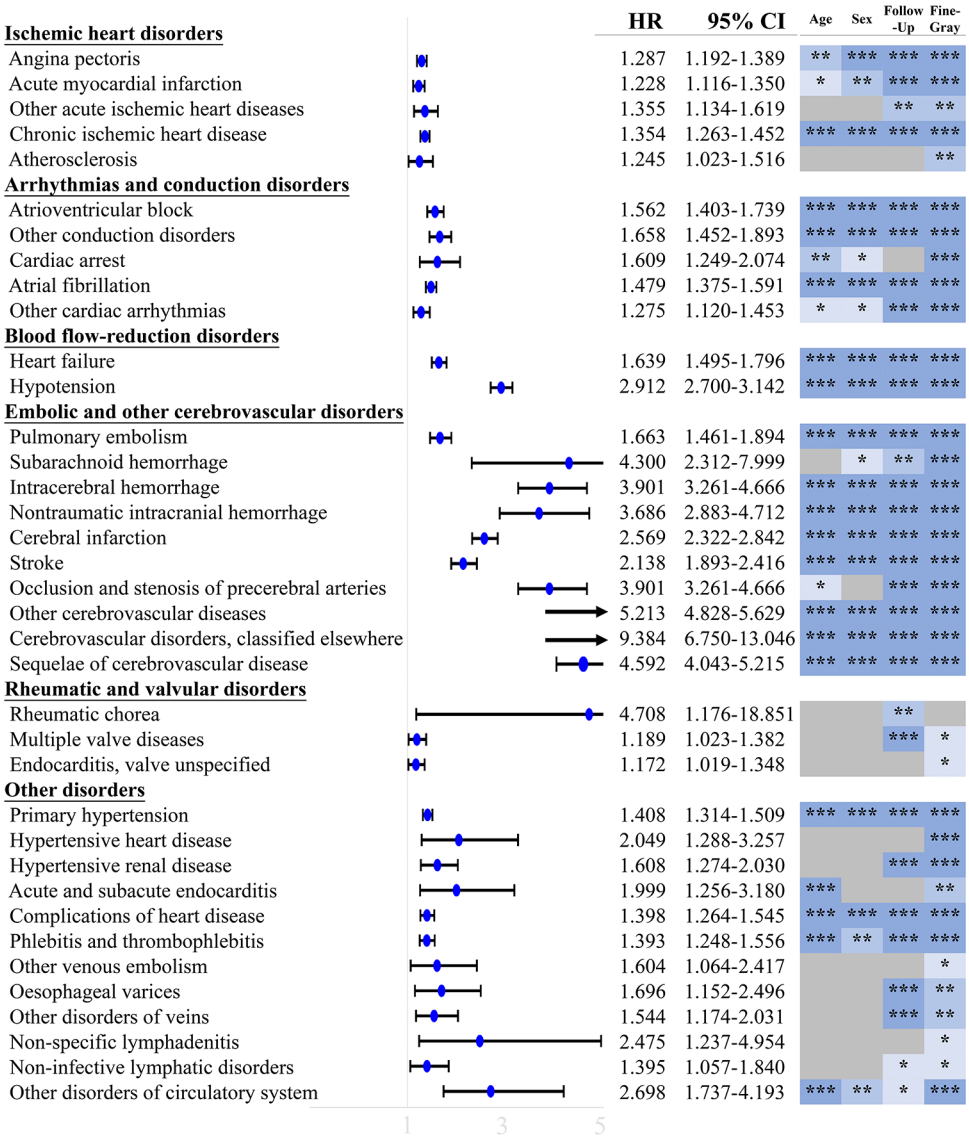

Figure 2 Associations between cardiovascular traits and all-cause dementia. Left: illustration of significant traits in multivariate Cox regression model of all-cause dementia. Right (colored box): overview of sensitivity analysis. Gray box indicated null significance; one * indicated P value <0.05; two * indicated P value; <0.01 Three * indicated P value < 0.001. HR, Hazard ratio; 95% CI, 95% confidential interval.

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 hypercholesteraemia.

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

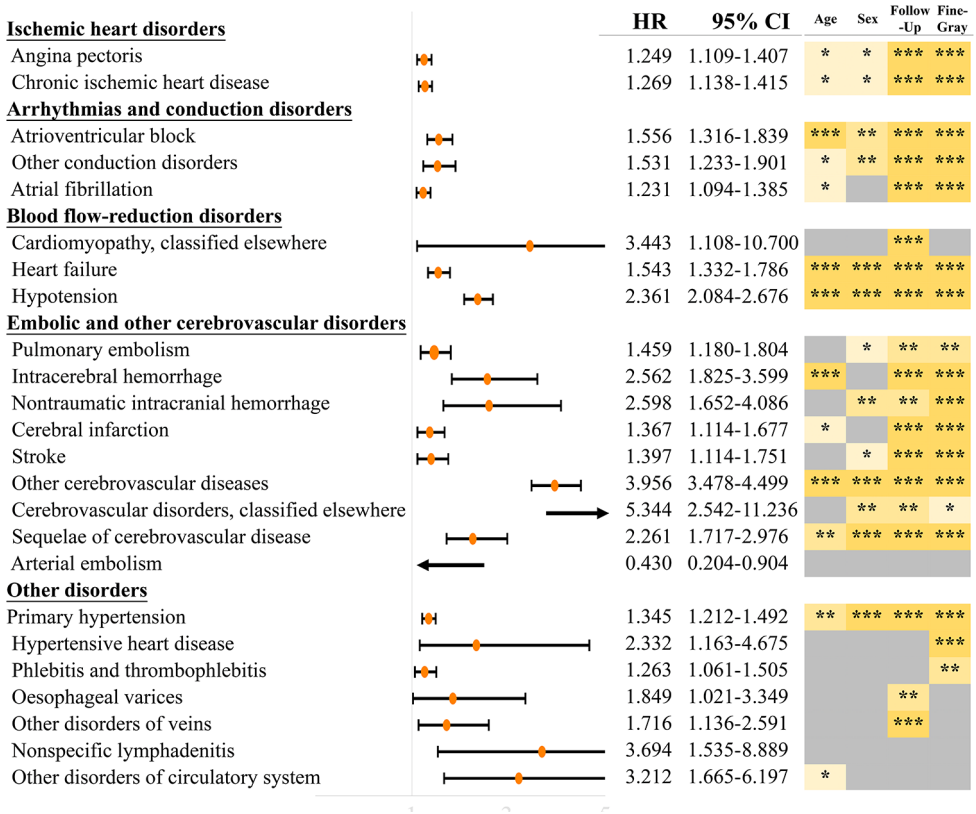

Figure 3 Associations between cardiovascular traits and Alzheimer's disease. Left: illustration of significant traits in multivariate Cox regression model of Alzheimer's disease. Right (colored box): overview of sensitivity analysis. Gray box indicated null significance; one * indicated P value <0.05; two * indicated P value; <0.01 Three * indicated P value < 0.001. HR, Hazard ratio; 95% CI, 95% confidential interval.

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.[15] 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, 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).

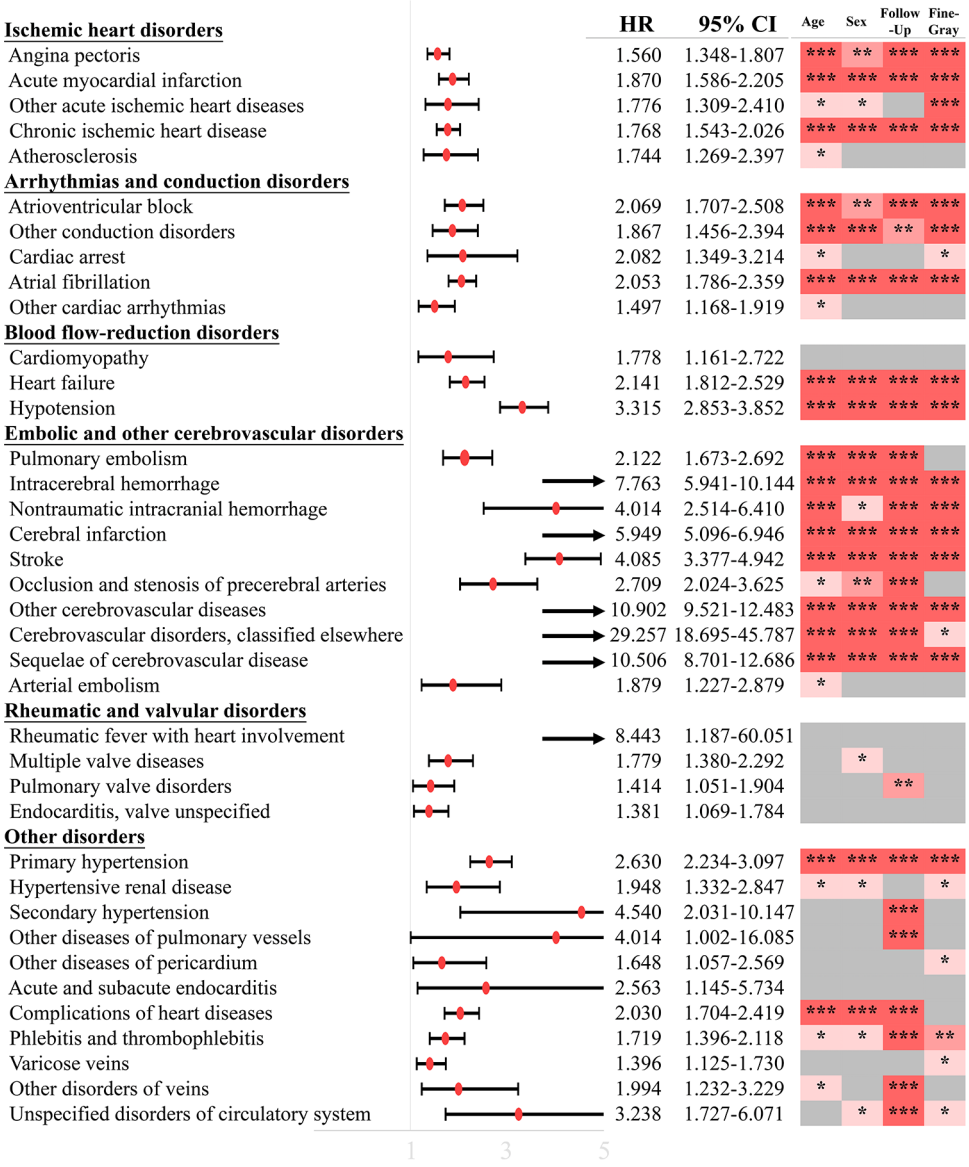

Figure 4 Associations between cardiovascular traits and vascular dementia. Left: illustration of significant traits in multivariate Cox regression model of vascular dementia. Right (colored box): overview of sensitivity analysis. Gray box indicated null significance; one * indicated P value <0.05; two * indicated P value; <0.01 Three * indicated P value < 0.001. HR, Hazard ratio; 95% CI, 95% confidential interval.

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 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 1.150 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; 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).

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 evidence (figure 2 and online supplemental materials 4).

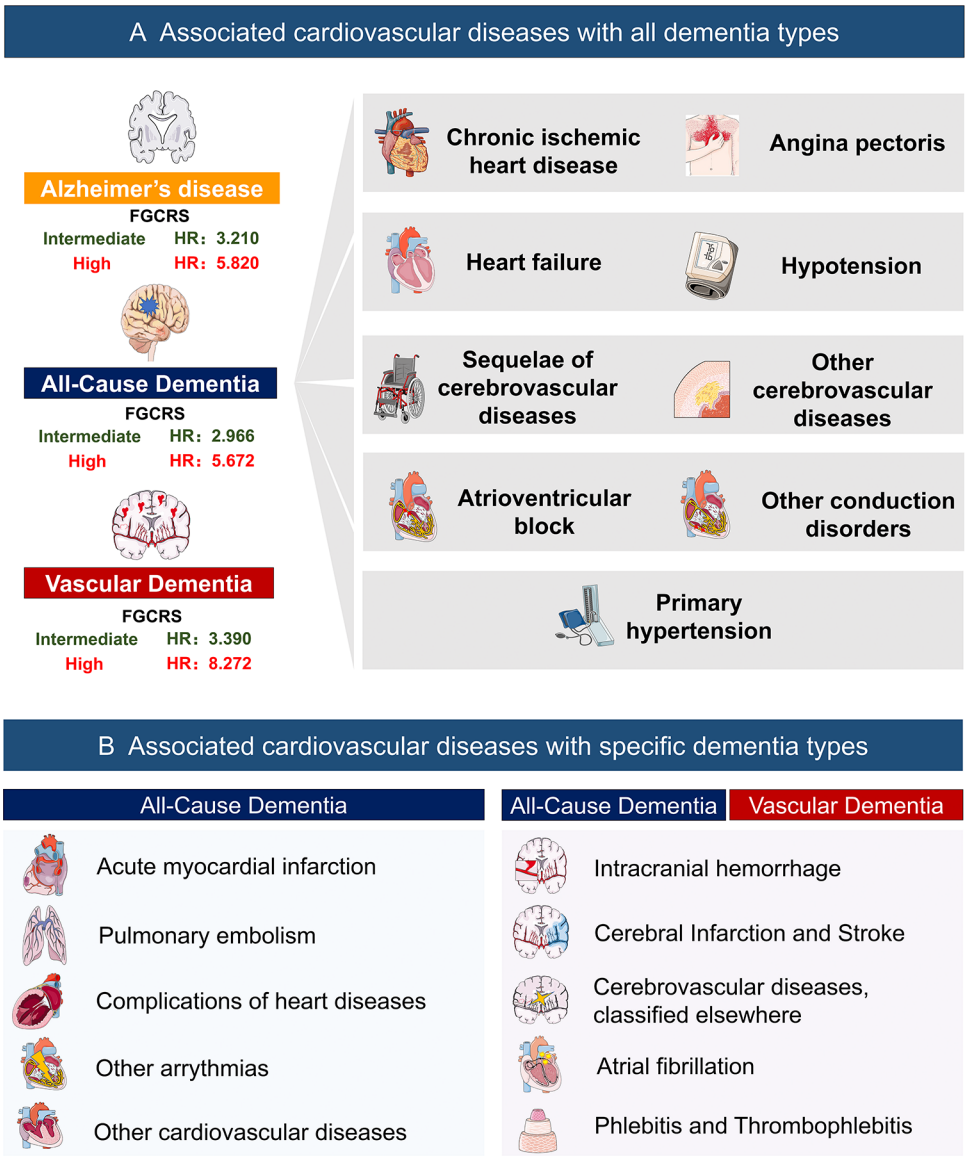

Figure 5 The 'mapping' of the associations between cardiovascular diseases and different types of dementia. Content Explanation: other cerebrovascular diseases include the diagnosis of cerebral atherosclerosis, dissection/aneurysm, progressive vascular leukoencephalopathy, progressive vascular leukoencephalopathy, 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.

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, 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, 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). Ischaemic heart disorders such as angina pectoris, acute myocardial infarction and chronic ischaemic 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. Multiadjusted 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 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 compliment 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.[16 17] Other consistent findings are angina pectoris and chronic ischaemic heart diseases, where the prospective associations have been abundantly described.[18 19] 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.[20] However, whether such associations extend to specific dementia types remains controversial, as evidence has shown HF may not necessarily be linked with AD.[21] Nevertheless, one explanation is that long-term cerebral hypoperfusion due to low cardiac output can lead to persistent oxygen deficiency,[22] which then exacerbates the vulnerability of neurons and drives the formation of pathological hallmarks of AD.[23 24] 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.[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 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.[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,[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.[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,[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.[29] 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,[30] which are known risk factors for dementia in older people.[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 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.

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REFERENCES

1 Feigin VL, Nichols E, Alam T, *et al*. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the global burden of disease study 2016. *The Lancet Neurology* 2019;18:459–80.
2 Iadecola C, Duering M, Hachinski V, *et al*. Vascular cognitive impairment and dementia: JACC scientific expert panel. *J Am Coll Cardiol* 2019;73:3326–44.
3 Baumgart M, Snyder HM, Carrillo MC, *et al*. Summary of the evidence on Modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimer's &Amp; Dementia* 2015;11:718–26.
4 Livingston G, Huntley J, Sommerlad A, *et al*. Dementia prevention, intervention, and care: 2020 report of the lancet Commission. *The Lancet* 2020;396:413–46.
5 D'Agostino RB, Vasan RS, Pencina MJ, *et al*. General cardiovascular risk profile for use in primary care: the Framingham heart study. *Circulation* 2008;117:743–53.
6 Iadecola C, Parikh NS. Framingham general cardiovascular risk score and cognitive impairment: the power of foresight. *J Am Coll Cardiol* 2020;75:2535–7.
7 Diener HC, Hart RG, Koudstaal PJ, *et al*. Atrial fibrillation and cognitive function. *Journal of the American College of Cardiology* 2019;73:612–9.
8 Wolters FJ, Segufa RA, Darweesh SKL, *et al*. Coronary heart disease, heart failure, and the risk of dementia: A systematic review and meta-analysis. *Alzheimer's &Amp; Dementia* 2018;14:1493–504.
9 Ritchie K, Lovestone S. The Dementias. *Lancet* 2002;360:1759–66.
10 Cermakova P, Johnell K, Fastbom J, *et al*. Cardiovascular diseases in ~30,000 patients in the Swedish dementia Registry. *J Alzheimers Dis* 2015;48:949–58.
11 Wolters FJ, Zonneveld HI, Hofman A, *et al*. Ikram MA: cerebral perfusion and the risk of dementia: A population-based study. *Circulation* 2017;136:719–28.
12 Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: Current evidence and future directions. *Alzheimer's &Amp; Dementia* 2016;12:719–32.
13 Sudlow C, Gallacher J, Allen N, *et al*. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015;12:e1001779.
14 Whelton PK, Carey RM, Aronow WS, *et al*. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/Apha/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American college of cardiology/American heart Association task force on clinical practice guidelines. *J Am Coll Cardiol* 2018;71:e127–248.
15 Fine JP, Gray RJ. Gray RJ: A proportional hazards model for the Subdistribution of a competing risk. *Journal of the American Statistical Association* 1999;94:496–509.
16 Hughes D, Judge C, Murphy R, *et al*. Association of blood pressure lowering with incident dementia or cognitive impairment: A systematic review and meta-analysis. *JAMA* 2020;323:1934–44.
17 Ou YN, Tan CC, Shen XN, *et al*. Blood pressure and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 209 prospective studies. *Hypertension* 2020;76:217–25.
18 Deckers K, Schievink SHJ, Rodriquez MMF, *et al*. Coronary heart disease and risk for cognitive impairment or dementia: systematic review and meta-analysis. *PLoS One* 2017;12:e0184244.
19 van Oijen M, de Jong FJ, Witteman JCM, *et al*. Atherosclerosis and risk for dementia. *Ann Neurol* 2007;61:403–10.
20 Jefferson AL, Himali JJ, Beiser AS, *et al*. Cardiac index is associated with brain aging: the Framingham heart study. *Circulation* 2010;122:690–7.
21 Adelborg K, Horváth-Puhó E, Ording A, *et al*. Heart failure and risk of dementia: a Danish nationwide population-based cohort study. *Eur J Heart Fail* 2017;19:253–60.
22 Duncombe J, Kitamura A, Hase Y, *et al*. Chronic cerebral hypoperfusion: a key mechanism leading to vascular cognitive impairment and dementia. closing the Translational gap between rodent models and human vascular cognitive impairment and dementia. clinical science. *Clinical Science* 2017;131:2451–68.
23 Bennett S, Grant MM, Aldred S. Oxidative stress in vascular dementia and Alzheimer's disease: a common pathology. *J Alzheimers Dis* 2009;17:245–57.
24 Tublin JM, Adelstein JM, Del Monte F, *et al*. Getting to the heart of Alzheimer disease. *Circ Res* 2019;124:142–9.
25 Cheng S, Keyes MJ, Larson MG, *et al*. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA* 2009;301:2571–7.
26 Xia X, Wang R, Vetrano DL, *et al*. From normal cognition to cognitive impairment and dementia: impact of orthostatic hypotension. *Hypertension* 2021;78:769–78.
27 Song R, Xu H, Dintica CS, *et al*. Associations between cardiovascular risk, structural brain changes, and cognitive decline. *J Am Coll Cardiol* 2020;75:2525–34.
28 Song R, Pan K-Y, Xu H, *et al*. Association of cardiovascular risk burden with risk of dementia and brain Pathologies: A population-based cohort study. *Alzheimers Dement* 2021;17:1914–22.
29 Cui K, Song R, Xu H, *et al*. Association of cardiovascular risk burden with risk and progression of disability: mediating role of cardiovascular disease and cognitive decline. *J Am Heart Assoc* 2020;9:e017346.
30 Debette S, Seshadri S, Beiser A, *et al*. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology* 2011;77:461–8.
31 Lo RY, Jagust WJ. Alzheimer's disease neuroimaging initiative. Jagust WJ: vascular burden and Alzheimer disease pathologic progression. *Neurology* 2012;79:1349–55.
32 Kantarci K, Weigand SD, Przybelski SA, *et al*. MRI and MRS predictors of mild cognitive impairment in a population-based sample. *Neurology* 2013;81:126–33.