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Cardiovascular risk burden, dementia risk and brain structural imaging markers: a study from UK Biobank

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ABSTRACT

Background Cardiovascular risk burden is associated with dementia risk and neurodegeneration-related brain structure, while the role of genetics and incident cardiovascular disease (CVD) remains unclear.

Aims To examine the association of overall cardiovascular risk burden with the risk of major dementia subtypes and volumes of related brain regions in a large sample, and to explore the role of genetics and CVD onset.

Methods A prospective study among 354 654 participants free of CVD and dementia (2006–2010, mean age 56.4 years) was conducted within the UK Biobank, with brain magnetic resonance imaging (MRI) measurement available for 15 104 participants since 2014. CVD risk burden was evaluated by the Framingham General Cardiovascular Risk Score (FGCRS). Dementia diagnosis was ascertained from inpatient and death register data.

Results Over a median 12.0-year follow-up, 3998 all-cause dementia cases were identified. Higher FGCRS was associated with increased all-cause dementia risk after adjusting for demographic, major lifestyle, clinical factors and the polygenic risk score (PRS) of Alzheimer's disease. Comparing the high versus low tertile of FGCRS, the odds ratios (ORs) and 95% confidence intervals (CIs) were 1.26 (1.12 to 1.41) for all-cause dementia, 1.67 (1.33 to 2.09) for Alzheimer's disease and 1.53 (1.07 to 2.16) for vascular dementia (all $p_{trend}<0.05$). Incident stroke and coronary heart disease accounted for 14% (95% CI: 9% to 21%) of the association between FGCRS and all-cause dementia. Interactions were not detected for FGCRS and PRS on the risk of any dementia subtype. We observed an 83% (95% CI: 47% to 128%) higher all-cause dementia risk comparing the high–high versus low–low FGCRS–PRS category. For brain volumes, higher FGCRS was associated with greater log-transformed white matter hyperintensities, smaller cortical volume and smaller grey matter volume.

Conclusions Our findings suggest that the positive association of cardiovascular risk burden with dementia risk also applies to major dementia subtypes. The association of cardiovascular risk burden with all-cause dementia is largely independent of CVD onset and genetic predisposition to dementia.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Existing evidence largely supports that cardiovascular risk burden is associated with higher all-cause dementia risk, although some studies have reported null results.

WHAT THIS STUDY ADDS

⇒ This large-scale cohort study supports that cardiovascular risk burden is associated with an elevated risk of Alzheimer's disease and vascular dementia, in addition to all-cause dementia. The association between cardiovascular risk burden and all-cause dementia is independent of genetic predisposition to dementia and can be partially explained by the onset of major cardiovascular diseases.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In terms of dementia, improvements in cardiovascular health may benefit populations with different genetic burdens of dementia equally.

INTRODUCTION

Current evidence suggests that cardiovascular disease (CVD) and dementia may share common risk factors and pathophysiological mechanisms.[1] For an integral evaluation of CVD risk, scores of cardiovascular risk burden have been created. Twelve potentially modifiable risk factors proposed by the Lancet Commission for Dementia Prevention, Intervention and Care might account for up to 40% of dementia, which was estimated to be as high as 60.1% of the overall population aged 60 years or above, in China.[2] Research on the association of dementia risk and cardiovascular risk burden, which included part of modifiable factors for dementia prevention, has been constrained by limited sample sizes.[3–8] Although most studies support the adverse influence of cardiovascular risk burden on dementia, there are also reports of null associations.[8]

Genetic studies have reported high heritability of dementia, ranging from 60% to 80% for Alzheimer's disease as the most common type.[9] In previous studies exploring the relationship between cardiovascular risk burden and dementia risk, the role of genetic risk was often overlooked[6–8] or represented solely by *APOE* genotype.[3 4 10 11] Therefore, whether the association between CVD risk burden and dementia varies based on or is independent of the overall genetic predisposition to dementia, needs to be explored.

Stroke has been shown to prominently accelerate the development of dementia. According to the population-based Oxford Vascular Study, the prevalence of dementia in 1-year survivors of stroke was accelerated by approximately 25 years for severe strokes and 4 years for minor strokes.[12] In addition, certain treatments for CVD have been associated with reduced future dementia risk.[13] The potential role of CVD in the association of cardiovascular risk burden with dementia remains to be re-evaluated among individuals without current CVD. Clarifying the role is essential for enhancing the efficiency of public health management in both CVD and dementia, by targeting CVD risk factors.

Dementia is predisposed to brain atrophy and could be predicted by white matter lesions.[14 15] Previous studies on the associations of overall cardiovascular risk burden with brain structure showed inconsistent results and were conducted with small sample sizes.[7 16 17] For instance, overall cardiovascular risk burden was shown to be associated with smaller volumes of whole brain and grey matter and greater white matter hyperintensities (WMHs), and yet, these associations were not consistently observed across studies.[7 16]

In the current study, we analysed the association of the overall cardiovascular burden, reflected by the Framingham General Cardiovascular Risk Score (FGCRS), with the long-term risk of dementia and brain structure change, the interaction between the FGCRS and genetic predisposition to dementia, as well as the potential mediating role of CVD onset.

METHODS

Study population

The UK Biobank (UKB) Project is a large population-based prospective study with extensive genetic and phenotypical data, covering over 500 000 participants aged 40–69 years at recruitment between 2006 and 2010.[18] For the current analysis, participants were excluded if they self-reported a non-White racial/ethnic background, had a missing polygenic risk score (PRS) of dementia or 2 standard deviations (SDs) from the mean of the first two genetic principal components, had baseline dementia, had a missing FGCRS or had baseline CVD (figure 1).

The FGCRS

The sex-specific FGCRS incorporates baseline age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking and diabetes status (online supplemental tables 1 and 2). In

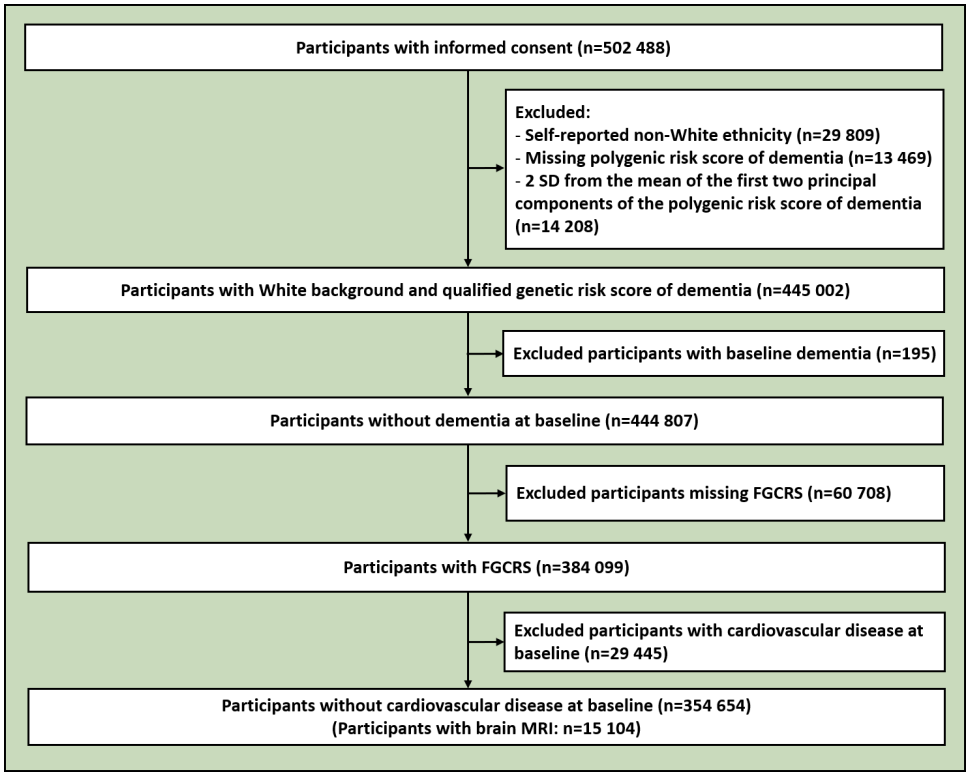

Figure 1 Flowchart for the study of cardiovascular risk burden with dementia and brain structure. FGCRS, Framingham general cardiovascular risk score; MRI, magnetic resonance imaging; SD, standard deviation.

the current study, CVD includes a composite of coronary heart disease (CHD), cerebrovascular disease, peripheral vascular disease and heart failure as defined in the FGCRS (online supplemental table 3). Sex-specific points of FGCRS were summed and categorised into tertiles. A higher FGCRS indicates a greater risk of future cardiovascular events. The exposure was the score of FGCRS in sex-specific tertiles as well as in the unit of sex-specific standardised deviation.

Dementia diagnosis

Dementia diagnosis was ascertained through hospital inpatient records and linkage to death register data (online supplemental methods). All-cause dementia and its subtypes were identified using the International Classification of Disease coding system (online supplemental table 4). Participants diagnosed with any dementia were monitored until the onset of the first dementia event and then classified as the case of the corresponding subtype. The end of the follow-up period for our analysis was 28 February 2021 for England and Scotland, and 28 February 2018 for Wales, or the onset of the first dementia event, whichever came first. Incidence of all-cause dementia and its subtypes were the categorical outcomes of the current study.

Brain volume measurement

Brain structure data were obtained from magnetic resonance imaging (MRI) since 2014 (https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/brain_mri.pdf). In this study, the volumes (in cubic millimetres) of the whole brain, white matter, grey matter and cortex were derived from T1 structural brain MRI. The volume of WMHs was derived from T2-weighted brain MRI. The external surface of the skull was estimated from the T1 and used to normalise brain tissue volumes for head size. Brain tissue volumes were added correspondingly (left and right sides) and then z-standardised. For WMHs, the volume was transformed by taking the logarithm before z-standardisation because of its skewed distribution. The neurodegeneration-related brain volumes, including whole brain volume, white matter volume, WMHs, total grey matter volume and cortical volume, were the numerical outcomes of the current study.

Polygenic risk score

A PRS capturing the load of common genetic variants associated with Alzheimer's disease and dementia risk was constructed.[19] Briefly, single-nucleotide polymorphisms (SNPs) based on a previously published genome-wide association study of Alzheimer's disease were selected using 'clumped' results so that the remaining SNPs were the most significant variant per linkage disequilibrium block, common and available in the UKB. The inclusion threshold for a p value was less than 0.5. The associated allele at each SNP was selected and weighted according to the regression coefficient with Alzheimer's disease in the discovery stage of genome-wide association study results, summed, z-standardised and then divided into tertiles. The constructed PRS was shown to predict incident all-cause dementia and provide a quantitative measurement of the genetic risk of dementia.

Covariates

Missing data with a missing rate of <5% were imputed as medians for continuous variables and as modes for categorical variable; otherwise, a missing category was created (online supplemental table 5). Multivariable-adjusted models were adjusted for age, sex, education (higher, vocational, upper secondary, lower secondary or other; definitions in online supplemental methods), Townsend deprivation index (as a continuous variable, with a higher value indicating lower socioeconomic status), depression (diagnosis from hospital inpatient and death registry), body mass index (BMI) category (<18.5, 18.5–24.9, 25–29.9, 30–34.9 or ≥35 kg/m^2), alcohol consumption (current or non-current; definitions in online supplemental methods), physical activity (irregular or regular; definitions in online supplemental methods), third-degree relatedness of individuals, the first 20 principal components of ancestry, z-standardised PRS and the number of alleles included in the PRS unless specifically mentioned.

Statistical analysis

Variables of baseline characteristics were shown as mean (standard deviation (SD)) for the continuous variable and n (%) for the categorical variables. The Schoenfeld residual test for the proportional hazard assumption of Cox proportional hazards model showed a violation for the variable FGCRS. Logistic regression models were used for the association of FGCRS and its components with dementia risk, and the effects were presented as odds ratios (ORs) and 95% confidence intervals (CIs). We first examined the association of FGCRS tertiles (with low tertile as reference) with all-cause dementia. A linear trend was tested by assigning the median value to each category. Then, the association was also evaluated in the form of OR (95% CI). The dose-response relationship of FGCRS with all-cause dementia was evaluated using restricted cubic spline regressions.

We conducted several sensitivity analyses to test the robustness of our findings, including (1) imputing missing covariates by multiple imputation; (2) excluding participants with missing covariates; (3) excluding participants diagnosed with dementia within the 2-year follow-up; (4) excluding those on antihypertensive medication at baseline; (5) excluding age as the component of FGCRS or (6) calculating the risk ratio (RR) using log as the link based on logistic regression, respectively. We conducted the joint analysis for FGCRS tertile and PRS tertile for dementia risk, with low FGCRS and low PRS as the reference groups. We also performed analyses with stratification by age group, sex, education, socioeconomic status, BMI, alcohol consumption and physical activity. The effect of FGCRS was calculated as OR

(95% CI). For the test of interaction, the cross-product terms of standardised FGCRS and stratification variables were adjusted.

To explore the potential role of incident major CVD events (stroke and CHD) in the association of FGCRS with all-cause dementia, we evaluated the proportional contribution of incident major CVD events in causal mediation analysis using the 'mediation' package in R. We also examined the association by further adjusting for incident major CVD status or among participants without incident major CVD events. In addition, we examined the association of individual FGCRS components with all-cause dementia by simultaneously adjusting for all components. Linear regression models were applied for the association of FGCRS and its components with total and regional brain volumes by MRI. The cross-product of standardised FGCRS and standardised PRS was adjusted for interaction on dementia risk and brain volumes.

All analyses were conducted using R V.3.6.0, and p<0.05 was considered statistically significant (2-tailed).

RESULTS

A total of 354 654 participants with an average age of 56.4 years at baseline were included. Over a median follow-up of 12.0 years (up to 15.0 years), 3998 cases of all-cause dementia were identified. Participant characteristics according to the FGCRS tertiles are presented in table 1. In brief, participants with a higher FGCRS score tended to be older, with lower high-density lipoprotein cholesterol, with higher total cholesterol and systolic blood pressure levels, and more likely to be current smokers and have prevalent diabetes. Moreover, they had lower education, physical activities and alcohol consumption.

As shown in table 2, FGCRS was consistently associated with a higher all-cause dementia risk in age-adjusted, multivariable-adjusted and PRS-adjusted models. In the PRS-adjusted model, the corresponding ORs (95% CIs) across increasing FGCRS tertiles were 1.00 (ref), 1.10 (0.98 to 1.23) and 1.26 (1.12 to 1.41); $p_{for\ trend}$<0.001 with OR (95% CI) being 1.17 (1.12 to 1.23). Associations for both sexes were similar. Restricted cubic spline models showed no firm evidence of a non-linear association between FGCRS and all-cause dementia (online supplemental figure 1; all $p_{for\ non\text{-}linearity}$>0.05). For dementia subtypes, higher FGCRS was associated with an elevated risk of Alzheimer's disease (high vs low tertile: 1.67; 95% CI: 1.33 to 2.09) and vascular dementia (high vs low tertile: 1.53; 95% CI: 1.07 to 2.16), while not with other dementias (high vs low tertile: 1.06; 95% CI 0.91 to 1.23) (online supplemental table 6). In sensitivity analyses (online supplemental table 7), the associations of FGCRS with all-cause dementia risk were similar when missing values of covariates were imputed by multiple imputation, among those with complete information of covariates, with all-cause dementia occurred within the 2-year follow-up period excluded, with age as the component of FGCRS excluded or the association was estimated as RR, respectively. When participants on antihypertensive medication at baseline were excluded, the association was slightly attenuated while remaining significant.

The association of FGCRS with all-cause dementia was similar according to the standardised dementia PRS level (χ^2 value=0.998, $p_{for\ interaction}$=0.318). As the joint analysis showed (figure 2), the risk of all-cause dementia was 83% higher when comparing those in high PRS and high FGCRS with those in low PRS and low FGCRS. The association of FGCRS with all-cause dementia remained when stratified by age group, sex, education level, socioeconomic status, BMI category and level of dementia PRS. The association was stronger among current drinkers and those with regular physical activity (both $p_{for\ interaction}$<0.05) (online supplemental figure 2).

In total, 26 212 cases of incident stroke and CHD occurred during the follow-up period. The mediated proportion in the association of FGCRS with all-cause dementia was 9% for incident stroke, 4% for incident CHD and 14% for the first event as stroke and CHD (online supplemental figure 3 and online supplemental table 8). The association was similar when restricted to participants without incident major CVD and was slightly attenuated when further adjusted for incident major CVD (online supplemental table 9). In addition, the associations of FGCRS components with all-cause dementia were all significant except high-density lipoprotein cholesterol and total cholesterol (online supplemental table 10).

Brain MRI data were available for 15 104 participants, and their characteristics compared with those without MRI are presented in online supplemental table 11. In terms of brain structure, higher FGCRS was associated with greater WMHs (high vs low tertile: 0.311; 95% CI: 0.265 to 0.357), smaller total grey matter (high vs low tertile: −0.060; 95% CI: −0.106 to −0.014) and smaller cortical volume (high vs low tertile: −0.100; 95% CI: −0.147 to −0.053) (figure 3 and online supplemental table 12). No significant interactions between FGCRS and PRS were found for whole brain volume, white matter volume, total grey matter volume or cortical volume (all $p_{for\ interaction}$>0.05). For WMHs, the association of FGCRS was greater in participants with lower standardised PRS level of dementia (t value=−2.108, $p_{for\ interaction}$=0.035) (online supplemental table 13). Associations of individual FGCRS components with brain structure differed by region of interest (online supplemental table 14). For example, diabetes was associated with all indicators of neurodegeneration-related brain structure except for white matter volume. In addition, all components in the FGCRS were associated with WMHs but not with other indicators.

DISCUSSION

Main findings

We found that the higher cardiovascular burden, as measured by FGCRS, was associated with an increased risk of dementia. This association was further supported

Table 1 Participant characteristics according to the FGCRS (in tertile) at baseline*

Variables	FGCRS			F/χ^2 value	P value
	Low	Medium	High		
Median (Q1, Q3)					
Female	6 (4, 8)	12 (11, 13)	16 (15, 17)		
Male	10 (8, 11)	14 (13, 15)	17 (16, 19)		
N	134 809	110 787	109 058		
Age (year), mean (SD)	49.9 (6.7)	58.5 (6.1)	62.3 (5.0)	1.395×10^5	<0.001
Female, n (%)	72 096 (53.5)	61 994 (56.0)	62 631 (57.4)	3.962×10^2	<0.001
Education, n (%)				1.814×10^4	<0.001
Higher	74 078 (55.0)	53 329 (48.1)	43 802 (40.2)		
Vocational	19 575 (14.5)	13 818 (12.5)	12 386 (11.4)		
Upper secondary	8426 (6.3)	5991 (5.4)	5152 (4.7)		
Lower secondary	23 435 (17.4)	18 982 (17.1)	18 684 (17.1)		
Other	9295 (6.9)	18 667 (16.8)	29 034 (26.6)		
Townsend deprivation index, mean (SD)	−1.5 (2.9)	−1.7 (2.9)	−1.5 (3.0)	1.037×10^2	<0.001
BMI (kg/m^2), n (%)				1.684×10^4	<0.001
<18.5	1071 (0.8)	489 (0.4)	308 (0.3)		
18.5–24.9	59 324 (44.0)	35 424 (32.0)	24 367 (22.3)		
25.0–29.9	53 355 (39.6)	49 179 (44.4)	49 299 (45.2)		
30.0–34.9	15 942 (11.8)	18 954 (17.1)	24 514 (22.5)		
≥35.0	5117 (3.8)	6741 (6.1)	10 570 (9.7)		
Current drinker, n (%)	127 949 (94.9)	104 057 (93.9)	100 519 (92.2)	7.818×10^2	<0.001
Physical activity, n (%)				1.561×10^3	<0.001
Irregular	54 360 (40.3)	45 980 (41.5)	46 102 (42.3)		
Regular	75 121 (55.7)	58 724 (53.0)	55 070 (50.5)		
Missing	5328 (4.0)	6083 (5.5)	7886 (7.2)		
Depression diagnosis, n (%)				1.332×10^2	<0.001
Depressed	7127 (5.3)	5098 (4.6)	4810 (4.4)		
Non-depressed	120 089 (89.1)	99 461 (89.8)	97 690 (89.6)		
Missing	7593 (5.6)	6228 (5.6)	6558 (6.0)		
HDL-c (mg/dL), mean (SD)	58.1 (13.9)	58.0 (14.9)	54.1 (15.3)	2.566×10^3	<0.001
TC (mg/dL), mean (SD)	212.5 (37.1)	228.6 (41.3)	233.7 (47.8)	9.121×10^3	<0.001
SBP (mm Hg), mean (SD)	125.7 (13.9)	138.7 (14.2)	152.9 (16.4)	9.552×10^4	<0.001
Current smoker, n (%)	7583 (5.6)	9581 (8.6)	18 884 (17.3)	9.429×10^3	<0.001
Diabetes, n (%)	972 (0.7)	2483 (2.2)	12 474 (11.4)	1.804×10^4	<0.001
PRS of Alzheimer's disease, n (%)				2.756	0.599
Low	44 748 (33.2)	37 006 (33.4)	36 468 (33.4)		
Medium	45 047 (33.4)	36 968 (33.4)	36 205 (33.2)		
High	45 014 (33.4)	36 813 (33.2)	36 385 (33.4)		

*Percentages may not sum to 100 because of rounding.
BMI, body mass index; FGCRS, Framingham General Cardiovascular Risk Score; HDL-c, high-density lipoprotein cholesterol; PRS, polygenic risk score; SBP, systolic blood pressure; SD, standard deivation; TC, total cholesterol.

by the association with greater WMHs, smaller total grey matter and smaller cortical volumes. These associations were largely free of genetic modification in dementia. Furthermore, incident CVD played a partial role in the association of cardiovascular risk burden with dementia, and higher cardiovascular risk burden was also associated with elevated dementia risk in the absence of CVD.

Our study extended the current understanding of overall cardiovascular risk burden and dementia risk by examining the potential role of CVD events. Previous studies with limited sample sizes reported elevated dementia risk with a higher cardiovascular risk burden.[3 6 10 20] However, most studies did not account for CVD events, and in only a few studies, CVD events were adjusted as covariates. For instance, CVD events were not addressed in either the Framingham Heart Study, including 1211[5] or 3547 participants based on German insurance data.[8] Baseline CVD was adjusted in the Finnish Cardiovascular Risk Factors, Aging, and Dementia Study, which included 1449 participants.[10] Nevertheless, reverse causation may exist since

Table 2 Risk of incident all-cause dementia according to the FGCRS (in tertile) at baseline*

	FGCRS				
	Low	Medium	High	$P_{for\ trend}$	OR (95% CI)
Female+male					
Case/N	426/134 809	1240/110 787	2332/109 058		
Model 1†, OR (95% CI)	1 (reference)	1.07 (0.95 to 1.20)	1.25 (1.12 to 1.41)	<0.001	1.20 (1.14 to 1.25)
Model 2‡, OR (95% CI)	1 (reference)	1.10 (0.98 to 1.24)	1.26 (1.12 to 1.42)	<0.001	1.17 (1.12 to 1.23)
Model 3§, OR (95% CI)	1 (reference)	1.10 (0.98 to 1.23)	1.26 (1.12 to 1.41)	<0.001	1.17 (1.12 to 1.23)
Female					
Case/N	214/72 096	571/61 994	1236/62 631		
Model 1†, OR (95% CI)	1 (reference)	1.00 (0.85 to 1.18)	1.24 (1.06 to 1.46)	<0.001	1.22 (1.14 to 1.30)
Model 2‡, OR (95% CI)	1 (reference)	1.02 (0.86 to 1.20)	1.24 (1.05 to 1.46)	0.001	1.19 (1.12 to 1.27)
Model 3§, OR (95% CI)	1 (reference)	1.01 (0.86 to 1.19)	1.23 (1.04 to 1.45)	0.001	1.19 (1.11 to 1.27)
Male					
Case/N	212/62 713	669/48 793	1096/46 427		
Model 1†, OR (95% CI)	1 (reference)	1.15 (0.98 to 1.36)	1.29 (1.09 to 1.52)	0.001	1.18 (1.10 to 1.26)
Model 2‡, OR (95% CI)	1 (reference)	1.19 (1.01 to 1.41)	1.30 (1.10 to 1.54)	0.002	1.16 (1.08 to 1.24)
Model 3§, OR (95% CI)	1 (reference)	1.19 (1.01 to 1.41)	1.29 (1.09 to 1.53)	0.003	1.15 (1.08 to 1.23)

*Models were based on logistic regression.
†Model 1: adjusted for age.
‡Model 2: model 1 plus sex, education, Townsend deprivation index, depression diagnosis, BMI category, alcohol consumption, physical activity, third-degree relatedness and principal components of ancestry.
§Model 3: model 2 plus polygenic risk score of Alzheimer's disease (standardised) and the number of alleles included in polygenic risk score of Alzheimer's disease.
BMI, body mass index; CI, confidence interval; FGCRS, Framingham General Cardiovascular Risk Score; OR, odds ratio.

drastic changes in lifestyle may occur after CVD diagnosis. In addition, CVD treatment could influence both the cardiovascular risk burden and the risk of dementia.[13] Our research was conducted among participants without baseline CVD, which may result in a relatively stable FGCRS and minimise the potential impact of treatment. Our findings of elevated dementia risk and higher cardiovascular risk burden align with a previous study in French participants aged 65 years or older without a history of CVD.[4]

Our study suggested a partial role of incident major CVD in the occurrence of dementia. The association of cardiovascular risk burden in our study with dementia risk was attenuated after adjusting for incident CHD and stroke, similar to the slightly attenuated association for vascular dementia after adjusting for interim stroke in the Chicago Heart Association Detection Project in Industry Study.[6] Meanwhile, we found that only 14% of dementia occurrences in our study could be attributed to incident major CVD events, suggesting CVD events do not fully account for the association between cardiovascular risk burden and dementia. This result is supported by the strong association of cardiovascular risk burden with all-cause dementia among participants without incident

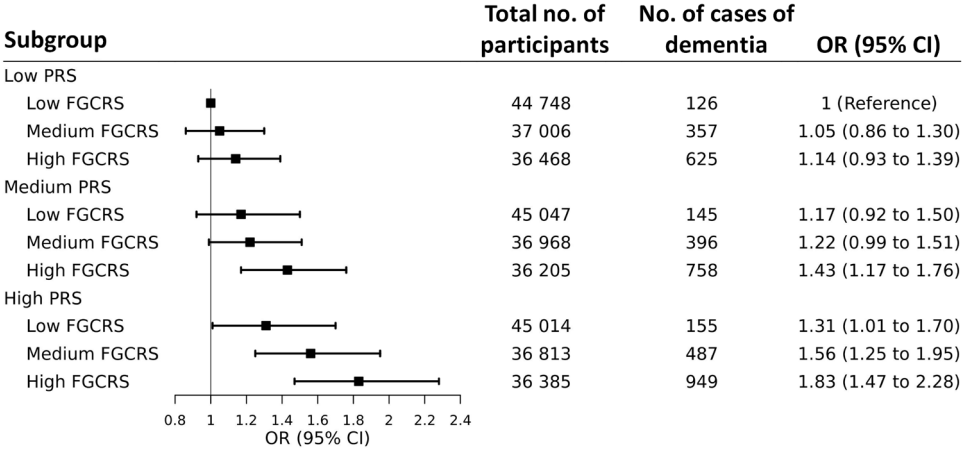

Figure 2 Joint analysis of the FGCRS at baseline and polygenic risk score (PRS) with all-cause dementia. The model was based on logistic regression and was adjusted for age, sex, Townsend deprivation index, education, BMI category, alcohol consumption, physical activity, third-degree relatedness, principal components of ancestry and the number of alleles included in genetic risk score of dementia. BMI, body mass index; CI, confidence interval; FGCRS, Framingham General Cardiovascular Risk Score; OR, odds ratio; PRS, polygenic risk score.

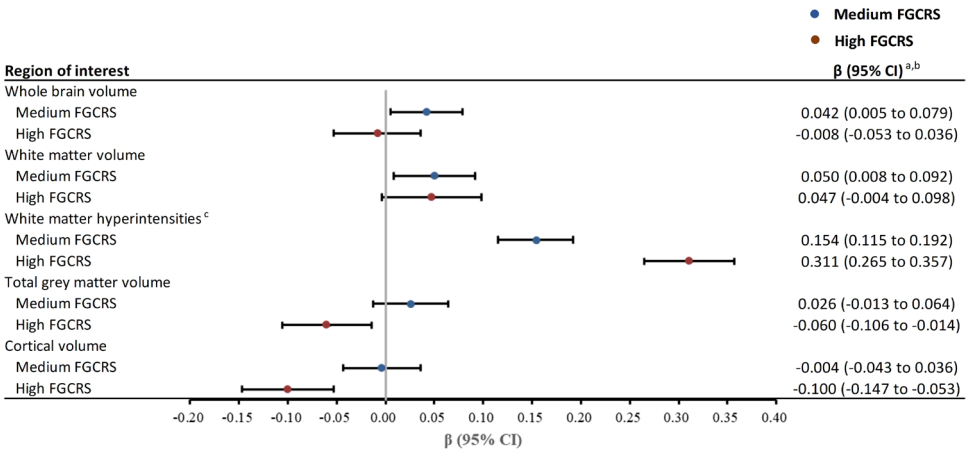

Figure 3 Association between the FGCRS at baseline and brain structure (standardised) by MRI with low tertile FGCRS as the reference group.[a,b,c] [a]Models were based on linear regression. [b]Models were adjusted for age, sex, education, Townsend deprivation index, depression diagnosis, BMI category, alcohol consumption, physical activity, third-degree relatedness and principal components of ancestry, polygenic risk score of Alzheimer's disease (standardised) and the number of alleles included in polygenic risk score of Alzheimer's disease. [c]White matter hyperintensity volume was log-transformed and then z-standardised. BMI, body mass index; FGCRS, Framingham General Cardiovascular Risk Score; MRI, magnetic resonance imaging.

stroke and CHD events during follow-up in our study, consistent with the results among participants free of CVD over the follow-up among the British civil service population in the Whitehall II Study.[3] The limited mediating role of CVD indicates that changeable individual components of the cardiovascular risk burden could be targeted to reduce dementia risk in addition to CVD onset. The pathogenesis of dementia subtypes varies: Alzheimer's disease is characterised by extracellular amyloid plaques and intracellular neurofibrillary tangles,[21] whereas vascular dementia is caused by reduced blood flow to the brain. Nevertheless, existing studies were unable to examine the associations for dementia subtypes due to the limited sample sizes. The Rush Memory and Aging Project especially examined FGCRS with Alzheimer's disease,[20] but dementia cases from other causes were limited (n=35). The UKB offers a relatively large sample for major subtypes of dementia, which has facilitated findings such as the disparate associations of telomere length with Alzheimer's disease and vascular dementia.[22] We provided additional evidence on the association of a higher cardiovascular risk burden with an elevated risk of Alzheimer's disease, vascular dementia and other dementias.

WMHs are the consequence of cerebral small vessel disease, and the presence of large confluent WMHs has been associated with decreased cognitive function, suggesting a causal link with dementia.[23] Alzheimer's disease signature based on cortical thinning could identify subtle but reliable atrophy in asymptomatic individuals nearly a decade before dementia.[24] Compared with the Rush Memory and Aging Project,[17] our study validated in a larger sample that cardiovascular risk burden was associated with greater WMH volume, smaller total grey matter and smaller cortical volumes, independent of a comprehensive genetic risk score of dementia rather than *APOE* ε4 status alone. The PRS incorporates a much more comprehensive indicator of genetic risk and provides a quantitative measurement that allows for more genetic variations in dementia. Cardiovascular risk burden was not found to be associated with whole brain volume in our study, possibly due to a relatively younger population with moderate follow-up duration. The Framingham Heart Study Offspring Cohort[7] and the CARDIA Study[16] suggested a time window (14 and 25 years, respectively) between cardiovascular risk burden measurement and whole brain atrophy.

Few studies have evaluated the modification role of the overall genetic predisposition to dementia on the association between cardiovascular burden and dementia-related outcomes. Most of the studies only used *APOE* genotype as a covariate[3 4 10 11] or a stratification variable.[4] In the Rotterdam Study among 6352 individuals aged 55 years with a median follow-up of 14.1 years, an interaction was found between the Ideal Cardiovascular Health Score and *APOE* genotype on dementia risk, with no significant association among *APOE* ε4 carriers.[25] In the Atherosclerosis Risk in Communities Study with 2226 incident dementia cases identified over a median follow-up of 25 years, no interaction was found between *APOE* status and cardiovascular health on dementia risk.[11] The inconsistent findings of interactions between cardiovascular burden and genetic risk of dementia may partly be due to the incomplete representativeness of the *APOE* genotype for the genetic burden of dementia. Our study did not observe a significant interaction between cardiovascular burden and the genetic background of dementia risk from a more comprehensive set of genetic variants. This aligns with the result from the Framingham Heart Study offspring cohort,[5] suggesting that reducing cardiovascular burden may be equally efficient for preventing dementia regardless of the genetic risk level.

The elevated dementia risk related to higher cardiovascular risk burden is partially due to chronic cerebral hypoperfusion. Cerebrovascular reserve serves as a potential biomarker for monitoring pressure–perfusion–cognition relationships since the decline of vascular reserve capacity can lead to impairment in neurovascular coupling and reduced cognitive function.[26] Mechanisms associated with stroke may also include enhanced amyloid deposition, the additive effect of amyloid deposition on cerebrovascular damage, inflammation and disturbed cholesterol metabolism.[27] The most common and plausible mechanisms that link atrial fibrillation, ischaemic heart disease and heart failure to dementia may involve cerebral hypoperfusion and hypoxia, cerebral ischaemia or microbleeds, and the release of natriuretic peptides.[28] The unexplained dementia risk of the cardiovascular burden caused by major CVD events may involve other mechanisms, including cerebral small vessel lesions and microinfarctions not reaching the stage of clinically diagnosed CVD, oxidative stress, inflammation and aberrant brain energy metabolism,[29] which warrant confirmation by further studies.

Limitations

The UKB, covering half a million people with diverse data, enables detailed analysis of gene-environment interactions, effect modification by possible confounding factors, dose-response relations and brain structure, which is a major strength of our study. However, several limitations warrant attention. First, dementia diagnosis was based on hospital admission and death registry data, and underdiagnosis is inevitable. Nevertheless, validation research has established good sensitivity for hospital admission and death registry data compared with expert adjudication of full-text medical records.[30] Second, participants included in the current study were Caucasians, and caution should be paid when extrapolating findings to the broader population. However, there is no reason to expect that the association would be qualitatively different across races and ethnicities. Third, FGCRS was only assessed at baseline; therefore, potential associations of changes in cardiovascular burden with dementia and brain structure could not be evaluated. Fourth, although we have carefully adjusted for a large set of established major environmental and genetic risk factors, residual confounding is inevitable in an observational study. Finally, reverse causation may be a concern since cardiovascular burden may be modified by the intervention of caregivers within a short period before the diagnosis of dementia. Nevertheless, associations remained similar when dementia cases within 2 years of follow-up were excluded.

Implications

Our findings support the adverse role of cardiovascular risk burden in dementia risk and neurodegeneration-related brain structure. The association of cardiovascular risk burden with dementia is largely independent of CVD onset and the genetic predisposition to dementia. Managing a low FGCRS might prove beneficial in preventing or delaying the onset of dementia.

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Competing interests As of June 2021, WG is a full-time employee of Novo Nordisk.

Patient consent for publication Not required.

Ethics approval This study involves human participants. The project of UK Biobank received ethical approval from the North West Multi-center Research Ethics Committee (REC reference: 21/NW/0157). Informed consent through electronic signature at baseline was obtained from all participants. Our study conforms to the principles outlined in the Declaration of Helsinki.

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