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Original Article

Cardiovascular health, genetic predisposition, and dementia risk among atherosclerotic cardiovascular disease patients

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ABSTRACT

Background: While optimal cardiovascular health (CVH) has been linked to a lower risk of dementia, few studies considered individuals' genetic background. We aimed to examine the interaction between CVH and genetic predisposition on dementia risk among individuals with atherosclerotic cardiovascular disease (ASCVD).
Methods: We included 30,818 ASCVD patients from the UK Biobank. CVH was assessed using Life's Essential 8, and genetic predisposition determined by a genetic risk score (GRS) incorporating 85 genetic variants. Cox proportional hazard models were used to estimate hazard ratios (HRs) for all-cause dementia, Alzheimer's disease (AD), and vascular dementia (VaD).
Results: Over a median follow-up of 13.5 years, 1,360 cases of all-cause dementia were identified, including 489 AD and 440 VaD cases. Higher CVH levels were associated with a reduced risk of all-cause dementia (HR for high vs. low CVH: 0.60; 95 % CI: 0.47–0.77) and VaD (HR for high vs. low CVH: 0.32; 95 % CI: 0.19–0.54), with a stronger association in individuals with lower GRS. Although the overall CVH score was not associated with the risk of dementia in individuals with high GRS, higher levels of sleep and glucose control were associated with a lower risk of VaD. CVH levels showed no association with the risk of AD.
Conclusion: Higher CVH levels were associated with a lower risk of VaD, not AD, with a stronger association in individuals with low GRS. Improvements in specific LE8 components, particularly sleep health and blood glucose management, were associated with reduced VaD risk across various genetic risk strata.

1. Introduction

Dementia, which includes Alzheimer's disease (AD) and vascular dementia (VaD), has been a leading cause of disability and dependency among older adults worldwide and poses a significant public health challenge [1]. It currently affects around 57 million individuals worldwide [2]. With the aging population and increased life expectancy, projections suggest that this number could triple by 2050 [3]. Atherosclerotic cardiovascular disease (ASCVD), such as ischemic heart disease and stroke, is recognized as an independent risk factor for dementia [4,5]. Studies indicated that the incidence of cognitive impairment markedly increased following an ASCVD event, with around 20 % of patients developing dementia within the first year after a stroke [6]. With no definitive cure for dementia, therefore, it is imperative to prevent the onset and progression of dementia within the ASCVD patients.

Dementia is a complex and multifaceted disease influenced by a combination of genetic, environmental, lifestyle, and metabolic elements. Previous research has shown that maintaining optimal cardiovascular health (CVH), as measured by Life's Essential 8 (LE8) [7], is associated with a lower risk of dementia and CVD [8–11]. However, these studies have primarily focused on the general population, without considering individuals' genetic background. Since the individual components

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of CVH have distinct biological effects, their influence on dementia risk may vary based on genetic predisposition. A recent genome-wide association study (GWAS) developed a novel genetic risk score (GRS) strongly associated with the incidence of all-cause dementia [12,13], providing an opportunity to explore the interaction between CVH and genetic predisposition on dementia risk.

In this study, we aimed to 1) investigate the association between CVH levels, as assessed by LE8, and the risk of dementia in individuals with ASCVD, 2) examine the interaction between genetic predisposition and LE8 CVH scores on dementia risk, and 3) explore the associations of individual LE8 components with the risk of dementia across different genetic risk strata. Our study underscores the importance of personalized prevention strategies that integrate both CVH modification and genetic risk assessment in ASCVD patients.

2. Methods

2.1. Study population

The United Kingdom Biobank (UKB) is an ongoing population-based prospective cohort that recruited more than 500,000 participants aged 40–70 years from England, Scotland, and Wales throughout the United Kingdom between 2006 and 2010 [14]. The present study included 31,876 participants with diagnosed coronary heart disease (CHD) and ischemic stroke (including transient ischemic attack) at baseline (Supplemental Table S1). We further excluded participants without genetic data (n = 1036), with missing data on the components of LE8 (n = 24), or with a history of cardioembolic stroke (CES) (n = 23) or dementia/cognitive impairment (n = 42). Finally, a total of 30,818 ASCVD patients were included in the analysis (Supplemental Figure S1).

2.2. Assessment of CVH and genetic predisposition to dementia

We evaluated CVH for individuals based on the LE8 criteria. The components of LE8 included four behavioral factors, including dietary quality, physical activity, nicotine exposure, and sleep health, and four metabolic factors, including BMI, blood lipids, blood glucose, and blood pressure. Dietary quality was assessed through a proxy measure for the Dietary Approaches to Stop Hypertension (DASH) [15], encompassing the habitual dietary intakes of fruits, vegetables, whole grains, fish, dairy, vegetable oils, refined grains, processed meats, unprocessed meats, and sugar-sweetened beverages. Physical activity, nicotine exposure, sleep duration, as well as the usage of medications for cholesterol, blood pressure, and diabetes management were assessed using a touchscreen questionnaire. BMI was measured by dividing the weight in kilograms by the square of the individual's standing height in meters. Serum levels of cholesterol (mmol/L) and blood glucose (mmol/L) were measured using the blood samples collected at baseline. Non-high-density lipoprotein (HDL) cholesterol was measured by subtracting HDL cholesterol from the total serum cholesterol. Diabetes was identified through inpatient hospital records, death registrations, and self-reported diagnoses. Both diastolic and systolic blood pressure measurements were recorded as the average of two consecutive readings. The CVH scoring algorithm for each component was defined by the American Heart Association (AHA), with each component scored ranging from 0 to 100 points. The overall LE8 score was calculated as the unweighted average score across all eight metrics. CVH levels were categorized as high (80–100), moderate (50–79), and low (0–49) according to the LE8 score. Detailed algorithms for calculating the LE8 scores were shown in Supplemental Table S2.

The genotyping process and arrays used in the UKB study have been described elsewhere [16]. A weighted GRS comprising 85 single nucleotide polymorphisms (SNPs), including rs429,358 and rs7412 on APOE gene, was constructed to evaluate the genetic predisposition to dementia [12] (Supplemental Table S3). The number of risk alleles (0, 1, or 2) at each SNP was weighted by its effect size, summed across all SNPs, and then Z-score standardized to derive a GRS for each participant. Genetic risk was stratified into low (quintile 1), moderate (quintiles 2–4), and high (quintile 5) based on the GRS.

2.3. Ascertainment of outcomes

Dementia diagnoses were based on algorithmically defined outcomes obtained from inpatient hospital records, death registrations, and self-reported diagnoses. All diagnoses were coded according to the International Classification of Diseases (ICD) system (Supplemental Table S1). All-cause dementia was identified using ICD-9 codes (290.2, 290.3, 290.4, 291.2, 294.1, 331.0, 331.1, 331.2, 331.5) and ICD-10 codes (A81.0, F00-F03, F05.1, F10.6, G30, G31.0, G31.1, G31.8), covering various forms of dementia. Specifically, AD was identified using ICD-9 code 331.0 and ICD-10 codes F00 and G30 and VaD using ICD-9 code 290.4 and ICD-10 codes F01 and I67.3. The follow-up duration for each participant was calculated from the date of enrollment until the first occurrence of dementia, loss to follow-up, death, or the end of follow-up (December 9, 2022 in England, December 8, 2022 in Wales, and December 19, 2022 in Scotland), whichever occurred first.

2.4. Covariates

We included the following covariates in analysis to account for potential confounding factors: demographic factors (age, sex, ethnicity, and assessment center), socioeconomic status (education, household income, the index of multiple deprivation [IMD]), medical history (family history of heart disease, stroke, AD, or Parkinson's), use of medications (antihypertensive, cholesterol-lowering, antidiabetic, and antiplatelet medications), and BMI. Information on these covariates was obtained through a self-administered questionnaire at baseline. For medication use, the categories were as follows: 1) antihypertensive medications, such as diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers; 2) cholesterol-lowering medications, including statins, fibrates, and cholesterol absorption inhibitors; 3) antiplatelet medications; and 4) antidiabetic medications, including sulfonylureas, insulin products, alpha-glucosidase inhibitors, metformin, meglitinides, and other agents. Missing values for covariates were imputed with median for continuous variables and mode for categorical variables.

2.5. Statistical methods

Multivariable Cox proportional hazard regression model was used to estimate the associations of CVH and GRS with the risks of all-cause dementia, AD and VaD, with hazard ratios (HRs) and 95 % confidence intervals (CIs) being calculated. In model 1, age, sex, ethnicity, and center were adjusted. Model 2 included variables in model 1 with an additional adjustment for education attainment, IMD, and household income. Model 3 was additionally adjusted for family history of heart disease, stroke, AD, or Parkinson and use of antidiabetic, antiplatelet, antihypertensive, or cholesterol-lowering medication. Furthermore, we examined the dose-response relationship between CVH and GRS and dementia risk by treating CVH and GRS as continuous variables and integrating a restricted cubic spline (RCS) term with three knots located at the 5th, 50th, and 95th percentiles into the model 3. The significance of non-linearity in these relationships was examined using the likelihood ratio test.

We also calculated population-attributable fractions (PAFs) to estimate the theoretical reduction in population-level risks for incident dementia attributed to improvements in each component of LE8. PAF represents the proportion of incident dementia cases that could be theoretically reduced if the exposures were eliminated from the population [17], assuming a causal relation between the exposure and outcome.

We examined the interactions between CVH and GRS on dementia risk by including a cross-product term into the model, with a $P < 0.05$ for the interaction term defined as the significant multiplicative interaction. We also evaluated the association between improvement in each LE8 component and incident dementia across GRS groups.

Table 1
Baseline characteristics of 30,818 UKB participants with pre-existing ASCVD.

Characteristics	Overall	Without incident dementia	With incident dementia
No. of participants	30818	29458	1360
Type of ASCVD[§]			
CHD	27243 (88.4)	26015 (88.3)	1228 (90.3)
Ischemic stroke	7377 (23.9)	6889 (23.4)	488 (35.9)
Follow-up time, y, median (IQR)	13.5 (12.6, 14.4)	13.5 (12.6, 14.4)	12.4(10.1, 13.7)
Men, No. (%)	20737 (67.3)	19836 (67.3)	901 (66.2)
Age, y, mean (SD)	61.8 (6.1)	61.7 (6.1)	65.0 (4.2)
White ethnicity, No. (%)	29107 (94.4)	27819 (94.4)	1288 (94.7)
Education, No. (%)			
College or university	6416 (20.8)	6208 (21.1)	208 (15.3)
A levels/AS levels or	2640 (8.6)	2528 (8.6)	112 (8.2)
O levels/GCSE levels	5762 (18.7)	5555 (18.9)	207 (15.2)
CSEs or equivalent	1170 (3.8)	1138 (3.9)	32 (2.4)
NVQ or HND or HNC	2735 (8.9)	2613 (8.9)	122 (9.0)
Other professional qualifications	1882 (6.1)	1794 (6.1)	88 (6.5)
None of above	10213 (33.1)	9622 (32.7)	591 (43.5)
Index Multiple deprivation (IMD), median (IQR)	15.7 (8.5, 29.4)	15.7 (8.4, 29.2)	17.3 (9.1, 33.4)
Household income, No. (%)			
Less than £18,000	13499 (43.8)	12734 (43.2)	765 (56.2)
£18,000 to £ 30,999	8495 (27.6)	8137 (27.6)	358 (26.3)
£31,000 to £51,999	5349 (17.4)	5191 (17.6)	158 (11.6)
£52,000 to £100,000	2824 (9.2)	2756 (9.4)	68 (5.0)
Greater than £100,000	651 (2.1)	640 (2.2)	11 (0.8)
Family history disease, No. (%)			
Heart disease	16884 (54.8)	16193 (55.0)	691 (50.8)
Stroke	8508 (27.6)	8137 (27.6)	371 (27.3)
Alzheimer	3451 (11.2)	3254 (11.0)	197 (14.5)
Parkinson	1008 (3.3)	961 (3.3)	47 (3.5)
Use of medication, No. (%)			
Antihypertensive	23653 (76.8)	22546 (76.5)	1107 (81.4)
Antidiabetic	3879 (12.6)	3601 (12.2)	278 (20.4)
Cholesterol-lowering	24878 (80.7)	23717 (80.5)	1161 (85.4)
Antiplatelet	23700 (76.9)	22644 (76.9)	1056 (77.6)
Scores for each CVH component, mean (SD)			
LE8 score	64.7 (12.3)	64.8 (12.3)	62.5 (12.2)
Dietary score	52.0 (30.3)	52.0 (30.3)	52.4 (30.0)
Physical activity score	78.5 (35.1)	78.7 (35.0)	74.5 (37.2)
Nicotine exposure score	71.9 (31.5)	71.9 (31.6)	72.9 (29.7)
Sleep health score	83.9 (24.2)	84.1 (24.1)	80.0 (27.3)
BMI score	57.8 (29.3)	57.8 (29.3)	57.2 (29.0)
Blood pressure score	37.0 (26.4)	37.1 (26.4)	33.9 (26.7)
Blood lipids score	58.9 (25.2)	58.9 (25.2)	58.8 (25.4)
Blood glucose score	77.5 (28.0)	77.8 (27.9)	70.6 (30.3)
CVH levels, No. (%)			
Low (0-49)	4479 (14.5)	4235 (14.4)	244 (17.9)
Moderate (50-79)	22560 (73.2)	21565 (73.2)	995 (73.2)
High (80-100)	3779 (12.3)	3658 (12.4)	121 (8.9)
APOE-e4, No. (%)			
0 risk alleles	21584 (70.0)	20878 (70.9)	706 (51.9)
1 risk alleles	8426 (27.3)	7891 (26.8)	535 (39.3)
2 risk alleles	808 (2.6)	689 (2.3)	119 (8.8)
GRS levels, No. (%)			
Low (Q1)	6166 (20.0)	5991 (20.3)	175 (12.9)
Moderate (Q2-Q4)	18484 (60.0)	17802 (60.4)	682 (50.1)
High (Q5)	6168 (20.0)	5665 (19.2)	503 (37.0)

Continuous variables are described as mean (SD) for those with normal distribution and median (Interquartile Rang, IQR) for those with non-normal distribution in continuous variables. Categorical variables are described as number (percent).

[§] The cumulative percentage surpasses one hundred percent, acknowledging the coexistence of multiple comorbidities within individual patients.

R (Version 4.2.1) was used for analyses and two-sided *P* values were calculated for statistical inference.

3. Results

3.1. Baseline characteristics

Among the 30,818 participants with prevalent ASCVD included in the study, 94.4 % were White and 67.3 % were men. The average age was 61.8 years (SD = 6.1), with 88.4 % having pre-existing CHD and 23.9 % having ischemic stroke. Compared to participants who did not develop dementia during the follow-up period, those with incident dementia were older and had lower levels of educational achievement, higher IMD, lower household income, a higher family history of AD, a greater use of antihypertensive, antidiabetic, cholesterol-lowering, and antiplatelet medications, lower levels of LE8 CVH, and a higher genetic predisposition to dementia (Table 1).

3.2. Cumulative incidence of dementia among ASCVD participants

Over a median follow-up period of 13.5 years (IQR: 12.6–14.4), there were 1,360 newly diagnosed cases of all-cause dementia, of which 489

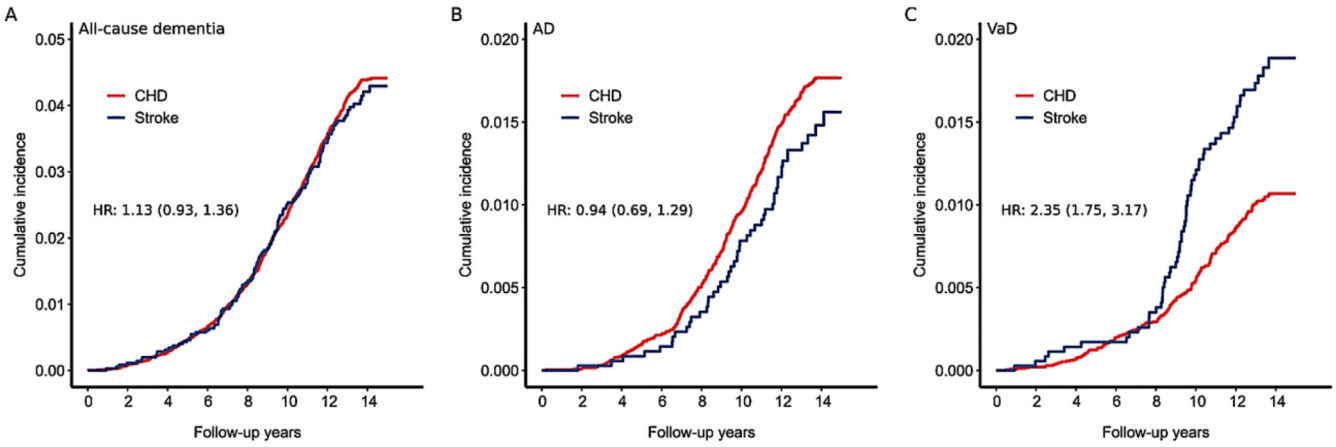

Fig. 1. Cumulative incidence of all-cause dementia (A), AD (B), and VaD (C) over a median of 13.5 years of follow-up among UKB participants with pre-existing CHD (Red) and stroke (Blue).
HR was calculated for dementia with different types of ASCVD, treating CHD as the reference, which was adjusted for age (continuous), sex (men or women), ethnicity (white or not), center, education (college degree or not), IMD (continuous), household income (less than £18,000; £18,000 to £30,999; £31,000 to £51,999; £52,000 to £100,000 or greater than £100,000), BMI (continuous), family history of heart disease, stroke, AD, or Parkinson (yes or no), and use of antidiabetic, antiplatelet, antihypertensive, or cholesterol-lowering medications (yes or no). AD Alzheimer's disease, VaD vascular dementia, CHD coronary heart disease.

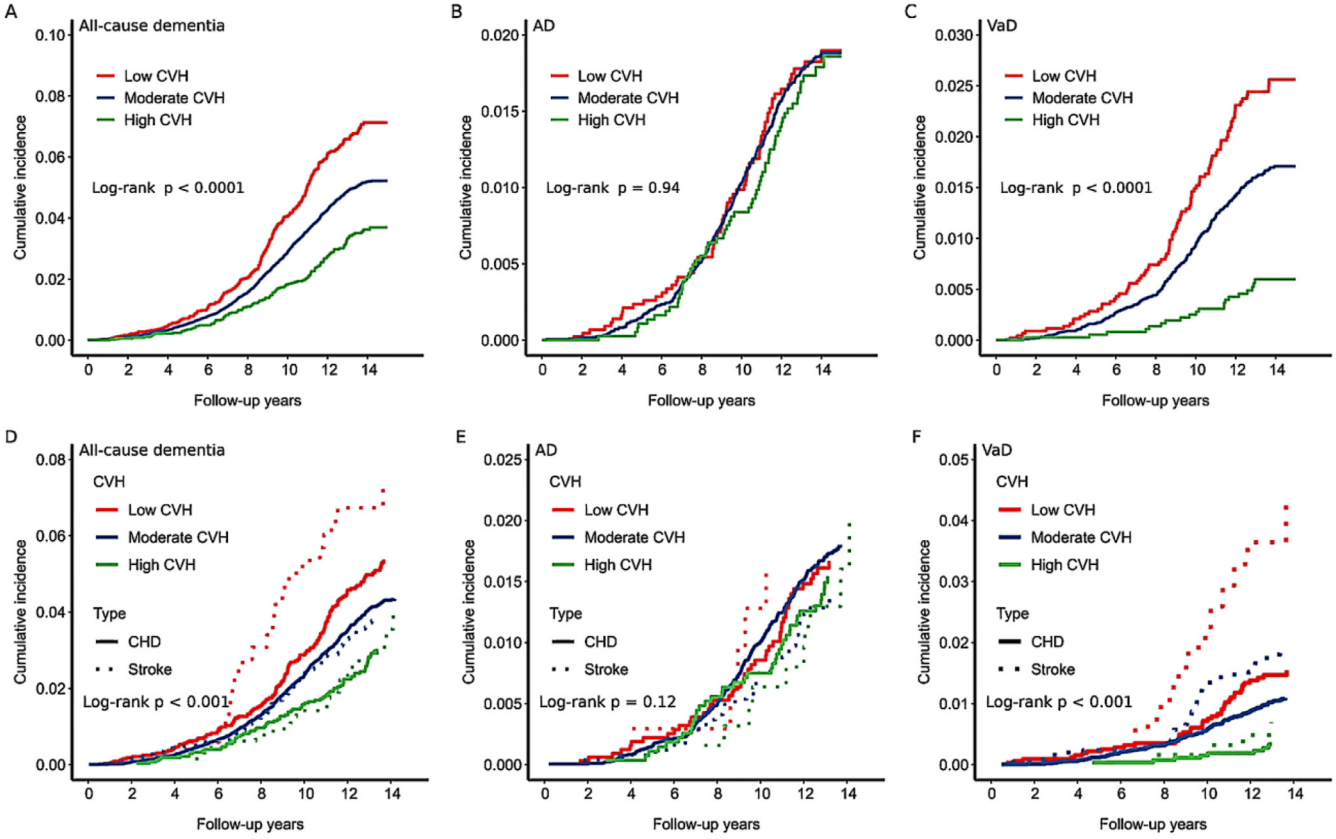

Fig. 2. Cumulative incidence of dementia over a median of 13.5 years of follow-up by CVH levels (Red: Low, Blue: Moderate, Green: High) and ASCVD types (solid line: History of CHD, dotted line: History of stroke).

were AD and 440 were VaD. Compared to participants with pre-existing CHD, those with a history of stroke exhibited a 135 % higher risk of developing VaD (HR:2.35, 95 % CI: 1.75–3.17), although their risks of all-cause dementia and AD were similar (Fig. 1).

3.3. Associations of LE8 CVH levels with incident dementia among ASCVD participants

Compared with the ASCVD participants with low CVH levels, those with moderate CVH levels had 25 % lower risk of all-cause dementia (HR: 0.75, 95 % CI: 0.64–0.87) and those with high CVH levels had 40 % lower risk of all-cause dementia (HR: 0.60, 95 % CI: 0.47–0.77). For specific types of dementia, we observed that higher levels of CVH were associated with a decreased risk of VaD (high vs low, HR: 0.32, 95 % CI: 0.19–0.54) but not AD (high vs low, HR: 1.13, 95 % CI: 0.76–1.69). We also observed consistent results among CHD or ischemic stroke participants (Fig. 2A-C, Table 2). Furthermore, after categorizing participants by ASCVD subtypes and CVH levels, we found that those with a history of stroke and low CVH levels exhibited the highest incidence rates of

Table 2
Incidence and hazard ratios of dementia according to CVH levels assessed by LE8 among 30,818 UKB participants with pre-existing ASCVD.

	All-cause dementia			AD			VaD		
	CVH			CVH			CVH		
	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High
ASCVD (n = 30818)									
Cases/PY	244/52321	995/283114	121/49314	66/52807	362/284980	61/49458	90/52787	330/285090	20/49546
Model 1	Ref.	0.59 (0.52, 0.68)	0.42 (0.34, 0.52)	Ref.	0.77 (0.59, 1.00)	0.75 (0.53, 1.06)	Ref.	0.54 (0.42, 0.68)	0.19 (0.12, 0.31)
Model 2	Ref.	0.66 (0.58, 0.77)	0.51 (0.41, 0.64)	Ref.	0.86 (0.66, 1.12)	0.93 (0.65, 1.32)	Ref.	0.62 (0.49, 0.78)	0.25 (0.15, 0.41)
Model 3	Ref.	0.75 (0.64, 0.87)	0.60 (0.47, 0.77)	Ref.	1.00 (0.75, 1.33)	1.13 (0.76, 1.69)	Ref.	0.72 (0.56, 0.93)	0.32 (0.19, 0.54)
CHD (n = 27243)									
Cases/PY	222/48028	906/250282	100/40601	61/48468	330/251958	51/40724	78/48454	287/252104	16/40812
Model 1	Ref.	0.62 (0.54, 0.72)	0.42 (0.33, 0.53)	Ref.	0.79 (0.60, 1.04)	0.75 (0.52, 1.09)	Ref.	0.56 (0.44, 0.73)	0.20 (0.11, 0.34)
Model 2	Ref.	0.69 (0.59, 0.80)	0.51 (0.40, 0.65)	Ref.	0.88 (0.67, 1.16)	0.92 (0.63, 1.35)	Ref.	0.65 (0.51, 0.85)	0.26 (0.15, 0.45)
Model 3	Ref.	0.78 (0.66, 0.91)	0.61 (0.47, 0.80)	Ref.	1.03 (0.77, 1.38)	1.15 (0.75, 1.75)	Ref.	0.79 (0.60, 1.04)	0.35 (0.20, 0.63)
Stroke (n = 7378)									
Cases/PY	101/12785	342/65020	45/12801	21/12996	91/65787	22/12849	49/12959	166/65595	11/12850
Model	Ref.	0.53 (0.43, 0.67)	0.37 (0.26, 0.53)	Ref.	0.62 (0.38, 1.00)	0.79 (0.44, 1.45)	Ref.	0.53 (0.39, 0.74)	0.20 (0.10, 0.38)
Model 2	Ref.	0.61 (0.49, 0.77)	0.47 (0.33, 0.68)	Ref.	0.69 (0.42, 1.13)	0.96 (0.51, 1.79)	Ref.	0.60 (0.43, 0.84)	0.24 (0.12, 0.47)
Model 3	Ref.	0.67 (0.52, 0.85)	0.55 (0.37, 0.82)	Ref.	0.77 (0.46, 1.30)	1.15 (0.56, 2.34)	Ref.	0.69 (0.49, 0.98)	0.32 (0.16, 0.65)

Cox proportional hazard ratio was used to calculate the hazard ratio with 95 % CI.
Model 1 was adjusted for age (continuous), sex (men or women), ethnicity (white or not), and center.
Model 2 was additionally adjusted for education (college degree or not), IMD (continuous), and household income (less than £18,000; £18,000 to £30,999; £31,000 to £51,999; £52,000 to £100,000 and greater than £100,000).
Model 3 was further adjusted for BMI (continuous), family history of heart disease, stroke, AD, or Parkinson (yes or no), and use of antidiabetic, antiplatelet, antihypertensive, or cholesterol-lowering medications (yes or no).
ASCVD atherosclerotic cardiovascular diseases, AD Alzheimer's disease, VaD vascular dementia. CHD coronary heart disease, BMI body mass index, PY person-year.

both all-cause dementia and VaD (Fig. 2D-F). We also observed linear relationships of LE8 score with the risks of all-cause dementia (overall $P < 0.001$, nonlinear $P = 0.85$) and VaD (overall $P < 0.001$, nonlinear $P = 0.02$). However, there was no evidence to support a relationship with AD (Supplemental Fig. S2A-C).

The PAF of four low behavioral CVH metrics for all-cause dementia was 12.54 % (95 % CI: 6.72 %–18.37 %) and 25.39 % (95 % CI: 15.03 %–35.76) for VaD, suggesting that 12.54 % of all-cause dementia and 25.39 % of VaD could have been prevented if individuals with ASCVD had attained moderate/high levels in the four behavioral CVH metrics. When the biological metrics of LE8, such as BMI, blood lipids, blood glucose, and blood pressure, were incorporated into the risk factor combination separately, the PAFs for all-cause dementia, especially for VaD, increased to 28.88 %, 23.30 %, 34.61, and 36.8 %, respectively (Supplemental Table S4).

3.4. Associations of GRS with incident dementia among ASCVD participants

Compared with the ASCVD participants with high GRS, those with moderate GRS had 57 % lower risk of all-cause dementia (HR: 0.43, 95 % CI: 0.38–0.48) and those with low GRS had 67 % lower risk of all-cause dementia (HR: 0.33, 95 % CI: 0.28–0.39). We observed consistent results among participants with CHD or stroke, as well as for different types of dementia (Supplemental Table S5). Our further analyses using restricted cubic spline regression revealed a significant J-shaped relationship between GRS and dementia risk (Supplemental Fig. S2D-F).

3.5. Joint associations of CVH and GRS with dementia risk among ASCVD participants

We found significant interactions between CVH levels and GRS on the risks of all-cause dementia (P for interaction < 0.001) and VaD (P for interaction $= 0.005$). In the high GRS group, CVH levels were not linked to the risks of all-cause dementia and VaD. Conversely, in the moderate and low GRS groups, higher CVH levels were associated with decreased risks of both conditions. Compared with the ASCVD participants with high GRS and low CVH, those with low GRS and high CVH had the lowest risks of all-cause dementia (HR: 0.15, 95 % CI: 0.08–0.30) and VaD (HR: 0.10, 95 % CI: 0.02–0.44). However, no significant interactions between GRS and CVH were found in relation to the risk of AD (Fig. 3).

Among the eight LE8 components, improvement in physical activity, sleep health, BMI, blood lipids, and blood glucose were associated with reduced risk of VaD in participants with low or moderate GRS. However, improvement only in sleep health (HR for per unit SD increment: 0.83, 95 % CI 0.72-0.96) and blood glucose (HR for per unit SD increment: 0.77, 95 % CI 0.62-0.95) was associated with reduced risk of VaD in participants with high GRS (Fig. 4 and Supplemental Table S6).

4. Discussion

This prospective cohort study demonstrated that higher CVH levels, as measured by LE8, are associated with a significantly reduced risk of all-cause dementia and VaD among individuals with ASCVD. Notably, higher levels of CVH were particularly associated with a lower risk of VaD, while no significant associations were observed for AD. Genetic predisposition played a crucial role, with a higher GRS being associated with an elevated risk of dementia. Importantly, the protective association between higher CVH levels and reduced VaD risk was more pronounced in individuals with low to moderate genetic risk compared to those with high genetic risk. Additionally, higher scores in specific LE8 components—such as physical activity, sleep health, BMI, blood lipids, and blood glucose—were associated with a lower risk of VaD in individuals with low or moderate GRS, while only sleep health and blood glucose showed a protective association in those with high GRS.

Our findings align with and expand upon existing epidemiological evidence that has established a strong link between stroke, cognitive impairment, and dementia [18–20]. For example, the Atherosclerosis Risk in Communities (ARIC) study, which followed 15,792 participants with a history of stroke over 25.5 years, demonstrated that both the severity and recurrence of stroke were significantly associated with an increased risk of dementia [19]. Similarly, a large-scale study involving 218,192 participants from the FinnGen cohort confirmed that stroke was strongly associated with dementia risk, particularly VaD, when compared with MI and PAD [21]. Our study corroborates these findings by showing an increased risk of dementia among ASCVD participants, with particularly

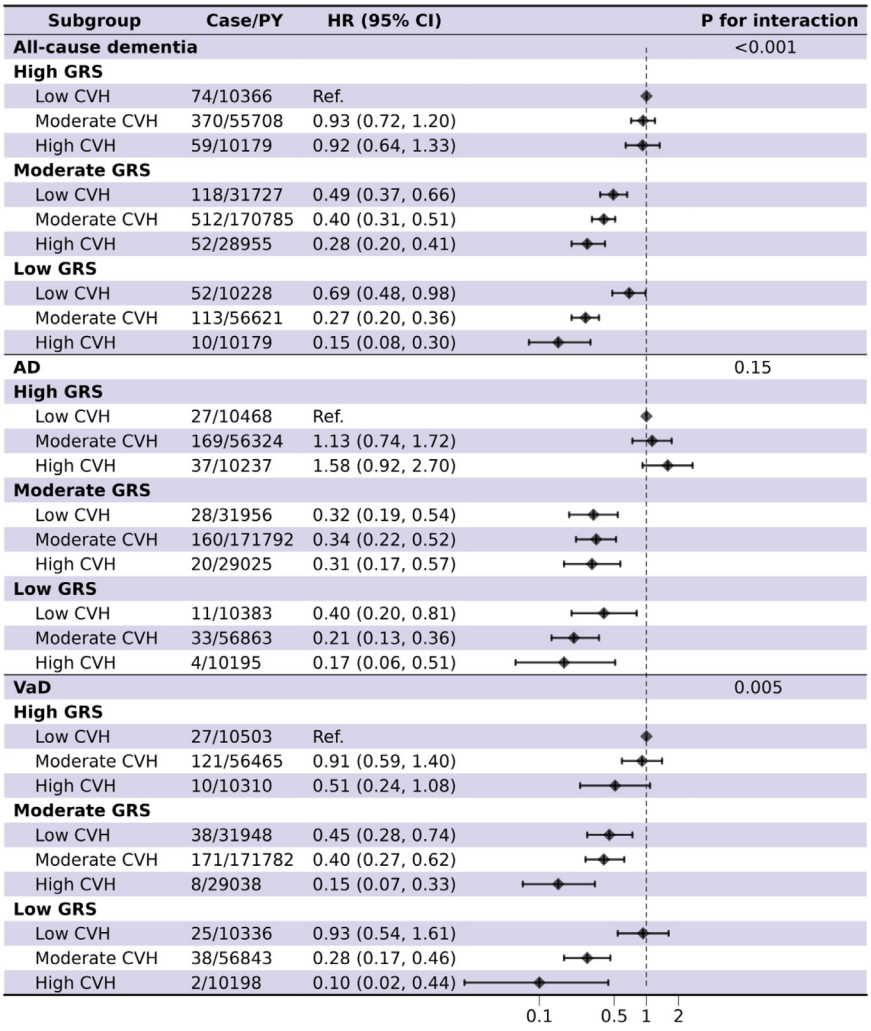

Fig. 3. Joint association of CVH and GRS with dementia risk among 30,818 UKB participants with pre-existing ASCVD.
Hazard ratios (95 % CIs) of incident dementia from Cox regression models was adjusted for age, sex, ethnicity, center, education, IMD, household income, BMI, family history of heart disease, stroke, AD, or Parkinson, and use of antidiabetic, antiplatelet, antihypertensive, or cholesterol-lowering medications. AD Alzheimer's disease, VaD vascular dementia, CVH cardiovascular health, GRS genetic risk score.

strong associations in those with a history of ischemic stroke. Moreover, our results further emphasize that VaD, rather than AD, is more strongly linked to ASCVD, reinforcing the notion that vascular factors play a crucial role in the development of VaD.

Previous studies, such as the UKB analysis involving 496,251 participants, have shown that a healthy lifestyle can mitigate the increased risk of dementia among those with a history of stroke [22]. However, evidence regarding the combined effects of behavioral and biological factors on dementia in ASCVD individuals has been limited. Our study addresses this gap by demonstrating that ideal CVH, as evaluated by LE8, was associated with a decreased risk of VaD—but not AD—among ASCVD patients. Furthermore, we found that adopting moderate to high levels of health behaviors could prevent 25.39 % of VaD cases. When biological factors like BMI, blood glucose, blood lipids, and blood pressure were included in the risk factor combination, the potential reduction in VaD cases increased to 36.8 %.

The differential association between CVH and dementia subtypes, particularly the stronger relationship with VaD compared to AD, can be explained by several underlying mechanisms. VaD primarily results from vascular pathology, including cerebral artery sclerosis, multi-infarct lesions, and small vessel disease [23]. These vascular insults directly impact brain regions essential for cognitive function, making factors that promote CVH more effective in preventing or delaying the onset of VaD. In contrast, AD is predominantly characterized by amyloid-β plaques and neurofibrillary tangles, with less direct involvement of vascular mechanisms, although vascular factors may exacerbate the condition [24]. The relationship between CVH and AD is likely more complex due to the primary role of amyloid and tau proteins in AD's pathogenesis. While improvements in CVH may lower the risk of VaD through direct vascular pathways, the impact on AD is less straightforward. Additionally, the weaker association between CVH and AD may be influenced by the stronger genetic contribution to AD, particularly from APOE-ε4 and other genetic risk factors. These genetic factors may limit the extent to which lifestyle interventions, including improvements in CVH, may reduce AD risk.

Both genetic and environmental factors contribute to dementia development, with evidence highlighting the role of the APOE gene in modifying the associations between CVH and dementia [8,25–27]. Studies involving large cohorts, such as the one with 316,669 participants, have shown that higher LE8 scores are associated with lower dementia risk across different APOE statuses, with more pronounced protective associations observed in APOE-ε4 noncarriers [8]. Recent advancements in GWAS have further expanded our understanding of dementia's genetic landscape beyond APOE, identifying numerous risk loci for AD and AD-related dementia [26,28,29]. However, there have been inconsistent findings regarding the interplay between genetic risk and lifestyle factors on dementia risk. While some studies have reported that a favorable lifestyle was associated with a lower risk of dementia regardless of genetic predisposition [27,30,31], others, like the Rotterdam Study [32], have indicated that the protective associations of modifiable risk factors diminished in individuals with high genetic risk. Our study supports the latter, showing significant interactions between LE8 scores and genetic risk in relation to all-cause dementia and VaD, suggesting that the protective associa-

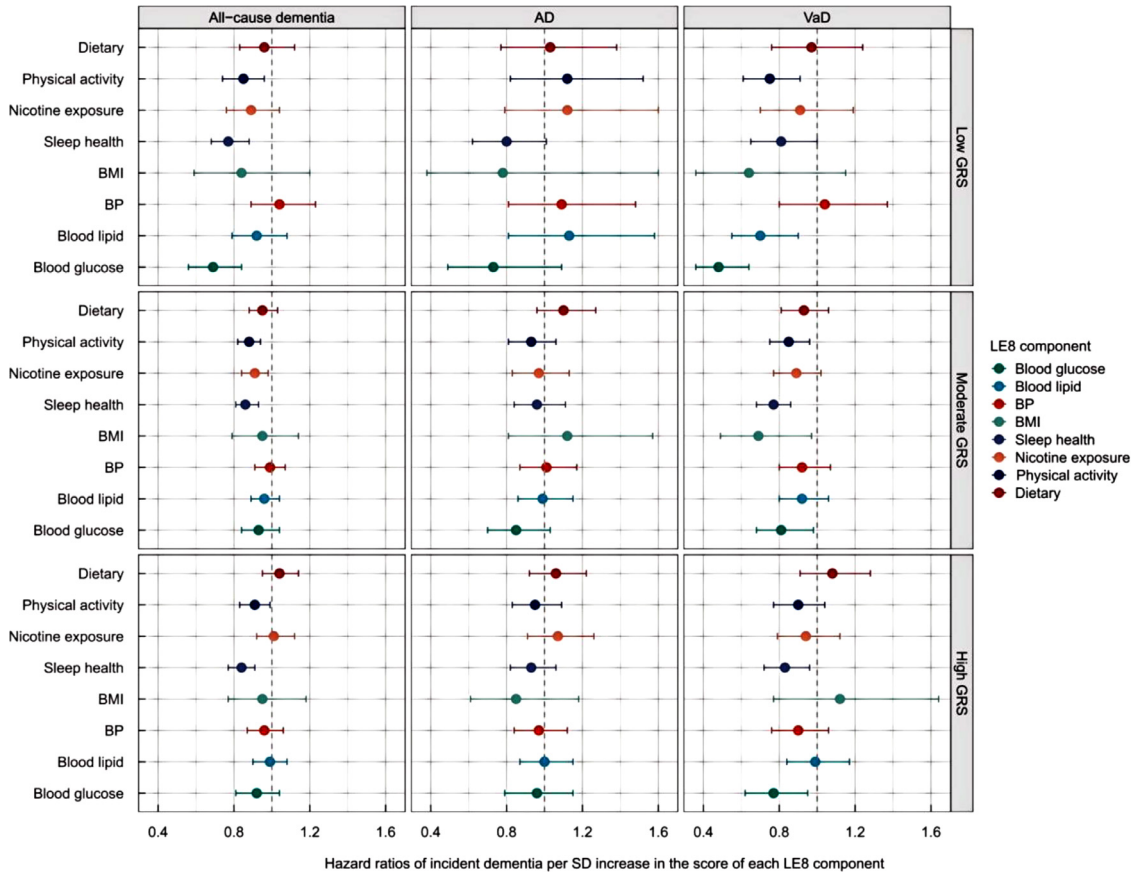

Fig. 4. Associations of each LE8 component with the risk of dementia according to genetic risk among 30,818 UKB participants with pre-existing ASCVD. HRs and their 95 % CI were calculated using Cox regression models with adjustment for age, sex, ethnicity, center, education, IMD, household income, BMI, family history of heart disease, stroke, AD, or Parkinson, and use of antidiabetic, antiplatelet, antihypertensive, or cholesterol-lowering medications.

tions of high CVH may be less pronounced in those with high genetic risk.

Despite the growing body of evidence linking ideal CVH to a reduced risk of dementia, particularly VaD, the individual contributions of each CVH component in preventing VaD across different genetic risk levels have remained underexplored. Our findings reveal that improvements in physical activity, sleep health, BMI, blood pressure, lipids, and glucose may be associated with a decreased risk of VaD in individuals with low or moderate GRS. However, among those with high GRS, only improvements in sleep health and blood glucose were linked to reduced VaD risk. These results suggest a significant interaction between CVH and genetic risk, underscoring the need for further research to explore these relationships and to develop targeted interventions based on both genetic and lifestyle factors.

This study has several key strengths that enhance its robustness and impact. The prospective design, with a median follow-up of 13.5 years, ensured that the study captured long-term outcomes, particularly the development of dementia, while minimizing the risk of reverse causation. The comprehensive assessment of CVH using LE8 allowed for a detailed exploration of how various health behaviors and biological factors collectively influence dementia risk. Incorporating a GRS further strengthened the study by enabling an examination of the interplay between genetic predisposition and CVH. By differentiating between dementia subtypes—such as VaD and AD—the study provided a more nuanced understanding of how CVH and genetic factors affect specific forms of dementia. Additionally, the analysis of individual LE8 components offered actionable insights for public health interventions, emphasizing the importance of a comprehensive approach to dementia prevention in high-risk populations.

Despite the strengths of this study, several limitations should be acknowledged. First, the cohort predominantly consisted of White British individuals, which may limit the generalizability of the findings to more diverse populations. Future research should aim to include a broader range of ethnicities to determine whether the observed associations hold across different demographic groups. Second, the assessment of CVH using LE8 was based on baseline measurements, and the study did not account for potential changes in CVH over time. Third, the reliance on observational data means that causal relationships between CVH and dementia risk cannot be definitively established. Although the prospective design and extended follow-up period reduce the likelihood of reverse causation, unmeasured confounding factors could still influence the results. Finally, while the study incorporated a GRS based on 85 genetic variants, the potential influence of other genetic factors not included in the GRS was not explored. This could mean that the genetic contribution to dementia risk may be underrepresented in this analysis. Additionally, the interaction between CVH and genetic risk may differ depending on the specific genetic variants considered.

In conclusion, our findings show that higher CVH levels were strongly associated with a lower risk of dementia, with the most significant protective associations observed for VaD rather than AD. The associations between CVH and both all-cause dementia and VaD were stronger in individuals with low GRS as compared with those with high GRS. Although overall CVH scores were not associated with a reduced risk of VaD in individuals with high GRS, higher levels of specific LE8 components, such as sleep health and blood glucose management, showed protective associations. This study contributes valuable insights into the prevention of dementia in high-risk populations, emphasizing the need for a multifaceted approach that integrates both lifestyle and

genetic factors. By promoting CVH and recognizing the influence of genetic risk, public health strategies can play a pivotal role in reducing the burden of dementia, particularly VaD, on individuals and healthcare systems worldwide.

Role of the funder

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Ethical standards

This study was performed under ethical approval obtained by UKB from the National Health Service National Research Ethics Service (21/NW/0157), and participants provided informed consent.

Data sharing statement

Data supporting the conclusions of this article are available on request from the UK Biobank team that the authors do not have permission to distribute (https://www.ukbiobank.ac.uk).

Author contribution

L.D. and J.L. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. J.L. and Y.Z. contributed to the conception and design of the study. L.D. conducted the statistical analyses. C.J. led the interpretation of the results. Q.C. performed the literature search. J.L. drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors made a significant contribution to finalizing the manuscript and approved the final version for publication.

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Declaration of competing interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2024.100020.

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