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Original Article

Associations of early-onset coronary heart disease and genetic susceptibility with incident dementia and white matter hyperintensity: A prospective cohort study

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ABSTRACT

Background: The associations of early-onset coronary heart disease (CHD) and genetic susceptibility with incident dementia and brain white matter hyperintensity (WMH) remain unclear. Elucidation of this problem could promote understanding of the neurocognitive impact of early-onset CHD and provide suggestions for the prevention of dementia.

Objectives: This study aimed to investigate whether observed and genetically predicted early-onset CHD were related to subsequent dementia and WMH volume.

Design: Prospective cohort study.

Setting: UK Biobank.

Participants: 500 671 individuals without dementia at baseline.

Measurements: Early-onset CHD (male ≤55 years; female ≤65 years) was ascertained using hospital inpatient records. Incident dementia including all-cause dementia, Alzheimer's disease, and vascular dementia was ascertained using hospital inpatient records, mortality register data, and self-reported data. WMH volume was measured through brain magnetic resonance imaging (MRI). Cox proportional hazards models and linear regression models were used to analyze the associations of early-onset CHD with incident dementia and WMH. Subsequently, a polygenetic risk score (PRS) analysis was conducted to investigate the associations of genetically predicted early-onset CHD with outcomes.

Results: Among 500 671 individuals (female: 272 669, 54.5%; mean age: 57.0 ± 8.1 years), 9 294 dementia occurred during a median follow-up of 13.8 years. Compared with the non-CHD group, both early-onset (n = 16 133) and late-onset CHD (n = 43 944) groups had higher risks of developing dementia (hazard ratio [HR]: 1.99, 95% confidence interval [CI]: 1.81 to 2.19 for early-onset group; HR: 1.20, 95% CI: 1.14 to 1.27 for late-onset group). Among CHD participants, early-onset CHD was associated with a significantly higher risk of incident dementia, compared with late-onset CHD (HR: 1.56, 95% CI: 1.39 to 1.75). In a subset of 40 290 individuals who completed brain MRI scans during a median follow-up of 9.3 years, participants with early-onset CHD exhibited the largest WMH volume among the three groups (early-onset CHD, late-onset CHD, and non-CHD, P_{trend}<0.001). The PRS analysis supported the associations of early-onset CHD with dementia (odds ratio [OR] for the highest quartile: 1.37, 95% CI: 1.28 to 1.46, P_{trend}<0.001) and WMH volume (β for the highest quartile: 0.042, 95% CI: 0.017 to 0.068, P_{trend}=0.002).

Conclusions: Early-onset CHD and genetic susceptibility are associated with a higher risk of incident dementia and a larger WMH volume. Additional attention should be paid to the neurocognitive status of individuals with early-onset CHD.

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1. Introduction

Due to the rapidly aging population and the increased exposure to risk factors, the number of people living with dementia is rising dramatically and doubled over the past 30 years, reaching 55.2 million in 2019 [1,2]. The high burden of morbidity, mortality, and disability from dementia has made it a major concern of health and social care community throughout the world [3]. To tackle this challenge, it is of vital significance to have a full understanding of its risk factors [4], especially given that there are few effective therapies and the novel drugs are costly and have strict eligibility [5,6]. Evidence has shown that management of modifiable risk factors, such as obesity, diabetes, and hypertension is conducive to prevention or delay of dementia, and near 40% of cases worldwide are theoretically preventable [7,8].

Coronary heart disease (CHD), another dominating source of global disease burden, is a primary risk factor for dementia and has been extensively studied over the past decades [9]. Due to changes in lifestyle, an increase in CHD incidence among young adults aged <50 years has been observed over the past 30 years [10–12]. Early-onset CHD, defined as CHD diagnosed before or at 55 years for men and diagnosed before or at 65 years for women according to the American College of Cardiology/American Heart Association guideline [13], is gaining increased attention on its prognosis among health professionals and researchers given the improved life expectancy of survivors. Interestingly, our recent work has revealed that the risk of incident dementia increased with the descending onset age of CHD, with per 10-year decrement in the onset age of CHD being associated with a 1.25-, 1.29-, and 1.22-fold of risk of all-cause dementia, Alzheimer's disease (AD), and vascular dementia (VD), respectively [14]. As suggested by prior studies, midlife was a sensitive period for the impact of cardiovascular risk factors on dementia [15,16], and survivors of cardiovascular disease diagnosed in midlife or earlier exhibited higher risk of subsequent all-cause dementia, AD, and VD [14,17–19].

Notably, subtle pathophysiologic changes in brain structure take place gradually over years before the diagnosis of dementia [20,21]. One of the cerebrovascular pathologies that has been frequently seen on brain magnetic resonance imaging (MRI) scans in older adults is white matter hyperintensity (WMH) [22], which is a consequence of chronic ischemia caused by cerebral microangiopathy [23,24]. WMH has been found to be involved in the etiology of both VD and AD, and could be a neuroimaging indicator of dementia [25–27]. Genetic predisposition, as well as traditional vascular risk factors, plays an important role in the pathogenesis of early-onset CHD [28,29], and a previous study has revealed the polygenic contribution to early-onset CHD based on the 1000 Genomes Project [30], which attracted us to further explore the associations of the genetic susceptibility of early-onset CHD with dementia and WMH.

To date, the associations of early-onset CHD and its genetic susceptibility with incident dementia and WMH have been rarely explored. Therefore, by using data from the UK Biobank, we conducted a prospective cohort study and a PRS analysis to investigate whether observed and genetically predicted early-onset CHD were related to subsequent dementia and brain WMH volume.

2. Materials and methods

2.1. Study design and population

The UK Biobank is an ongoing, population-based cohort involving demographic, socioeconomic, and health information of over 500 000 community-dwelling adults aged 40 to 69 years from 22 assessment centers in England, Scotland, and Wales. The baseline survey was conducted between 2006 and 2010. Detailed information concerning the study design, sampling method, and data collection of the UK Biobank was previously published [31,32]. The UK Biobank has received ethical approval from the North West Multi-center Research Ethics Committee (MREC) (299116). Written informed consent was obtained from all participants. The process of participant selection for this study was depicted in Fig. 1.

2.2. Ascertainment of early-onset CHD

Participants diagnosed with CHD at baseline or during follow-up before dementia were included in the analysis. CHD was ascertained using the health-related outcomes of hospital inpatient with the International Classification of Diseases Tenth Revision [ICD-10] codes of I20–I25. Early-onset CHD was defined as CHD diagnosed before or at 55 years for men and diagnosed before or at 65 years for women according to the American College of Cardiology/American Heart Association guideline [13]. Late-onset CHD was defined as CHD diagnosed after 55 years for men and diagnosed after 65 years for women. Detailed information is presented in Table S1.

2.3. PRS for early-onset CHD

In a large genome-wide association study (GWAS) meta-analysis, 202 SNPs were found to be associated with CHD (false discovery rate<5%) [33]. In addition, previous studies suggested that increased PRS might be associated with early onset of CHD [30,34,35]. Therefore, 202 SNPs were served as references, and new β were calculated for constructing weighted PRS of early-onset CHD. Briefly, we further restricted the subset to unrelated individuals of European ancestry. A GWAS for early-onset CHD was conducted in the UK Biobank, including 12 538 early-onset CHD cases and 358 184 participants without CHD serving as controls. To arrive at an independent set, the clumping process (R^2<0.05, window size=1000 kb) was performed using Europeans from 1000 Genomes phase 3 as reference panel. The SNP with the higher P value was excluded among each pair of SNPs in linkage disequilibrium (LD). Finally, 177 SNPs were retrieved from the UK Biobank imputed genetic data, and detailed information regarding the genotyping process, imputation, and stringent quality control has been described elsewhere [36] (Figure S1).

The logistic regression model was firstly applied, adjusting for age, sex, and the top 10 principal genetic components. Subsequently, the weighted PRS for early-onset CHD was calculated using the following formula:

$$\mathrm{PRS} = \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_k x_k + \beta_n x_n$$

Where β is the per-allele log odds ratio (OR) of the early-onset CHD-associated risk allele for SNP, x_k is the number of alleles for the same SNP (0, 1, 2), and n is the total number of early-onset CHD SNPs. The detailed information of selected SNPs was summarized in Table S2.

2.4. Brain MRI

White matter hyperintensity (WMH) volume was measured through brain MRI scans, which was performed in a subset of 40 290 participants during a median follow-up of 9.3 years (interquartile range [IQR]: 4.3 to 13.8 years) since baseline (2014–2024), using the 3T Siemens Skyra scanner with a standard 32-channel head coil according to a public protocol [37]. Further detailed information was available elsewhere [38]. Among participants with CHD, brain MRI were performed during a median of 6.8 years (IQR: 0.1 to 22.8 years) after the diagnosis of CHD.

2.5. Ascertainment of dementia

Dementia was ascertained using the algorithmically defined outcome in the UK Biobank as did in previous studies [17,18], which was based on hospital inpatient records, self-reported data, and mortality register data to identify the earliest recorded date of AD, VD, and other types of dementia, with a high positive predictive value of all-cause dementia (82.5%) [39]. Details about the ICD-10 codes of dementia are presented in Table S3. Follow-up started from the date of baseline assessment and continued until December 31, 2022 in the study.

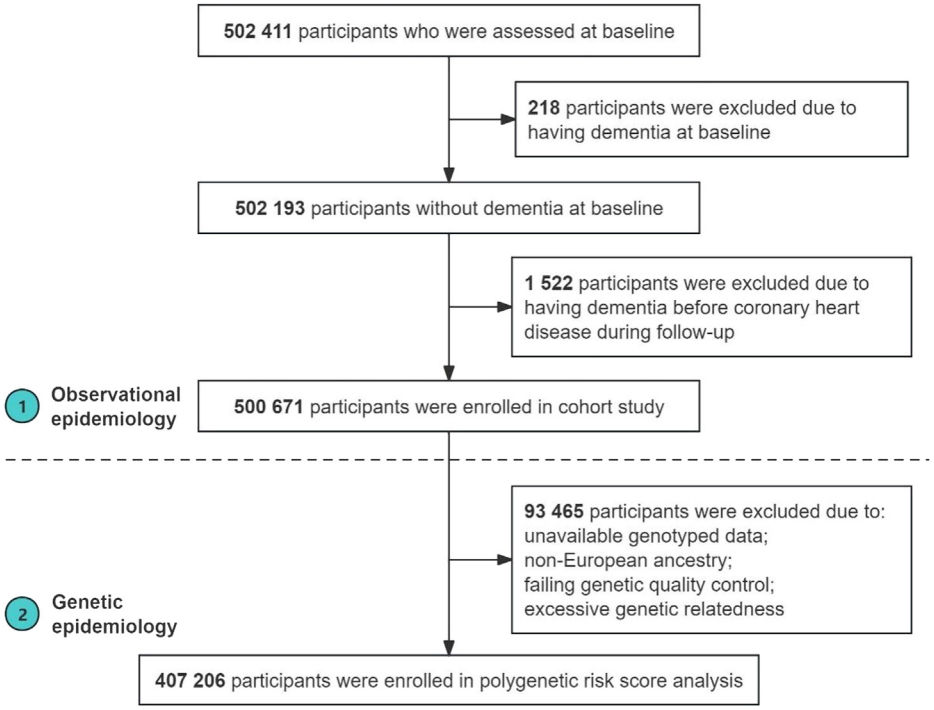

Fig. 1. Flow chart of participant selection for this study.

2.6. Covariates

Covariates included age; sex; race (white or non-white); education (higher educational level or not); current drinking; current smoking (yes or no); physical activity; depressed mood; obesity; chronic comorbidities including hypertension, diabetes, and stroke, and apolipoprotein E4 (ApoE4) status (carrier, or non-carrier). A higher educational level was referred to college or university degree or other professional qualifications. Current drinking was referred to drinking more than once per week. Physical activity was defined as attending moderate or vigorous physical activity for over 10 min at a frequency of more than twice per week. Depressed mood was ascertained if an individual reported feeling down, depressed or hopeless nearly every day or more than half the days over the past two weeks. Obesity was defined as a body mass index $\geq$30 kg/m^2. Hypertension was defined as systolic blood pressure (SBP) $\geq$140 mmHg, diastolic blood pressure (DBP) $\geq$90 mmHg, self-reported diagnosis of hypertension, or use of anti-hypertensive medications. Diabetes was defined as glycated hemoglobin (HbA_{1c}) $\geq$ 48 mmol/mol (6.5%), self-reported diagnosis of diabetes, or use of anti-diabetic treatments. Stroke was defined as self-reported previous stroke or transient ischaemic attack. The details of the covariates are summarized in Table S4.

2.7. Statistical analysis

The analytical baseline used for follow-up was defined as the baseline of UK Biobank (2006–2010). Baseline characteristics are presented as the mean±standard deviation (SD) or the median (IQR) for continuous variables and as frequency (percentage) for categorical variables. Differences in baseline characteristics among participants with early-onset CHD, late-onset CHD, and non-CHD were examined using the linear regression test, the Jonckheere–Terpstra trend test, or the Mantel–Haenszel χ^2 test.

Cox proportional hazards models were applied to calculate hazard ratio (HR) and 95% confidence interval (CI) as measures of the relative risk of all-cause dementia, AD, and VD. Analyses were performed among all participants to investigate the relative risk of dementia with early-onset CHD and late-onset CHD compared with those without CHD. Time (years) from the date of baseline assessment to incident dementia, death, loss to follow-up, or December 31, 2022, whichever occurred first, was used as the time scale. In the fully adjusted models, age, sex, race, education, current drinking, current smoking, physical activity, depressed mood, obesity, hypertension, diabetes, stroke, and ApoE4 status were adjusted. In addition, among 60 077 participants with CHD, we investigated whether participants with early-onset CHD had a higher risk of dementia than those with late-onset CHD. Linear regression models were adopted to examine the association of early-onset CHD with WMH volume, and WMH was transformed to log(WMH) in the models given its skewed distribution. According to the UK Biobank Brain Imaging Documentation, WMH was normalized for head size and was further adjusted for brain MRI measuring positions [37].

Logistic regression model was firstly applied to validate the association between PRS for early-onset CHD and early-onset CHD incidence. To further explore whether having a genetic predisposition to early-onset CHD is associated with incident dementia and WMH, the logistic regression and linear regression models were performed. All models were adjusted for age, sex, and the top 10 principal genetic components. Principal components analysis was used to measure population structure, and principal genetic components were available in the UK Biobank [36]. The PRS for early-onset CHD was analyzed as quartiles based on its overall distribution and as a standardized continuous variable (per 1 SD increment).

In addition, we have conducted several sensitivity analyses to assess the stability of our main results. First, we adopted the Fine-Gray models to account for the competing risk of death [40]. Second, in order to control for possible reverse causality because of the inclusion of prodromal dementia, we excluded participants who developed dementia within 5 years since baseline. Third, we restricted the analyses to a subset of participants aged $\geq$50 years at baseline, as the prevalence of dementia is relatively low in younger adults [1]. Fourth, we ended follow-up on December 31, 2019, to account for the impact of the COVID-19 pandemic, since healthcare services to chronic diseases have been interfered dramatically. Fifth, we further adjusted for antihypertensive drug use, antidiabetic drug use, antithrombotic drug use, low-density lipoprotein cholesterol, and statin use. Sixth, we further adjusted for invasive treatments for CHD including angioplasty, coronary artery bypass grafting,

Table 1
Baseline characteristics of the study participants (n = 500 671).

Characteristic	Early-onset CHD (n = 16 133)	Late-onset CHD (n = 43 944)	Non-CHD (n = 440 594)	P value
Age, years	56.1 ± 7.4	63.1 ± 5.2	56.4 ± 8.1	<0.001*
Female	9 823 (60.9)	11 347 (25.8)	251 499 (57.1)	<0.001§
White	14 593 (90.5)	41 591 (94.7)	414 227 (94.0)	<0.001§
Higher education	5 725 (35.5)	16 533 (37.6)	210 706 (47.8)	<0.001§
Current drinking	8 744 (54.2)	30 165 (68.6)	306 434 (69.6)	<0.001§
Current smoking	2 864 (17.8)	5 132 (11.7)	44 656 (10.1)	<0.001§
Physical activity	11 300 (70.0)	33 291 (75.8)	344 902 (78.3)	<0.001§
Depressed mood	1 717 (10.6)	2 183 (5.0)	20 271 (4.6)	<0.001§
Obesity	6 623 (41.1)	14 572 (33.2)	100 491 (22.8)	<0.001§
BMI, kg/m^2	29.6 ± 5.7	28.7 ± 4.7	27.2 ± 4.7	<0.001*
Hypertension	11 226 (69.6)	34 295 (78.0)	230 156 (52.2)	<0.001§
Diabetes	2 691 (16.7)	6 464 (14.7)	21 274 (4.8)	<0.001§
Stroke	849 (5.3)	1 958 (4.5)	5 575 (1.3)	<0.001§
SBP, mmHg	136.8 ± 18.5	143.7 ± 18.8	137.3 ± 18.6	<0.001*
DBP, mmHg	81.3 ± 10.8	82.4 ± 10.5	82.3 ± 10.1	<0.001*
HbA_{1c}, mmol/mol	39.51±10.81	38.85±8.84	35.72±6.21	<0.001*
LDL-C, mmol/L	3.26±0.97	3.33±0.97	3.60±0.84	<0.001*
Antihypertensive drug use	7 789 (48.3)	20 446 (46.5)	75 027 (17.0)	<0.001§
Antidiabetic drug use	1 817 (11.3)	4 125 (9.4)	12 072 (2.7)	<0.001§
Stain use	6 183 (46.8)	15 247 (41.3)	41 497 (10.9)	<0.001§
Antithrombotic drug use	1 495 (9.3)	3 241 (7.4)	3 728 (0.9)	<0.001§
Invasive treatments for CHD	3 190 (19.8)	7 418 (16.9)	32 (0.1)	<0.001§
ApoE4 carrier	3 818 (23.7)	10 345 (23.5)	103 208 (23.4)	0.382§
Follow-up time	13.6 (12.8–14.5)	13.6 (12.7–14.4)	13.8 (13.1–14.5)	<0.001†

The results are presented as the mean±standard deviation, No. (%) or median (interquartile range).
* Calculated by using the linear regression test.
† Calculated by using the Jonckheere–Terpstra trend test.
§ Calculated by using the Mantel–Haenszel χ^2.BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA_{1c}, glycated hemoglobin; ApoE4, apolipoprotein E4; LDL-C, low-density lipoprotein cholesterol; Invasive treatments for CHD including angioplasty, coronary artery bypass grafting, etc.

etc. Seventh, 12 538 participants with early-onset CHD were further excluded to explore whether PRS for early-onset CHD is associated with dementia incidence and WMH among participants without early-onset CHD. Eighth, we conducted subgroup analyses and compared the difference between the two regression coefficients by using the Z test proposed by Altman and Bland to identify potential modifying effects from covariates on the associations of early-onset CHD with dementia [41].

Statistical analyses were performed with SAS 9.4 and R 4.2.2. All analyses were two-sided, with $P < 0.05$ considered significant.

3. Results

3.1. Baseline characteristics

A total of 500 671 individuals (female: 272 669, 54.5%; mean age: 57.0 ± 8.1 years) were included in the prospective cohort study and 407 206 individuals were included in the PRS analysis (Fig. 1). Among 60 077 participants with CHD, 16 133 (26.9%) participants were identified as early-onset CHD, and 43 944 participants were identified as late-onset CHD. Table 1 shows the baseline characteristics of participants. Generally, participants with early-onset CHD were younger and had larger proportions of women, current smoking, depressed mood, obesity, diabetes, stroke, antihypertensive drug use, antidiabetic drug use, stain use, antithrombotic drug use, and invasive treatments for CHD.

3.2. Associations of early-onset CHD and its PRS with incident dementia

During a median follow-up of 13.8 years (IQR: 13.0 to 14.5 years), 9 294 all-cause dementia, 4 157 AD, and 2 001 VD occurred. As presented in Table 2, those who had early-onset CHD exhibited a significantly highest risk of dementia. Compared with participants without CHD, fully adjusted HRs of early-onset CHD for incident all-cause dementia, AD, and VD were 1.99 (95% CI: 1.81 to 2.19), 1.61 (95% CI: 1.38 to 1.89), and 2.66 (95% CI: 2.22 to 3.20), respectively. Furthermore, significant trends were found for per-group increase (all-cause dementia: HR=1.31, 95% CI: 1.26 to 1.36, $P < 0.001$; AD: HR=1.12, 95% CI: 1.05 to 1.20, $P = 0.001$; VD: HR=1.57, 95% CI: 1.46 to 1.70, $P < 0.001$).

Table 2
Association of early-onset coronary heart disease (CHD) with incident dementia among all participants (n = 500 671).

Outcome	Events/Total	HR (95% CI)*	P value
All-cause dementia			
Non-CHD	6 908/440 594	Reference	/
Late-onset CHD	1 904/43 944	1.20 (1.14 to 1.27)	<0.001
Early-onset CHD	482/16 133	1.99 (1.81 to 2.19)	<0.001
Trend	/	1.31 (1.26 to 1.36)	<0.001
Alzheimer's disease			
Non-CHD	3 269/440 594	Reference	/
Late-onset CHD	714/43 944	0.99 (0.91 to 1.07)	0.746
Early-onset CHD	174/16 133	1.61 (1.38 to 1.89)	<0.001
Trend	/	1.12 (1.05 to 1.20)	0.001
Vascular dementia			
Non-CHD	1 306/440 594	Reference	/
Late-onset CHD	556/43 944	1.50 (1.35 to 1.67)	<0.001
Early-onset CHD	139/16 133	2.66 (2.22 to 3.20)	<0.001
Trend	/	1.57 (1.46 to 1.70)	<0.001

* Adjusted for age, sex, race, and education, current drinking, current smoking, physical activity, depressed mood, obesity, hypertension, diabetes, stroke, and apolipoprotein E4 status.HR, hazard ratio; CI, confidence interval.

Table 3
Associations of early-onset coronary heart disease (CHD) with incident dementia among participants with CHD (n = 60 077).

Outcome	HR (95% CI)*	P value
All-cause dementia	1.56 (1.39 to 1.75)	<0.001
Alzheimer's disease	1.58 (1.30 to 1.91)	<0.001
Vascular dementia	1.55 (1.24 to 1.93)	<0.001

* Adjusted for age, sex, race, and education, current drinking, current smoking, physical activity, depressed mood, obesity, hypertension, diabetes, stroke, and apolipoprotein E4 status.HR, hazard ratio; CI, confidence interval.

In addition, among 60 077 participants with CHD, early-onset CHD was associated with a higher risk of all-cause dementia, AD, and VD compared with late-onset CHD with a HR of 1.56 (95% CI: 1.39 to 1.75), 1.58 (95% CI: 1.30 to 1.91), and 1.55 (95% CI: 1.24 to 1.93), respectively (Table 3).

The PRS analysis revealed that PRS was significantly associated with early-onset CHD (OR for the highest quartile: 2.36, 95% CI: 2.24 to 2.49, Table S5), and per 1 SD increment in PRS corresponded to an OR of 1.12, 1.15, and 1.13 for all-cause dementia, AD, and VD, respectively (Table 4). When divided into quartiles, individuals in the highest quartile had the highest risk of dementia when compared with those in the lowest quartile, and there was a trend that the dementia risk increased with quartiles (P < 0.001).

3.3. Associations of early-onset CHD and its PRS with WMH volume

In 40 290 participants completed brain MRI scans during a median follow-up of 9.3 years (IQR: 4.3 to 13.8 years) since baseline, a significant trend was detected, with early-onset CHD being related to the largest WMH volume (per-group increment: β: 0.031, 95% CI: 0.005 to 0.057, P = 0.018, Table 5).

In the PRS analysis, we observed a positive association between PRS for early-onset CHD and WMH (per 1 SD increment: β: 0.012, 95% CI: 0.003 to 0.021, P = 0.011). Individuals in the highest quartile had the largest volume of WMH when compared with those in the lowest quartile (β: 0.042, 95% CI: 0.017 to 0.068, P = 0.001), and a trend was found that the volume of WMH increased with quartiles (P = 0.002, Table 6).

3.4. Sensitivity analysis

The main results remained robust after further adjusting for the competing risk of death, excluding participants diagnosed with dementia within 5 years since baseline, restricting to participants aged ≥50 years at baseline, ending follow-up on December 31, 2019, further adjusting for medication use and invasive treatment for CHD (Tables S6–S11). In addition, the associations of early-onset CHD PRS with incident dementia and WMH did not differ appreciably after excluding participants with early-onset CHD (Tables S12–S13). Among participants with CHD, subgroup analyses revealed that current smoking modified the associations between early-onset CHD and incident all-cause dementia; race, higher education, current smoking, and physical activity modified the associations between early-onset CHD and incident AD; and current drinking modified the associations between early-onset CHD and incident VD (Figures S2–S4).

Table 5
Association of early-onset coronary heart disease (CHD) with white matter hyperintensity among all participants with brain MRI (n = 40 290).

Group	β (95% CI)*	P value**
Non-CHD	Reference	/
Late-onset CHD	0.012 (−0.034 to 0.059)	0.598
Early-onset CHD	0.077 (0.017 to 0.137)	0.012
Trend	0.031 (0.005 to 0.057)	0.018

* White matter hyperintensity volumes were log-transformed given its skewed distribution.

** Adjusted for age, sex, race, and education, current drinking, current smoking, physical activity, depressed mood, obesity, hypertension, diabetes, stroke, apolipoprotein E4 status, and brain MRI measuring positions.HR, hazard ratio; CI, confidence interval.

Table 6
Association of early-onset coronary heart disease (CHD) polygenic risk score (PRS) with white matter hyperintensity (n = 35 074).

PRS	β (95% CI)*	P value**
Q1	Reference	/
Q2	0.014 (−0.012 to 0.040)	0.284
Q3	0.014 (−0.011 to 0.040)	0.278
Q4	0.042 (0.017 to 0.068)	0.001
P for trend	0.002	/
Per 1 SD increment	0.012 (0.003 to 0.021)	0.011

* White matter hyperintensity volumes were log-transformed given its skewed distribution.

** Adjusted for age, sex, and the top 10 principal genetic components.SD, standard deviation.

4. Discussion

In this prospective cohort study of middle-aged and older adults, compared with participants without CHD, participants with early-onset CHD had an increased risk of incident all-cause dementia, AD, and VD over a median of 13.8 years and a larger WMH volume over a median of 9.3 years after adjusting for multiple known risk factors. Moreover, we observed that the genetic susceptibility of early-onset CHD was associated with a higher risk of dementia and a larger WMH volume.

The most important finding of our study is the increased risk of dementia related to observed and genetically predicted early-onset CHD. There is substantial evidence in the literature supporting that CHD

Table 4
Association of early-onset coronary heart disease (CHD) polygenic risk score (PRS) with incident dementia (n = 407 206).

PRS	All-cause dementia		Alzheimer's disease		Vascular dementia	
	Events	OR (95%CI)*	Events	OR (95%CI)*	Events	OR (95%CI)*
Q1	1 664	Reference	742	Reference	341	Reference
Q2	1 911	1.17 (1.09 to 1.25)	843	1.15 (1.04 to 1.27)	436	1.30 (1.13 to 1.50)
Q3	1 917	1.17 (1.09 to 1.25)	872	1.19 (1.08 to 1.31)	416	1.23 (1.07 to 1.42)
Q4	2 191	1.37 (1.28 to 1.46)	1 029	1.43 (1.30 to 1.57)	467	1.41 (1.23 to 1.62)
P for trend	/	<0.001	/	<0.001	/	<0.001
Per 1 SD increment	/	1.12 (1.09 to 1.15)	/	1.15 (1.11 to 1.19)	/	1.13 (1.08 to 1.19)

* Adjusted for age, sex, and the top 10 principal genetic components.SD, standard deviation.

events were associated with a higher risk of incident dementia, yet most studies were restricted to older adults [9]. Since CHD is a chronic disease with long durations, especially considering the trend towards a younger onset age in recent years [10], it is reasonable to assume that, compared with non-CHD and late-onset CHD, CHD occurring earlier in life could be accompanied with longer exposure to the cerebral ischemic and neurological insult from the CHD pathology, such as cerebral hypoperfusion and hypoxia [42,43], cerebral small vessel diseases [44–46], and neurodegeneration [47–49], and thus increase the risk of subsequent dementia. Indeed, a recent work by Jiang and colleagues supported this assumption, which demonstrated that early-onset CVD (≤60 years) contributed to worse cognitive function and accelerated cognitive decline over a follow-up period of 5 years [50]. Findings of the present study align with our prior research, which showed the risk of dementia increased with the descending onset age of CHD [14]. This association could be driven by the synergistic effect of a steeper cognitive decline activated by the occurrence of early-onset CHD and a greater cumulative cardiovascular burden accompanied with CHD [51]. To the best of our knowledge, this is the first study to explore the association of the genetic susceptibility of early-onset CHD with incident dementia, which provides further evidence supporting the association from the genetic perspective. Prior studies have reported the genetic risk of dementia [52,53], and our study demonstrates that the genetic susceptibility of known risk factors (i.e., CHD in this study) also correlates with dementia. Likewise, the genetic susceptibility of another risk factor of dementia, atrial fibrillation, has recently been found to be associated with all-cause dementia and VD [54].

Another principle finding of our study is the largest WMH volume in early-onset CHD participants. A similar result was observed in the Coronary Artery Risk Development in Young Adults study, which demonstrated that early-onset CVD (≤60 years) was associated with a larger WMH volume in 656 participants [50]. Moreover, a recent study has identified the genetic correlations between various heart and brain features, and adverse heart traits were found to be associated with poorer white matter microstructure in over 40 000 subjects [55]. This is compatible with findings of the present study, as adverse heart traits, such as a lower cardiac index, were identified in participants with early-onset CHD, along with the worse white matter health. According to previous research, the cumulative exposure to multiple vascular risk factors (VRFs) (e.g., hypertension, diabetes, smoking, obesity) was also associated with a larger WMH volume [56,57]. Since a larger WMH volume was closely related to accelerated cognitive decline and could be an indicator of dementia, which has been found in both previous studies and the present study [25,26] (Table S14), the larger WMH volume observed in participants with early-onset CHD might be one of the underlying biological mechanisms linking early-onset CHD to the increased risk of dementia.

Though the exact mechanisms linking early-onset CHD to increased risk of dementia are not fully elucidated, several hypotheses may be helpful to understand the association. First, Schievink et al. and our previous work have found that, before the occurrence of a CVD/CHD event, cognitive ageing was compensatory although VRF have existed for years, and a CVD/CHD event may act as a trigger of accelerated cognitive decline [51,58]. In addition, the Whitehall II study has demonstrated a dose-response relationship between CHD duration and cognitive function with a longer duration of CHD being related to poorer cognition [59]. In the context of a same life expectancy, there is no doubt that the surviving periods of early-onset CHD patients will be prolonged, which means an earlier timepoint of cognitive deterioration, accompanied by a greater cumulative burden of both CHD and shared vascular risk factors of CHD and dementia (hypertension, diabetes, smoking, etc.) during the lifespan. The pathophysiological changes driven by CHD and VRF [60], such as cerebral hypoperfusion and hypoxia [42,43], cerebral small vessel diseases [44–46], and neurodegeneration could be more serious and extensive [47–49]. In parallel with this, our prior work has shown that the cumulative burden of SBP and pulse pressure could increase risk of subsequent dementia [61]. Thus, it sounds quite reasonable that early-onset CHD occurring early in life may have a more profound impact on cognitive deterioration and brain morphology due to longer periods of exposure. The larger WMH volume observed in early-onset CHD participants may be a reflection of the detrimental impact on brain health. Second, apart from the longer exposure, early-onset CHD itself also exerted sustained neuropathological damage. An age-dependent association of CVD and VRF with dementia has been found recently, suggesting that the pathophysiology of dementia in young and older adults might be heterogeneous with a minor impact of CVD or VRF in advanced age [62,63]. Patients with early-onset CHD may represent a subset of individuals who are more susceptible to the negative consequences of VRF and therefore are predisposed to dementia, compared with individuals with late-onset CHD or remained CHD-free [63].

This study has important implications for public health practice by identifying early-onset CHD patients as a vulnerable population for dementia. First, additional attention should be paid to the neurocognitive health of early-onset CHD patients. For instance, cognitive assessments are warranted during the regular follow-up after the occurrence of early-onset CHD to screen for the early sign of cognitive deterioration and conduct timely intervention to postpone or halt the progression of disease. Second, in the context that global burdens and costs of CVDs and dementia are increasing dramatically, it is of critical significance to maintain an ideal cardiovascular health throughout the life course [64], as evidence is accumulating that a poor cardiovascular health in early adulthood or midlife is closely connected with early-onset CVDs (including early-onset CHD) and dementia [65–68]. Optimizing and preserving cardiovascular health by keeping a healthy lifestyle (i.e., Life's Essential 8 including diet, physical activity, nicotine exposure, sleep health, body mass index, blood lipids, blood glucose, and blood pressure) is highly recommended by the American College of Cardiology/American Heart Association [69].

There were several strengths of this study. First, this is the largest study examining the association between early-onset CHD and incident dementia. Empowered by the large sample size and adequate CHD and dementia events, we were able to further test the associations between early-onset CHD and three types of dementia. Second, we further validate the associations of early-onset CHD with dementia and WMH from the genetic perspective by using PRS analysis. Third, early-onset CHD diagnoses identified by ICD-10 from linked hospital inpatient records guaranteed a reliable measure of exposure. Besides, the algorithmically defined outcomes in the UK Biobank identified with a standardized approach had a high positive predictive value of dementia (82.5%) [39].

Despite these strengths, certain limitations should be noted. First, a conclusion of a causal relationship cannot be drawn from this study. Second, over 94% of included participants were white and this sample cannot represent the general UK population. Therefore, the present findings may only be applied to the UK white population and verification in other populations is needed. Third, brain MRI scans were only performed in a subset of participants instead of the whole population, further studies are warranted to validate this association. Since only a small sample of CHD participants had data on brain MRI, we were unable to examine the association of early-onset CHD with WMH among CHD participants. Fourth, though we have adjusted for many potential confounders, there might be residual confounding factors that have not been considered, such as the severity of CHD, changes in lifestyle, and medication use after the diagnosis of CHD, which might partly explain the gap between the HRs of observational study and the ORs of the PRS analysis (Table 2 & Table 4). Fifth, 1 740 (0.3%) participants were excluded, which might lead to selection bias (Table S15).

5. Conclusion

The present study demonstrated that early-onset CHD and genetic susceptibility were associated with an increased risk of incident dementia and a larger WMH volume. Our findings have important implications

for public health, as it underlines that survivors of early-onset CHD constitute important targets and deserve more attention in planning and conducting dementia prevention strategies in the future. Moreover, it emphasizes the importance of CHD prevention in young individuals from the neuropathological perspective.

Declaration of competing interest

All other authors declare that there are no competing interests.

CRediT authorship contribution statement

Jie Liang: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Yanyu Zhang:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Wenya Zhang:** Writing – review & editing. **Yang Pan:** Writing – review & editing. **Darui Gao:** Writing – review & editing. **Jingya Ma:** Writing – review & editing. **Yuling Liu:** Writing – review & editing. **Yiwen Dai:** Writing – review & editing. **Mengmeng Ji:** Writing – review & editing. **Wuxiang Xie:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Fanfan Zheng:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Ethical statement

The UK Biobank has received ethical approval from the North West Multi-center Research Ethics Committee (MREC) (299116). Written informed consent was obtained from all participants.

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Data sharing: The data used for analysis in this study is available from the UK Biobank project site, subject to registration and application process. Further details can be found at https://www.ukbiobank.ac.uk. Fanfan Zheng and Wuxiang Xie had full access to the data in the study.

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Declaration of Generative AI and AI-assisted technologies in the writing process

Generative AI and AI-assisted technologies were not used in the writing process.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2024.100041.

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