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ORIGINAL RESEARCH

Association Between Onset Age of Coronary Heart Disease and Incident Dementia: A Prospective Cohort Study

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BACKGROUND: The association of age at coronary heart disease (CHD) onset with incident dementia remains unexplored. This study aimed to examine whether younger onset age of CHD is associated with a higher risk of incident dementia.

METHODS AND RESULTS: Data were obtained from the UK Biobank. Information on the diagnosis of CHD and dementia was collected at baseline and follow-ups. Propensity score matching method and Cox proportional hazards models were used to evaluate the association between different ages at CHD onset and incident dementia. A total of 432 667 adults (mean±SD age, 56.9±8.1 years) were included, of whom 11.7% had CHD. Compared with participants without CHD, participants with CHD exhibited higher risks of developing all-cause dementia, Alzheimer's disease, and vascular dementia. More importantly, younger age at CHD onset (per 10-year decrease) was significantly associated with elevated risks of all-cause dementia (hazard ratio [HR], 1.25 [95% CI, 1.20–1.30]; $P<0.001$), Alzheimer's disease (HR, 1.29 [95% CI, 1.20–1.38]; $P<0.001$), and vascular dementia (HR, 1.22 [95% CI, 1.13–1.31]; $P<0.001$). After propensity score matching, patients with CHD had significantly higher risks of all-cause dementia, Alzheimer's disease, and vascular dementia than matched controls among all onset age groups, and the HRs gradually elevated with decreasing age at CHD onset.

CONCLUSIONS: Younger onset age of CHD is associated with higher risks of incident all-cause dementia, Alzheimer's disease, and vascular dementia, underscoring the necessity to pay attention to the neurocognitive status of individuals diagnosed with CHD at younger age to conduct timely interventions to attenuate subsequent risk of incident dementia.

Key Words: coronary heart disease ■ dementia ■ onset age ■ propensity score matching ■ UK Biobank

Dementia is one of the top-ranked causes of dependency and disability among older adults.[1,2] According to a recent report published by the World Health Organization, there were 55.2 million people worldwide living with dementia in 2019, and the number was estimated to increase to 78 million in 2030 based on the current prevalence rate.[1] Because of improved longevity and increase of dementia risk factors, death caused by dementia has increased dramatically during the past 20 years and reached 1.6 million in 2019, making dementia the seventh leading cause of death.[1] With its ever-increasing prevalence, dementia has produced huge public health burdens.[2,3] As there is no cure for dementia currently, early detection and intervention of risk factors for dementia are of vital significance to decelerate cognitive decline and prevent, or at least delay, the onset of dementia.[1,4]

Among the risk factors for dementia, cardiovascular diseases (CVDs) are gaining increasing attention because of the well-recognized shared risk factors

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CLINICAL PERSPECTIVE

What Is New?

- In this large cohort study of older adults (n=432 667), a younger onset age of coronary heart disease is associated with increased risks of all-cause dementia, Alzheimer disease, and vascular dementia.
- Individuals diagnosed with coronary heart disease before the age of 45 years were the most vulnerable to subsequent dementia.

What Are the Clinical Implications?

- For individuals diagnosed with coronary heart disease at a young age, additional attention should be paid to careful monitoring of cognitive status, and timely intervention, such as cognitive training, could be implemented once signs of cognitive deteriorations are detected.

Nonstandard Abbreviations and Acronyms

MAAS	Maastricht Aging Study
VD	vascular dementia

(eg, hypertension, diabetes, and smoking).[4–6] One of the dominant CVDs that has been found to be closely associated with cognitive impairment and dementia in recent years is coronary heart disease (CHD).[7–11] Previously, our group has explored the progression of cognitive decline before and after incident CHD and found that adults experienced accelerated cognitive decline after incident CHD.[10] Evidence from a meta-analysis showed that patients with CHD exhibited an increased risk of dementia, with a pooled relative risk of 1.26.[12] Because CHD occurs in a wide age range and longer duration of CHD often leads to worse health outcomes attributable to accumulated vascular lesions,[13–16] it is reasonable to assume that younger age at CHD onset might accelerate cognitive deterioration during the relatively longer period after the event and thus lead to a higher risk of incident dementia. To date, whether CHD diagnosed at a younger age is associated with an increased risk of developing dementia remains undetermined. Therefore, by using data from the UK Biobank, of which data on age at CHD onset and subsequent incident dementia were collected over a relatively long follow-up period, we aimed to investigate the association of age at CHD onset with subsequent risk of incident dementia.

METHODS

The data used for analysis in this study are available from the UK Biobank project site, subject to registration and application process. Further details can be found at https://www.ukbiobank.ac.uk.

Study Design and Population

The UK Biobank is an ongoing population-based cohort involving sociodemographic and medical information of >500 000 community dwellers, aged ≥40 years, in the United Kingdom. Baseline data were collected between 2006 and 2010. Details about the design of the UK Biobank have been well documented elsewhere.[17,18] The UK Biobank has received ethical consent from the North West Multi-Centre Research Ethics Committee (299116). Informed consents were obtained from all participants.

The Figure presents the participant selection of this study. Briefly, among the 502 411 participants assessed at baseline, participants with dementia or stroke before baseline (n=8689), without complete data on covariates (n=58 905), or having dementia before CHD onset during follow-ups (n=2150) were excluded. The remaining 432 667 participants were enrolled in the analysis to evaluate the association of CHD status with incident dementia. Then, 50 445 participants with data on age at CHD onset were included in the analysis to investigate the association between age of CHD onset and incident dementia. Finally, 50 346 participants with CHD and their matched controls were included in the propensity score matching analyses to evaluate the associations between CHD and incident dementia among different age groups of CHD onset.

Ascertainment of CHD and Age at CHD Onset

CHD was identified using self-reported data, hospital inpatient records, and mortality register data with the *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes of I20 to I25, including angina pectoris, acute myocardial infarction, subsequent myocardial infarction, certain current complications following acute myocardial infarction, other acute ischemic heart diseases, and chronic ischemic heart disease. Age at CHD onset was ascertained using self-reported age at CHD onset or calculated using date of birth and date of first occurrence of CHD. Detailed information is presented in Table S1.

Ascertainment of Dementia

Algorithmically defined dementia was ascertained using self-reported data, hospital inpatient records,

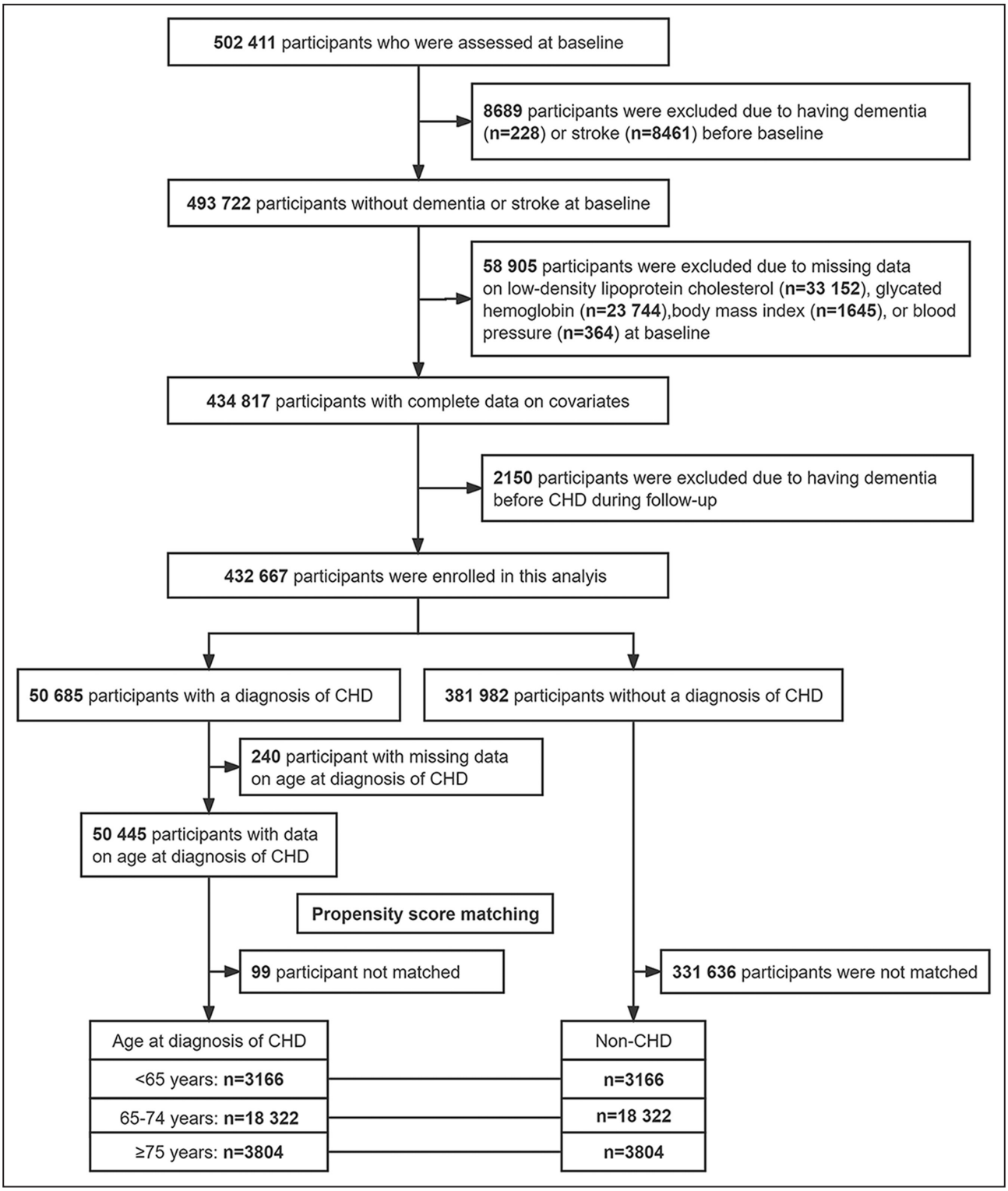

Figure. Flowchart of participant selection for this study.
CHD indicates coronary heart disease.

and mortality register data in the UK Biobank.[19] All-cause dementia, Alzheimer disease (AD), and vascular dementia (VD) were considered as outcomes in the present analyses. The *ICD-10* codes used to define dementia are detailed in Table S2. All outcomes were followed up to December 31, 2021.

Covariates

Covariates include age, sex, race (White or non-White [Mixed, Asian, Black, Chinese, and other ethnicities]), educational level (higher educational level or not), body mass index, low-density lipoprotein cholesterol, current smoking (yes or no), current drinking (once per week or more), exercise, depressed mood, hypertension, diabetes, statin use (yes or no), and apolipoprotein E4 status (carrier, noncarrier, or untyped). A higher educational level was defined as college or university degree or other professional qualifications. Exercise was defined as attending moderate or vigorous physical activity for >10 minutes at least twice per week. Depressed mood was defined if a participant reported feeling down, depressed, or hopeless nearly every day or more than half the days over the past 2 weeks. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, self-reported diagnosis of hypertension, or use of antihypertensive medications. Diabetes was defined as glycated hemoglobin ≥6.5%, self-reported diagnosis of diabetes, or use of antidiabetic therapy. The details of the covariates are summarized in Table S3.

Statistical Analysis

Baseline characteristics are presented as the mean±SD for continuous variables and frequency (percentage) for categorical variables. The effect sizes of differences in baseline characteristics between participants with and without CHD are presented as standardized mean differences for continuous outcomes and φ coefficient for dichotomous outcomes, with standardized mean difference or φ coefficient <–0.1 or >0.1 considered significant.

Cox proportional hazards models were used to evaluate the associations of CHD and its onset age with incident dementia. The proportional hazards assumptions were tested by using weighted Schoenfeld residuals.[20] Years since baseline to incident dementia, death, or the end of follow-up (years)×dementia (0 or 1) was the dependent variable in Cox proportional hazards models. First, we tested the association of CHD with dementia among the total population (n=432 667). Second, we tested the association between age at CHD onset and dementia among participants with CHD (n=50 445). Third, we divided participants with CHD into 3 groups according to their age at onset: <45, 45 to 59, and ≥60 years. Then, a matched control was randomly selected for each participant with CHD from CHD-free participants in each age group by using 1:1 propensity score matching with the nearest-neighbor method, which accounted for age, sex, race, education, body mass index, low-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, glycated hemoglobin, current smoking, current drinking, exercise, depressed mood, hypertension, diabetes, statin use, and apolipoprotein E4 status. The matched pairs were considered as a cluster when modeling. The association of CHD with dementia was tested in 3 age groups.

Several sensitivity analyses were conducted. First, subgroup analyses were performed to identify potential modifying effects from covariates on the associations of CHD and its onset age with incident dementia. The *Z* test proposed by Altman and Bland was used to compare the difference between the 2 regression coefficients from subgroup analysis.[21] Second, competing risk models were used to assess the influence of death as a competing event on the association of age at CHD onset with incident dementia.[22] Third, we excluded outcomes that occurred within 5 years since baseline and repeated our main analyses to control for potential reverse causality. Fourth, we restricted the analyses to a subgroup of participants aged ≥50 years at baseline because the prevalence of dementia is relatively low in younger participants. Fifth, because the CHD durations were not comparable among 3 onset age groups (median: ≥60 years, 6 years; 45–59 years, 17 years; and <45 years, 29 years; P_{trend}<0.001), we further adjusted for CHD duration to eliminate its effect on risk of dementia. Sixth, younger onset age group had larger proportion of antihypertensive drug and antidiabetic drug use (P_{trend}<0.001); thus, we further adjusted for antihypertensive drug use and antidiabetic drug use in our main analyses. Seventh, we set the deadline of follow-up as December 31, 2019, and repeated our main analyses to account for the influence of COVID-19 pandemic on diagnosis of CHD and dementia because hospital admission and primary care services to chronic diseases have been disrupted significantly during the period.

Statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC). All analyses were 2-sided, with P<0.05 considered significant.

RESULTS

Baseline Characteristics

A total of 432 667 participants (women, 236 084 [54.6%]; mean±SD age, 56.9±8.1 years) were included in the present analysis, of whom 50 685 (11.7%) had CHD. Among all participants with CHD, 10 719 (21.2%) underwent revascularization or coronary artery bypass grafting. Table 1 shows the baseline characteristics of participants grouped by CHD status. Overall, participants with CHD were older; had higher body mass index, systolic blood pressure, and glycated

Table 1. Baseline Characteristics of the Study Participants According to History of CHD at Baseline or Incident CHD During Follow-Up (n=432 667)

Characteristic	CHD (n=50 685)	Non-CHD (n=381 982)	Effect size*
Age, y	61.3±6.7	56.4±8.1	0.615
Female sex	17 892 (35.3)	218 192 (57.1)	0.141
White race	47 677 (94.1)	361 286 (94.6)	−0.007
Higher education	19 070 (37.6)	185 041 (48.4)	−0.070
Current smoking	6605 (13.0)	38 202 (10.0)	0.032
Current drinking	33 107 (65.3)	267 786 (70.1)	−0.033
Exercise	37 898 (74.8)	300 522 (78.7)	−0.030
Depressed mood	3242 (6.4)	16 947 (4.4)	0.030
Hypertension	38 317 (75.6)	198 128 (51.9)	0.153
Diabetes	7528 (14.9)	17 742 (4.6)	0.140
BMI, kg/m^2	28.9±5.0	27.2±4.7	0.373
SBP, mm Hg	141.7±18.9	137.3±18.5	0.239
DBP, mm Hg	82.1±10.5	82.3±10.1	−0.019
HbA_{1c}, mmol/mol	38.9±9.2	35.7±6.1	0.494
LDL-C, mmol/L	3.3±1.0	3.6±0.8	−0.369
Statin use	22 227 (43.9)	41 012 (10.7)	0.302
ApoE4 carrier	12 311 (24.3)	91 286 (23.9)	0.003

The results are presented as mean±SD or frequency (percentage). ApoE4 indicates apolipoprotein E4; BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; HbA_{1c}, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

*The effect sizes are standardized mean differences for continuous outcomes and φ coefficient for dichotomous outcomes.

hemoglobin levels; had lower levels of low-density lipoprotein cholesterol; had a smaller proportion of women; and had a larger proportion of hypertension, diabetes, and statin use. A nationwide multicenter study from the United States has revealed that women were at lower risk of coronary artery disease,[23] which was consistent with findings of the present study. According to a review published in *European Heart Journal*, women were relatively more underdiagnosed or had a delay in diagnosis of ischemic heart disease,[24] which may partly explain the lower rate of CHD in women in the present study.

Association of CHD With Incident Dementia

During a median follow-up of 12.8 years (interquartile range, 12.1–13.6 years), 5876 cases of all-cause dementia, 2540 cases of AD, and 1220 cases of VD were identified. As shown in Table 2, after adjusting for multiple covariates among the total population (n=432 667), participants with CHD exhibited significantly higher risks of developing all-cause dementia (hazard ratio [HR], 1.36 [95% CI, 1.28–1.45]; *P*<0.001), AD (HR, 1.13 [95% CI, 1.02–1.24]; *P*=0.019), and VD (HR, 1.78 [95% CI, 1.56–2.02]; *P*<0.001).

Table 2. Associations of CHD With Incident All-Cause Dementia, AD, and VD Among Total Participants (n=432 667)

Outcome	HR (95% CI) for CHD vs non-CHD	*P* value
All-cause dementia		
Model 1*	1.55 (1.46–1.65)	<0.001
Model 2†	1.36 (1.28–1.45)	<0.001
AD		
Model 1*	1.26 (1.14–1.38)	<0.001
Model 2†	1.13 (1.02–1.24)	0.019
VD		
Model 1*	2.21 (1.95–2.50)	<0.001
Model 2†	1.78 (1.56–2.02)	<0.001

AD indicates Alzheimer disease; CHD, coronary heart disease; HR, hazard ratio; and VD, vascular dementia.

*Adjusted for age, sex, race, and education.

†Further adjusted for baseline body mass index, low-density lipoprotein cholesterol, current smoking, current drinking, exercise, depressed mood, hypertension, diabetes, statin use, and apolipoprotein E4 status.

Association of Age at CHD Onset With Incident Dementia Among Participants With CHD

As presented in Table 3, among 50 445 participants with CHD, age at onset was significantly associated with subsequent dementia risk; that is, those diagnosed at younger age had higher risks for developing

Table 3. Associations of Age at CHD Onset With Incident All-Cause Dementia, AD, and VD Among Participants With CHD (n=50 445)

Outcome	HR (95% CI)*	*P* value
All-cause dementia		
≥60 y (n=28 911)	Reference	…
45–59 y (n=18 357)	1.32 (1.18–1.49)	<0.001
<45 y (n=3177)	1.71 (1.38–2.12)	<0.001
Per 10-y decrease	1.25 (1.20–1.30)	<0.001
AD		
≥60 y (n=28 911)	Reference	…
45–59 y (n=18 357)	1.25 (1.02–1.52)	0.029
<45 y (n=3177)	1.75 (1.22–2.50)	0.003
Per 10-y decrease	1.29 (1.20–1.38)	<0.001
VD		
≥60 y (n=28 911)	Reference	…
45–59 y (n=18 357)	1.33 (1.07–1.65)	0.010
<45 y (n=3177)	1.65 (1.10–2.47)	0.015
Per 10-y decrease	1.22 (1.13–1.31)	<0.001

AD indicates Alzheimer's disease; CHD, coronary heart disease; HR, hazard ratio; and VD, vascular dementia.

*Adjusted for age, sex, race, education, baseline body mass index, low-density lipoprotein cholesterol, current smoking, current drinking, exercise, depressed mood, hypertension, diabetes, statin use, and apolipoprotein E4 status.

all-cause dementia (per 10-year decrease: HR, 1.25 [95% CI, 1.20–1.30]; *P*<0.001), AD (per 10-year decrease: HR, 1.29 [95% CI, 1.20–1.38]; *P*<0.001), and VD (per 10-year decrease: HR, 1.22 [95% CI, 1.13–1.31]; *P*<0.001).

Association of CHD With Incident Dementia Among Different Onset Age Groups Based on Propensity Score Matching Data

We then further investigated the relationship between CHD and incident dementia in different onset age groups among 50 346 patients with CHD and their matched controls by using propensity score matching method. As shown in Table S4, after propensity score matching, no significant difference was detected between participants with and without CHD in all covariates. Table 4 shows that CHD diagnosed before the age of 45 years was associated with the highest HR for incident dementia compared with those without CHD (HR, 2.40 [95% CI, 1.79–3.20]; *P*<0.001), followed by CHD diagnosed between the ages of 45 and 59 years (HR, 1.46 [95% CI, 1.32–1.62]; *P*<0.001), and then CHD diagnosed at the age of ≥60 years (HR, 1.11 [95% CI, 1.03–1.19]; *P*=0.005). The results for AD and VD were similar.

Sensitivity Analysis

As shown in Figures S1 through S5, the results from subgroup analyses were similar to those from our main analyses. Interestingly, our subgroup analyses found that statin use, current drinking, and diabetes modified the association between CHD and incident dementia.

Table 4. Associations of CHD With Incident All-Cause Dementia, AD, and VD Among Different Onset Age Groups After Propensity Score Matching (n=100 692)

Outcome	HR (95% CI) for CHD vs non-CHD	*P* value
All-cause dementia		
≥60 y (n=57 716)	1.11 (1.03–1.19)	0.005
45–59 y (n=36 644)	1.46 (1.32–1.62)	<0.001
<45 y (n=6332)	2.40 (1.79–3.20)	<0.001
AD		
≥60 y (n=57 716)	0.92 (0.82–1.03)	0.140
45–59 y (n=36 644)	1.24 (1.06–1.47)	0.009
<45 y (n=6332)	2.43 (1.51–3.91)	<0.001
VD		
≥60 y (n=57 716)	1.64 (1.41–1.92)	<0.001
45–59 y (n=36 644)	1.94 (1.57–2.41)	<0.001
<45 y (n=6332)	2.60 (1.48–4.57)	0.001

AD indicates Alzheimer's disease; CHD, coronary heart disease; HR, hazard ratio; and VD, vascular dementia.

As presented in Tables S5 and S6, after further adjusting for competing risk of death, the association of age at CHD onset with incident dementia among participants with CHD (n=50 445) and the association of CHD with incident dementia among different onset age groups after propensity score matching (n=100 692) remained stable compared with the results from the main analyses. In addition, the results remained stable after excluding participants diagnosed with dementia within 5 years since baseline, excluding participants aged <50 years at baseline, further adjusting for CHD duration, antihypertensive drug use, and antidiabetic drug use, or setting the deadline of follow-up as December 31, 2019 (Tables S7–S15).

DISCUSSION

In this longitudinal population-based cohort study of the UK Biobank, patients with CHD exhibited an elevated risk of developing dementia than participants who remained CHD free. More importantly, among participants with CHD, a younger age at CHD onset was significantly associated with an increased risk of incident dementia after full adjustment. Analyses after propensity score matching also demonstrated that the strength of the association between CHD and incident dementia gradually increased with decreasing age at CHD onset.

Although the relationship between CHD and subsequent risk of incident dementia has been investigated by several studies previously, the findings were inconsistent, which may partly be attributable to the relatively small sample sizes and short follow-ups.[12] According to a meta-analysis, CHD was associated with a 26% increased risk of dementia among population-based cohorts.[12] This estimate is compatible with the findings of the present study, which demonstrated an HR of 1.32 for all-cause dementia based on a large population and >50 000 patients with CHD within the population. Empowered by the large sample size, we were able to further identify the associations between CHD and 2 major dementia subtypes (namely, AD and VD), with sufficient statistical power. After full adjustment, the HRs of CHD with AD and VD were 1.10 and 1.74, respectively, suggesting that, although the 2 subtypes have similar manifestations of dementia and share several common pathologic mechanisms, CHD may exert a more profound influence on the neuropathologic changes of VD. The precise neuropathologic mechanisms underlying the 2 subtypes were likely to differ in subtle ways and remain to be explored.

The most important finding of the present study is the association of age at CHD onset with incident dementia. To the best of our knowledge, this is the first and largest longitudinal cohort study exploring the association between CHD onset age and subsequent risk of incident dementia. On the basis of the precise

data of CHD onset age and subsequent events of incident dementia, the present study revealed robust and reliable associations of younger CHD onset age with elevated risks of incident all-cause dementia, AD, and VD. To date, studies particularly investigating the association between CHD onset age or CHD duration and incident dementia remain scarce, which may largely be attributable to a lack of explicit data on CHD onset age, as well as insufficient dementia cases during follow-up; however, our findings are in line with the results of a few prior studies exploring cognitive changes in patients with CHD. By using data from the Whitehall II study, a dose-dependent effect of CHD duration was revealed among 5837 middle-aged adults, and a longer duration of CHD (>10 years) was related to poorer cognitive performance.[25] Another study based on the Whitehall II cohort revealed younger onset age of multimorbidity, including CHD, was associated with incident dementia, which was partly in line with the results of the current study.[26] To determine the cognitive trajectory after the first occurrence of CVD, the MAAS (Maastricht Aging Study) observed a stronger effect of early onset of CVD on cognitive deterioration.[27] Despite these findings, our previous research on the progression of cognitive decline before and after CHD events found that the acceleration of cognitive decline only took place after incident CHD, whereas the rate of cognitive decline before CHD diagnosis was similar to those of CHD-free participants,[10] which may suggest that the atherosclerotic process and related hypoperfusion that link CHD to cognitive deterioration might be compensatory before the clinical manifestation of CHD. Intriguingly, both the MAAS and our previous research found that, although participants with incident CVD/CHD have a higher burden of vascular risk factors, this higher burden did not result in accelerated cognitive decline before the onset of incident CVD/CHD. Thus, the onset of CHD may act as a trigger that activates the detrimental effect of vascular risk factors in accelerating cognitive deterioration. In this way, it is plausible to assume that patients with CHD diagnosed at younger ages began to experience accelerated cognitive decline over a relatively longer period and eventually resulted in a higher risk of dementia, as demonstrated in the current study.

Although the exact pathophysiological mechanisms underlying the association between CHD and dementia remain unclear, potential pathways have been proposed. First, CHD and dementia share many risk factors,[5,6,28,29] which could induce atherosclerosis, resulting in cerebral hypoperfusion and hypoxia.[4,8] Second, cardiovascular risk factors may provoke oxidative stress, adverse immune responses, and endothelial dysfunction,[8,30] which could contribute to the neurodegenerative processes in the brain (ie, β-amyloid deposition).[31,32] Third, long-term cardiovascular burden could lead to cerebral small-vessel diseases (eg, lacunar infarcts, white matter hyperintensities, and microinfarcts), which play an important role in cognitive decline and dementia.[33] Indeed, we also found that, compared with individuals without CHD, patients with CHD were at higher risk of developing stroke (HR, 1.97 [95% CI, 1.88–2.07]; $P<0.001$), and compared with participants diagnosed with CHD at the age of ≥60 years, those diagnosed before the age of 45 years had higher risk of incident stroke (HR, 1.21 [95% CI, 1.02–1.44]; $P=0.033$). These findings of the association of CHD onset age with incident stroke also supported this assumption. Moreover, the onset of CHD could directly cause cerebral ischemic lesions,[8] which have been suggested to participate in the neuropathologic cascade of dementia,[34,35] and therefore exert their own effect on the neuropathologic changes of dementia in addition to the influence of cardiovascular factors. As observed in the present study, younger patients with CHD had lower left ventricular ejection fraction and cardiac output, and a higher risk of recurrent CHD; thus, they might experience more severe cerebral ischemic lesions. Altogether, apart from the coinciding independent neuropathologic cascades mentioned above, the onset of CHD may reciprocally interact with the cumulative exposure of vascular risk factors to synergistically exacerbate ischemic brain injury and compromise cognitive function, which may underlie the association between the early onset age of CHD and a higher risk of incident dementia.

The present study has several strengths. First, algorithmically defined outcomes in UK Biobank use a standardized approach to defining health outcomes, which identify the earliest recorded date of a given health outcome irrespective of source, including self-reported data, hospital inpatient records, and mortality register data, leading to a high positive predictive value of dementia (82.5%).[36] Second, the sample size of this study is large enough for sufficient power to investigate the associations of CHD and its onset age with dementia and its subtypes. Third, propensity score matching analyses after controlling for a series of traditional risk factors significantly reduced confounding bias.

Despite these strengths, the study has some limitations. First, a causal relationship cannot be concluded because of the nature of the observational study. Second, although we have adjusted for many potential confounders and the propensity matching method was used to exclude effects of traditional/known vascular risk factors on dementia to a large extent, the possibility of other unknown risk factors, which also contribute to the occurrence of CHD, cannot be totally ruled out. Third, 69 744 participants were excluded, which might cause selection bias. Comparison of baseline characteristics between participants included (n=432 667) and excluded demonstrated significant differences in glycated hemoglobin and low-density

lipoprotein cholesterol (Table S16). Fourth, because the current study population mainly consisted of the White race, with a proportion of >94%, which may not be representative of the general UK population, the generalization of the present findings should be cautious, and validations in other populations are warranted.

In conclusion, the study demonstrated that CHD is associated with elevated risks of all-cause dementia, AD, and VD. More important, a younger age of CHD onset is associated with a higher risk of dementia. The present findings have important public health implications as they contribute to ascertaining vulnerable populations with dementia by revealing that adults diagnosed with CHD at younger ages, especially before midlife (aged <45 years), might be the most vulnerable to future dementia. For clinical practice, our findings suggest, apart from traditional treatment for CHD, additional attention should be paid to the cognitive status of patients with CHD, especially the ones diagnosed with CHD at a young age, during their follow-up visits in health care settings. In addition, timely intervention, such as cognitive training, could be implemented once signs of cognitive deteriorations are detected.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S16
Figures S1–S5

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