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META-ANALYSIS

Premenopausal cardiovascular disease and age at natural menopause: a pooled analysis of over 170,000 women

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Abstract

Early menopause is associated with an increased risk of subsequent cardiovascular disease (CVD). Few studies have investigated the converse. We examined whether premenopausal CVD events are associated with early age at menopause. We pooled the individual data of 177,131 women from nine studies. We used multinomial logistic regression models to estimate multivariable relative risk ratios (RRR) and 95% confidence intervals (CI) for the associations between age at onset of premenopausal CVD events—including coronary heart disease (CHD) and stroke—and age at natural menopause. Altogether 1561 (0.9%) premenopausal participants reported CVD events (including 1130 CHD and 469 stroke) at a mean age of 41.3 years. Compared with women without any premenopausal CVD events, women who experienced a first CVD event before age 35 years had a twofold risk of menopause before age 45 years (early menopause); adjusted RRR (95% CI) of 1.92 (1.17, 3.14) for any CVD, 1.86 (1.01, 3.43) for CHD and 2.17 (1.43, 3.30) for stroke. Women who experienced a first premenopausal CVD event after age 40 years underwent a natural menopause at the expected age (around 51 years). These associations were robust to adjustment for smoking status, BMI, educational level, race/ethnicity, age at menarche, parity, hypertension and family history of CVD. For premenopausal women, a first CVD event before age 35 years is associated with a doubling of the risk of an early menopause, while a first CVD event occurred after 35 years indicates a normal menopause at around 51 years. Shared genetic and environmental factors (such as smoking), as well as compromised vasculature following CVD events, may contribute to this outcome.

Keywords Premenopausal · Cardiovascular disease · Age at menopause · Pooled analysis

Introduction

Menopause, defined as cessation of menstrual bleeding for at least 12 months, marks the end stage of reproductive ageing [1]. Average age at menopause is 51.4 years in high-income countries [2, 3]. Early menopause, i.e., occurring before the age of 45 years, affects approximately 5% of women [4] and entails increased risk of non-fatal and fatal cardiovascular disease (CVD) and of all-cause mortality [5–9].

The reduction in circulating estrogen concentration during the menopausal transition is accompanied by unfavorable changes to CVD risk factors such as body fat distribution, blood pressure, and blood lipid levels [10–16] and, is considered, thereby, to trigger vascular ageing [17]. However, this model has been challenged by the finding of no CVD risk reduction, and possibly even an increased risk [18], following exogenous menopausal hormone therapy (MHT). This inconsistency led us to consider the converse model, i.e., that cardiovascular damage itself is a driving factor in the process of ovarian ageing. This model is indirectly supported by two studies. In the Framingham Heart Study, Kok et al. found premenopausal cardiovascular risk factors were associated with younger age at menopause [19, 20]. Another study reported women who experienced early natural menopause were more often smokers, had diabetes, and had higher average body mass index (BMI) [21]. If premenopausal CVD

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risk factors are associated with women's age at natural menopause, the question that follows is whether premenopausal CVD events might also be linked to reproductive ageing and early age at natural menopause. To date, no study has examined this question directly. As premenopausal CVD events are rare, a study with a large sample size is required to answer this question with adequate precision.

To this end we pooled participant-level data from multiple studies in the International collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE) [22, 23]. We examined the association between premenopausal CVD events and age at natural menopause with detailed adjustment for confounding by race/ethnicity, education, BMI, smoking, hypertension, family history of CVD and other reproductive factors.

Methods

Study participants

InterLACE combines 25 observational, mostly longitudinal cohort studies with data on women's health. A more detailed description of the InterLACE collaboration has been published previously [22, 23]. In brief, participating studies collected retrospective as well as prospective data on key reproductive, sociodemographic, lifestyle and disease outcome variables using self-reported surveys.

There were 177,750 women who had reported their age at natural menopause and provided information on pre- or post-menopausal CVD events (yes/no) and their age at onset of the CVD event. Because we focused on early premenopausal CVD events, women who experienced premenopausal CVD events after age 50 years (the average age at menopause in this study) were excluded (n = 619). The final sample consisted of the 177,131 women who had either experienced no premenopausal CVD event (the reference group) or had experienced a premenopausal CVD event before age 50 years, and had complete data on key covariates at baseline including BMI, smoking status, education level, race/ethnicity, and parity. Consequently, nine studies were included in the analyses (Table 1).

Outcome and exposure variables

Age at natural menopause was the outcome variable and was defined as the time when a woman has experienced 12 consecutive months of amenorrhea which was not due to

Table 1 Characteristics of women in each study of the InterLACE consortium

Study	Country	N	Age at baseline, Mean (SD)	Age at last follow-up, Mean (SD)	Women's year of birth (%)				
					< 1930	1930–1939	1940–1949	1950–1959	1960 +
Australian Longitudinal Study on Women's Health (ALSWH)	Australia	7061	47.6 (1.4)	63.2 (3.3)	.	.	74.8	25.2	.
Melbourne Collaborative Cohort Study (MCCS)	Australia	12,814	58.7 (7.2)	67.9 (7.6)	35.6	42.6	19.8	2.0	.
Women's Lifestyle and Health Study (WLHS)	Sweden	10,659	45.0 (3.5)	55.8 (3.7)	.	.	77.0	22.7	0.3
MRC National Survey of Health and Development (NSHD)[a]	UK	631	47.0	53.9	.	.	100	.	.
National Child Development Study (NCDS)[a]	UK	2407	50.0	54.8	.	.	.	100	.
English Longitudinal Study of Ageing (ELSA)	UK	3595	60.1 (9.4)	68.7 (9.8)	16.4	25.6	35.8	22.1	0.2
Whitehall II study (WHITEHALL II)	UK	1460	46.0 (5.8)	64.8 (5.9)	.	46.4	46.8	6.7	.
Japan Nurse's Health Study (JNHS)	Japan	4933	54.7 (3.9)	54.7 (3.9)	.	1.5	63.6	34.2	0.7
UK Biobank (UK Biobank)	UK	133,571	59.6 (5.6)	60.1 (5.5)	.	4.0	55.4	37.5	3.0
All		177,131	57.8 (7.1)	60.5 (6.3)	2.9	7.1	54.1	33.6	2.3

In this study, the dataset included women who experienced premenopausal CVD events (including CHD and stroke) and had reported their age at onset of CVD events, and women who had no premenopausal CVD event (used as reference group). All women had complete information on age at natural menopause and key covariates

InterLACE International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events, *SD* standard deviation, *CVD* cardiovascular disease, *CHD* coronary heart disease

[a]NSHD (1946 British Birth Cohort) and NCDS (1958 British Birth Cohort) first collected information on women's health in 1993 (aged 47) and 2008 (aged 50), respectively, so we used 1993 and 2008 as the baseline year for the InterLACE

surgery (such as bilateral oophorectomy or hysterectomy). For some women, use of MHT and oral contraceptive pills (OCPs) made it difficult to ascertain their menopausal status; hence MHT or OCP users were excluded unless their age at natural menopause had been reported and the assumption of only post-menopausal MHT use could be made. Age at menopause was categorised as < 45 (early menopause), 45–49, 50–51 (reference category), 52–53, and 54 years and above (late menopause), according to the clinical recommendation [4] and also as defined in our previous papers [24, 25].

CVD events were a certained by self-report or/and hospital diagnosis, and were defined as the occurrence of coronary heart disease (CHD, including heart attack and angina) or stroke (including ischemic strokes and haemorrhagic strokes). The exposure variable was the age at onset of premenopausal CVD events, and was categorized as < 35, 35–39, and ≥ 40 years. We used 35 years as a cut-off point because patients with CVD onset before age 35 years were referred as "very young CVD" and might be genetic predisposed [26, 27]. Also, these CVD events fall into the optimal period of childbearing age [28, 29]. Women who experienced no premenopausal CVD event were used as the reference group.

Covariates

BMI, smoking status, years of education, race/ethnicity/region, parity and age at menarche collected at baseline were used as covariates. BMI was categorised according to World Health Organization (WHO) criteria as < 18.5 kg/m^2, 18.5 to 24.9 kg/m^2, 25 to 29.9 kg/m^2 and ≥ 30 kg/m^2. Smoking status was categorised as current, former, or never smokers. Years of education was categorised as follows: ≤ 10, 11–12, and > 12 years. Race/ethnicity/region was combined into one with four categories: Caucasian, Asian, African American/Black, and other. Parity was grouped as no children, one child, two, and three or more children. Age at menarche was divided into 5 categories as ≤ 11, 12, 13, 14, and 15 years or more.

Statistical analysis

We used multinomial (polytomous) logistic regression models to examine the associations between age at onset of premenopausal CVD events and age at natural menopause. CVD events were analysed both as a composite event and for CHD and stroke separately. For the outcome variable, women with an age at menopause of 50–51 years were used as the reference group, while for the exposure variable, women who had not experienced premenopausal CVD were the reference group. All models were adjusted for BMI, smoking status, education level, race/ethnicity and parity.

Multivariable relative risk ratios (RRR) [30] and 95% confidence intervals (95% CI) were used to quantify the association between age at onset of premenopausal CVD events and age at menopause. Because age at menarche is a potential confounder of the CVD-menopause association, it was later included in the model. For this analysis only eight studies were included because age at menarche was not available for the WHITEHALL II study.

We conducted several sensitivity analyses to test the robustness of our findings. First, to address the validity of the self-reported CVD events, we only included CVD cases that had a hospital record of diagnosis. Second, because the UK Biobank data contributed more than 50% of the total premenopausal CVD cases, we conducted an analysis excluding this study to assess its dominance. Third, women who experienced postmenopausal CVD events may have had unfavourable CVD risk profile before menopause, which might have led to an earlier menopause [19]. Thus, we excluded them from the reference group. Fourth, to guarantee the temporal direction from premenopausal CVD events to menopause, we performed an analysis by only including premenopausal CVD events which occurred at least 2 years before menopause. Fifth, smoking and BMI are two important factors that may influence age at menopause [24, 31]. We thus analysed the combined effects of premenopausal CVD events and smoking status, premenopausal CVD events and BMI levels on age at menopause. Sixth, because a previous study had found an association between premenopausal blood pressure and earlier age at menopause [19], we also adjusted for hypertension status before the premenopausal CVD event in the four studies with available information (MCCS, WLH, JNHS, and UK Biobank). Last, we adjusted for family history of CVD using the five studies (MCCS, NHSD, WHITEHALL II, JNHS, and UK Biobank) with relevant information.

We used the SURVEYLOGISTIC procedure in SAS software (SAS Version 9.4, SAS Institute Inc, 2008.) with the generalized logit link to adjust for the clustering of data within studies, and to obtain robust standard errors. For all hypothesis tests we used the two-sided 5% level of significance.

Ethics

Each study in the InterLACE consortium has been undertaken with ethical approval from the Institutional Review Board or Human Research Ethics Committee at each participating institution, and all participants provided consent for that study.

Results

Study characteristics

Overall, nine studies (177,131 women) had data on premenopausal CVD events. The majority of women were white (85.0%). The mean age (standard deviation, SD) at baseline was 57.8 (7.1) years and ranged from 45.0 (3.5) to 60.1 (9.4) years within studies. Over half of the participants were born between 1940 and 1949 (Table 1). There were 1561 women with premenopausal CVD events (including 1130 CHD and 469 stroke). The overall prevalence of premenopausal CVD was 0.9%. The overall mean age at natural menopause was 50.3 (4.4) years and the mean age at first premenopausal CVD event was 41.3(8.2) years (median 44.0 years, interquartile range 38.0–47.0 years). The mean age at natural menopause by age categories of premenopausal CVD < 35, 35–39, and ≥ 40 years were 49.2 (5.3), 49.4 (4.3) and 51.4 (3.3) years respectively. Early age at natural menopause was more common for women with premenopausal CVD events occurring before the age of 35 years than for other groups (Table 2, Fig. 1).

Association between premenopausal CVD events and age at menopause

Compared with women who experienced no premenopausal CVD events, women experiencing a first event before the age of 35 years had around a twofold increased risk of early age (< 45 years) at menopause with adjusted RRR (95% CI) 1.92 (1.17, 3.14) for CVD, 1.86 (1.01, 3.43) for CHD and 2.17 (1.43, 3.30) for stroke. There was a significant increasing trend of the associations between premenopausal CHD (< 35 years) and earlier age at menopause (P-trend < 0.001), while the trend with premenopausal stroke was not significant (P-trend > 0.05). Women experiencing first premenopausal CVD events when they were aged more than 35 or 40 years were less likely to experience either earlier

Table 2 Average age at onset of premenopausal CVD events, average age and distribution of natural menopause by age categories of premenopausal CVD/CHD/stroke events

	Number of premenopausal CVD/CHD/stroke events	Age at premenopausal CVD/CHD/stroke event		Age at natural menopause, Mean (SD)	Distribution of age at natural menopause				
		Mean (SD)	Median (Q1, Q3)		< 45	45–49	50–51	52–53	≥ 54
Age at onset of premenopausal CVD events									
< 35	287	27.0 (7.4)	29.4 (23.0, 33.0)	49.2 (5.3)	46 (16.0)	82 (28.6)	59 (20.6)	45 (15.7)	55 (19.2)
35–39	151	37.1 (1.4)	37.0 (36.0, 38.0)	49.4 (4.3)	16 (10.6)	45 (29.8)	45 (29.8)	23 (15.2)	22 (14.6)
≥ 40	1123	45.5 (2.9)	46.0 (43.0, 48.0)	51.4 (3.3)	17 (1.5)	240 (21.4)	358 (31.9)	240 (21.4)	268 (23.9)
No premenopausal CVD event	–	–	–	50.3 (4.4)	16,029 (9.1)	42,803 (24.4)	42,829 (24.4)	34,766 (19.8)	39,143 (22.3)
Age at onset of premenopausal CHD events									
< 35	185	27.2 (8.0)	31.0 (24.0, 33.0)	48.9 (5.0)	29 (15.7)	56 (30.3)	38 (20.5)	34 (18.4)	28 (15.1)
≥ 35	945	44.7 (3.7)	45.0 (42.0, 48.0)	51.3 (3.4)	21 (2.2)	207 (21.9)	300 (31.7)	191 (20.2)	226 (23.9)
No premenopausal CHD event	–	–	–	50.3 (4.4)	16,037 (9.1)	42,863 (24.4)	42,929 (24.4)	34,839 (19.8)	39,301 (22.3)
Age at onset of premenopausal stroke									
< 35	114	27.5 (6.5)	28.0 (24.0, 32.0)	49.6 (5.7)	19 (16.7)	28 (24.6)	22 (19.3)	15 (13.2)	30 (26.3)
≥ 35	355	44.2 (3.9)	45.0 (41.0, 48.0)	50.8 (3.4)	13 (3.7)	87 (24.5)	112 (31.5)	76 (21.4)	67 (18.9)
No premenopausal stroke	–	–	–	50.4 (4.4)	15,819 (9.1)	42,152 (24.1)	42,687 (24.5)	34,434 (19.7)	39,486 (22.6)

CVD cardiovascular disease, *CHD* coronary heart disease, *SD* standard deviation

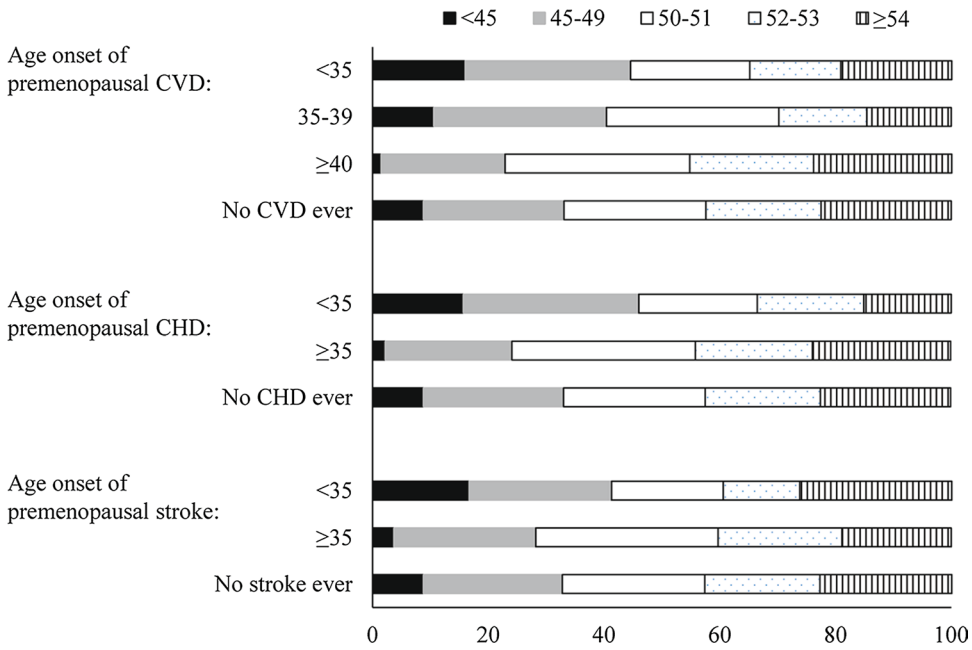

Fig. 1 Distribution of age at menopause in different age categories of premenopausal CVD/CHD/stroke events. *CVD* Cardiovascular disease, *CHD* coronary heart disease

(45–49 years) or later age at natural menopause (52 years or more) (Table 3), i.e., they were more likely to experience natural menopause at around 51 years of age (Table 2). For women who experienced premenopausal stroke before age 35 years, a statistically significant association was also found with late age at menopause (≥ 54 years) (1.45, 1.10–1.91) (Table 3).

Sensitivity analyses

When only CVD events with a hospital record of diagnosis were included in the analysis, we found results in a similar direction to those from the main analysis. Nevertheless, the association between premenopausal CHD events (< 35 years) and early menopause, and the association between premenopausal stroke (< 35 years) and late menopause were attenuated and no longer statistically significant (Table 4). Results were also similar when the UK Biobank study was excluded (Table 5) or when women who had experienced a postmenopausal CVD event were excluded from the reference group (Table S1). By including only premenopausal CVD events which occurred at least two years before menopause, similar results were observed (Table S 2). After analysing the combined effect with smoking and BMI, we found the significant associations between CVD events < 35 years and early menopause were mainly observed in ever smokers and in women who were normal weight (Table S3 and S4). In never smokers or women with overweight/obese, a suggested higher but not significant association was found. Similar results were also obtained when the analysis was further adjusted for hypertension prior to CVD (Table S5). After the adjustments for family history of CVD, only the association with CVD events was statistically significant, although the point estimates were not changed (Table S6).

Discussion

Our results show that compared with women who had not experienced any premenopausal CVD event, women experiencing CHD or stroke before age 35 years had twice the risk of having an early menopause (< 45 years) rather than a late menopause (≥ 54 years), while women who first experienced premenopausal CVD events at age 40 years or older were more likely to have menopause at the average age of 50 to 51 years.

The very young premenopausal CVD events

Coronary atherosclerosis begins at a young age with an estimated prevalence of 28% under 30 years of age [32]. The prevalence and extent of lesions increases rapidly during the 15 to 34 year age span [33]. Patients with symptomatic CVD onset before 35 years are at times referred as "very young CVD" [26, 27]. Around 1.5% of all documented CHD cases occur among individuals < 35 years of age, predominantly in males [27, 34]. Younger patients have relatively few traditional risk factors such as diabetes mellitus, hypertension, and hyperlipidemia although smoking and family history of CVD have been found to be common [26, 34, 35]. Within the InterLACE consortium the prevalence of family history of CVD was also significantly higher for women with premenopausal CVD events than those without (78% vs. 60%)

Table 3 Unadjusted and adjusted associations between age at premenopausal CVD/CHD/stroke events and age at natural menopause (n = 177,131)

	Age at natural menopause: crude RRRs (95% CI)				Age at natural menopause: adjusted RRRs (95% CI)[a]			
	< 45	45–49	52–53	≥ 54	< 45	45–49	52–53	≥ 54
Age at onset of premenopausal CVD events								
< 35	2.07 (1.29, 3.31)	1.36 (0.94, 1.96)	0.94 (0.69, 1.27)	1.05 (0.77, 1.52)	1.92 (1.17, 3.14)	1.30 (0.91, 1.85)	0.94 (0.70, 1.27)	1.05 (0.79, 1.41)
35–39	0.95 (0.69, 1.29)	0.99 (0.72, 1.35)	0.63 (0.50, 0.80)	0.54 (0.38, 0.76)	0.88 (0.65, 1.19)	0.95 (0.71, 1.29)	0.64 (0.50, 0.81)	0.54 (0.37, 0.79)
≥ 40[b]	–	0.66 (0.54, 0.80)	0.82 (0.69, 0.98)	0.84 (0.71, 1.00)	–	0.62 (0.51, 0.75)	0.84 (0.71, 0.99)	0.85 (0.72, 0.99)
No premenopausal CVD event	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Age at onset of premenopausal CHD events								
< 35	2.02 (1.14, 3.59)	1.43 (0.85, 2.39)	1.10 (0.85, 1.43)	0.83 (0.48, 1.45)	1.86 (1.01, 3.43)	1.34 (0.80, 2.23)	1.10 (0.84, 1.45)	0.86 (0.50, 1.47)
≥ 35[b]	–	0.67 (0.50, 0.91)	0.78 (0.65, 0.94)	0.84 (0.69, 1.04)	–	0.64 (0.47, 0.86)	0.80 (0.67, 0.95)	0.85 (0.72, 1.01)
No premenopausal CHD event	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Age at onset of premenopausal stroke								
< 35	2.33 (1.53, 3.54)	1.29 (0.86, 1.93)	0.85 (0.54, 1.33)	1.48 (1.13, 1.93)	2.17 (1.43, 3.30)	1.26 (0.84, 1.90)	0.85 (0.55, 1.33)	1.45 (1.10, 1.91)
≥ 35[b]	–	0.78 (0.64, 0.95)	0.84 (0.70, 1.01)	0.65 (0.57, 0.74)	–	0.74 (0.60, 0.93)	0.85 (0.71, 1.02)	0.65 (0.57, 0.74)
No premenopausal stroke	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Multinomial logistic regression model was used to estimate relative risk ratio (RRR) and 95% confidence interval (95% CI). The 50–51 age category was used as reference group for age at menopause

CVD cardiovascular disease, *CHD* coronary heart disease

[a]Body mass index, smoking status, years of education, race/ethnicity/region, number of children at baseline were adjusted

[b]The average age for premenopausal CVD event in the ≥ 40 years group, or premenopausal CHD and stroke in the ≥ 35 years group were all around 45 (Table 2), which means women with subsequent early menopause were less likely to be included in these groups. So we use a "–" to represent their effect on early menopause

Table 4 The associations between age at premenopausal CVD/CHD/stroke events and age at natural menopause–Only cases with hospital diagnosed record were included (n = 176,265)

	Age at menopause, n (%)					Adjusted RRRs (95% CI)[a]			
	< 45	45–49	50–51	52–53	≥ 54	< 45[b]	45–49	52–53	≥ 54
Age of onset of premenopausal CVD events									
< 35	18 (17.0)	28 (26.4)	24 (22.6)	14 (13.2)	22 (20.8)	1.73 (1.02, 3.00)	1.11 (0.88, 1.40)	0.73 (0.47, 1.15)	0.98 (0.89, 1.08)
≥ 35	19 (3.2)	145 (24.6)	172 (29.2)	123 (20.9)	130 (22.1)	–	0.80 (0.68, 0.94)	0.89 (0.71, 1.11)	0.80 (0.70, 0.91)
No premenopausal CVD event	16,029 (9.1)	42,803 (24.4)	42,829 (24.4)	34,766 (19.8)	39,143 (22.3)	1.00	1.00	1.00	1.00
Age of onset of premenopausal CHD events									
< 35	10 (16.1)	18 (29.0)	15 (24.2)	10 (16.1)	9 (14.5)	1.53 (0.65, 3.61)	1.15 (0.69, 1.89)	0.84 (0.47, 1.52)	0.65 (0.48, 0.88)
≥ 35	15 (3.3)	103 (22.5)	131 (28.6)	96 (21.0)	113 (24.7)	–	0.75 (0.61, 0.92)	0.91 (0.72, 1.16)	0.90 (0.79, 1.02)
No premenopausal CHD event	16,037 (9.1)	42,863 (24.4)	42,929 (24.4)	34,839 (19.8)	39,301 (22.3)	1.00	1.00	1.00	1.00
Age of onset of premenopausal stroke									
< 35	9 (21.4)	10 (23.8)	9 (21.4)	4 (9.5)	10 (23.8)	2.37 (1.53, 3.70)	1.09 (0.42, 2.80)	0.56 (0.25, 1.27)	1.17 (0.60, 2.30)
≥ 35	5 (3.7)	42 (30.9)	41 (30.1)	29 (21.3)	19 (14.0)	–	0.98 (0.73, 1.31)	0.88 (0.64, 1.22)	0.50 (0.30, 0.80)
No premenopausal stroke	15,819 (9.1)	42,152 (24.1)	42,687 (24.5)	34,434 (19.7)	39,486 (22.6)	1.00	1.00	1.00	1.00

Multinomial logistic regression model was used to estimate relative risk ratio (RRR) and 95% confidence interval (95% CI). The 50–51 age category was used as reference group for age at menopause

CVD cardiovascular disease, *CHD* coronary heart disease

[a]Body mass index, smoking status, years of education, race/ethnicity/region, number of children at baseline were adjusted

[b]The average age for premenopausal CVD event in the ≥ 40 years group, or premenopausal CHD and stroke in the ≥ 35 years group were all around 45 (Table 2), which means women with subsequent early menopause were less likely to be included in these groups. So we use a "–" to represent their effect on early menopause

Table 5 The associations between age at premenopausal CVD/CHD/stroke events and age at natural menopause—After excluding UK Biobank study

	Age at menopause, n (%)					Adjusted RRRs (95% CI)[a]			
	<45	45–49	50–51	52–53	≥54	<45[b]	45–49	52–53	≥54
Age of onset of premenopausal CVD events									
<35	29 (19.3)	49 (32.7)	26 (17.3)	25 (16.7)	21 (14.0)	2.82 (1.71, 4.63)	1.67 (1.19, 2.35)	1.17 (0.76, 1.81)	1.08 (0.55, 2.10)
≥35	12 (2.1)	126 (21.7)	202 (34.8)	115 (19.8)	126 (21.7)	–	0.56 (0.45, 0.69)	0.71 (0.58, 0.87)	0.82 (0.59, 1.12)
No premenopausal CVD event	3862 (9.0)	11,534 (26.9)	10,606 (24.8)	8589 (20.1)	8238 (19.2)	1.00	1.00	1.00	1.00
Age of onset of premenopausal CHD events									
<35	22 (18.2)	42 (34.7)	21 (17.4)	20 (16.5)	16 (13.2)	2.65(1.48, 4.74)	1.76 (1.22, 2.55)	1.16 (0.70, 1.94)	1.05 (0.44, 2.52)
≥35	9 (1.8)	99 (20.3)	174 (35.7)	97 (19.9)	109 (22.3)	–	0.50 (0.41, 0.63)	0.70 (0.59, 0.83)	0.83 (0.61, 1.13)
No premenopausal CHD event	3872 (9.0)	11,568 (26.9)	10,639 (24.8)	8621 (20.1)	8285 (19.3)	1.00	1.00	1.00	1.00
Age of onset of premenopausal stroke									
<35	8 (26.7)	6 (20.0)	6 (20.0)	4 (13.3)	6 (20.0)	3.42 (1.07, 10.9)	0.95 (0.25, 3.55)	0.86 (0.16, 4.44)	1.20 (0.52, 2.74)
≥35	3 (2.6)	34 (29.8)	36 (31.6)	21 (18.4)	20 (17.5)	–	0.89 (0.55, 1.42)	0.73 (0.44, 1.24)	0.65 (0.44, 0.96)
No premenopausal stroke	3651 (8.9)	10,787 (26.2)	10,329 (25.1)	8113 (19.7)	8266 (20.1)	1.00	1.00	1.00	1.00

Multinomial logistic regression model was used to estimate relative risk ratio (RRR) and 95% confidence interval (95% CI). The 50–51 age category was used as reference group for age at menopause

CVD cardiovascular disease, *CHD* coronary heart disease

[a]Body mass index, smoking status, years of education, race/ethnicity/region, number of children, age at menarche at baseline

[b]The average age for premenopausal CVD event in the ≥40 years group, or premenopausal CHD and stroke in the ≥35 years group were all around 45 (Table 2), which means women with subsequent early menopause were less likely to be included in these groups. So we use a "–" to represent their effect on early menopause

suggesting an inherited genetic predisposition to CVD in young cases.

Mechanisms underlying the link between premenopausal CVD events and age at menopause

Genetics plays an important role in age at natural menopause, with estimates of heritability ranging from 31 to 87% [36]. The genetic regions associated with premature or early-onset menopause may also tie to the occurrence of CVD [11]. Thus, our observation of a significant association between "very young CVD" and early menopause may arise due to shared genetic factors. Single nucleotide polymorphisms in several vascular-function-related genes are significantly associated also with age at menopause [36]. The coagulation Factor V Leiden gene, the methylene tetrahydrofolate reductase gene and the Apolipoprotein E gene have all been linked to earlier age at menopause [37–40], whereas the coagulation factor VII gene is related to delayed menopause [41].

An interplay between genetic and environmental factors that may expedite the compromise of vascular health and advance ovarian ageing is also conceivable [37], as well as shared environmental factors. Smoking, for example, is common in those who experience very young CVD events and is also associated with early menopause [26, 34, 42]. Smokers carrying single nucleotide polymorphisms CYP3A4*1B and CYP1B1*3 have a greater risk of menopause commencement compared with those not carrying these variants [43]. Smoking also induces the expression of the apoptosis-promoting gene Bcl2-associated X protein in oocytes leading to an increased rate of oocyte apoptosis, and thus earlier ovarian failure [44].

Vascular and ovarian ageing are connected [45]. Coronary disease occurring at a young age may carry a long-term adverse influence on the vasculature [35]. Vascular damage, in turn, may accelerate ovarian ageing and thus lead to early menopause [36, 45]. Additionally, fertility often starts declining at age 35 years [28, 29]. Hence, CVD events that occur before age 35 years fall into the optimal period of childbearing age (the average age at onset of premenopausal CVD in those aged ≤ 35 years' was 27.0 years in our study) [29]. It is possible that CVD occurring at optimal reproductive age may affect maternal vascular health in the long term and accelerate the process of reproductive ageing. Although we found no studies evaluating the relationship between damage in large vessels and ovarian ageing, microvascular complications in women with type 1 diabetes have been suggested to accelerate ovarian ageing [26, 46]. Our study also found that premenopausal stroke had a stronger association with early menopause than CHD suggesting that a damaged cerebrovascular system is a more sensitive marker of ovarian ageing. Further studies are needed to verify this proposition.

Smoking leads to early menopause and overweight/obese has been linked to later menopause [24, 31]. Our results showed the significant associations between CVD events < 35 years and early menopause were mainly observed in ever smokers and women with normal weight. In addition, the significant association between premenopausal stroke before age 35 years and late menopause (≥ 54 years) were only observed in women with overweight or obesity, which has been associated with both stroke and late menopause [24].

We also found that women with first CHD or stroke after age 35 years were less likely to experience either earlier (45–49 years) or later natural menopause (52 years or more). The average age at menopause in this group was 51.4 years (Table 2), similar to the mean age at menopause reported in high-income countries [2, 3]. Thus, they were more likely to experience menopause at the 'usual' age. The median age of premenopausal CVD in this group was 46 years, which means the downstream effect of vascular damage on ovarian ageing is limited. Ovarian ageing in this group to a large extent reflects natural ageing.

Strengths and limitations

To the best of our knowledge, the link between premenopausal CVD events and timing of menopause has remained untested [47]. The strengths of the current study include participant-level data from nine studies which provided sufficient number of CVD cases to examine in detail the association between premenopausal CVD and the multiple categories of age at menopause.

Several limitations need also to be acknowledged. First, around 47% of premenopausal CVD events were self-reported without validation by hospital records. This may have led to some degree of misclassification but findings were reassuringly consistent in the sensitivity analysis that used only hospital ascertained cases. Second, we used the BMI and smoking status values reported at baseline as covariates, which may not reflect their values proximal to the onset of premenopausal CVD. Women with early CVD may have modified their lifestyle resulting in changed BMI and smoking status before menopause. On the other hand, over 50% of women experienced premenopausal CVD events when aged in their mid-forties or later. For these women, we assume that the misclassification in reported BMI or smoking is limited. For women who had experienced very young CVD (< 35 years), their BMI level prior to CVD events might not have been an important risk factor. In two birth cohort studies (NSHD and NCDS) in the InterLACE consortium that also collected BMI and smoking at younger

age, the average BMI before 35 years (26–35 years) was 22.4–24.4 kg/m^2, and the concordance in smoking status between age 26 years and baseline age (mid age) was 84%. Third, due to the limited number of cases, we were unable to perform subgroup analysis between sub-types of CHD (angina and heart attack) and age at menopause. Also, most studies did not collect specific types of stroke, so we could not separate the hemorrhagic strokes from ischemic strokes. The associations between different sub-types of stroke with age at menopause may differ due to their dissimilar biological mechanisms. However, approximately 87% strokes are ischemic [48]. Thus, we believe the bias caused by hemorrhagic strokes was limited. Data that were collected from four countries might have heterogeneity among them. However, after performing country-specific random-effects meta-analysis, we found no significant heterogeneity between studies ($p > 0.05$) (data not shown). Last, because the majority of women were white (Caucasian), our results may need to be verified in other race/ethnicities.

Conclusions

Premenopausal CVD before age 35 years is associated with a higher risk of menopause before age 45 years, while premenopausal CVD after 35 years indicates a normal menopause at around 51 years. Shared genetic and environmental factors (such as smoking), as well as compromised vasculature after CVD events may contribute to this health outcome. Further studies that include measures of vascular damage are needed to examine its possible relationship with age at natural menopause. Additionally, women experiencing a CVD event prior to age 35 years should be alerted for their future high possibility of having early menopause.

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Author's contribution GDM and DZ conceptualized the study. GDM interpreted the results, and revised the manuscript critically. DZ analysed and interpreted data, and drafted the manuscript. HFC and NP harmonised the data and revised the manuscript. AJD, RH, DK, EJB, FB, GGG, PD, JSL, HM, KH, HOA, EW provided study data and revised the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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