

Type of menopause, age of menopause and variations in the risk of incident cardiovascular disease: pooled analysis of individual data from 10 international studies

Dongshan Zhu¹, Hsin-Fang Chung¹, Annette J. Dobson¹, Nirmala Pandeya^{1,2}, Eric J. Brunner³, Diana Kuh⁴, Darren C. Greenwood⁵, Rebecca Hardy⁶, Janet E. Cade⁵, Graham G. Giles^{7,8,9}, Fiona Bruinsma⁷, Panayotes Demakakos³, Mette Kildevæld Simonsen¹⁰, Sven Sandin^{11,12}, Elisabete Weiderpass¹³, and Gita D. Mishra^{1*}

¹The University of Queensland, Epidemiology and Biostatistics Division, School of Public Health, Brisbane, Queensland, Australia ²Department of Population Health, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia ³Department of Epidemiology and Public Health, University College London, London, UK ⁴Medical Research Council Unit for Lifelong Health and Ageing at UCL, London, UK ⁵Nutritional Epidemiology Group, School of Food Science and Nutrition, University of Leeds, Leeds, UK ⁶CLOSER, UCL Institute of Education, London, UK ⁷Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia ⁸Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia ⁹Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Melbourne, Victoria, Australia ¹⁰UcDiakonissen and Parker Institute, Frederiksberg, Denmark ¹¹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden ¹²Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA ¹³International Agency for Research on Cancer, World Health Organisation, Lyon, France

*Correspondence address. School of Public Health, University of Queensland, Brisbane, Queensland 4006, Australia.
Tel: +61-7-3365-5224; Fax: +61-7-3365-5540; E-mail: g.mishra@uq.edu.au

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STUDY QUESTION: How does the risk of cardiovascular disease (CVD) vary with type and age of menopause?

SUMMARY ANSWER: Earlier surgical menopause (e.g. <45 years) poses additional increased risk of incident CVD events, compared to women with natural menopause at the same age, and HRT use reduced the risk of CVD in women with early surgical menopause.

WHAT IS KNOWN ALREADY: Earlier age at menopause has been linked to an increased risk of CVD mortality and all-cause mortality, but the extent that this risk of CVD varies by type of menopause and the role of postmenopausal HRT use in reducing this risk is unclear.

STUDY DESIGN, SIZE, DURATION: Pooled individual-level data of 203 767 postmenopausal women from 10 observational studies that contribute to the International collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE) consortium were included in the analysis.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Postmenopausal women who had reported menopause (type and age of menopause) and information on non-fatal CVD events were included. Type of menopause (natural menopause and surgical menopause) and age at menopause (categorised as <35, 35–39, 40–44, 45–49, 50–54 and ≥55 years) were exposures of interest. Natural menopause was defined as absence of menstruation over a period of 12 months (no hysterectomy and/or oophorectomy) and surgical menopause as removal of both ovaries. The study outcome was the first non-fatal CVD (defined as either incident coronary heart disease (CHD) or stroke) event ascertained from hospital medical records or self-reported. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CI for non-fatal CVD events associated with natural menopause and surgical menopause.

MAIN RESULTS AND THE ROLE OF CHANCE: Compared with natural menopause, surgical menopause was associated with over 20% higher risk of CVD (HR 1.22, 95% CI 1.16–1.28). After the stratified analysis by age at menopause, a graded relationship for incident

CVD was observed with lower age at menopause in both types of natural and surgical menopause. There was also a significant interaction between type of menopause and age at menopause ($P < 0.001$). Compared with natural menopause at 50–54 years, women with surgical menopause before 35 (2.55, 2.22–2.94) and 35–39 years (1.91, 1.71–2.14) had higher risk of CVD than those with natural menopause (1.59, 1.23–2.05 and 1.51, 1.33–1.72, respectively). Women who experienced surgical menopause at earlier age (<50 years) and took HRT had lower risk of incident CHD than those who were not users of HRT.

LIMITATIONS, REASONS FOR CAUTION: Self-reported data on type and age of menopause, no information on indication for the surgery (e.g. endometriosis and fibroids) and the exclusion of fatal CVD events may bias our results.

WIDER IMPLICATIONS OF THE FINDINGS: In clinical practice, women who experienced natural menopause or had surgical menopause at an earlier age need close monitoring and engagement for preventive health measures and early diagnosis of CVD. Our findings also suggested that timing of menopause should be considered as an important factor in risk assessment of CVD for women. The findings on CVD lend some support to the position that elective bilateral oophorectomy (surgical menopause) at hysterectomy for benign diseases should be discouraged based on an increased risk of CVD.

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Key words: natural menopause / surgical menopause / age at menopause / cardiovascular disease / HRT / hazard ratio / pooled analysis

Introduction

Natural menopause is defined as absence of menstruation over a period of 12 months when not caused by medical treatment or surgery (Nelson, 2008), while surgical menopause refers to the removal of both ovaries (bilateral oophorectomy) prior to natural menopause (Rodriguez and Shoupe, 2015). The most significant physiological change during menopause is the decline of endogenous oestrogen and subsequent cessation of ovarian function (Bachmann, 2001). Oestrogen is cardioprotective and its decline may increase the risk of cardiovascular disease (CVD) among postmenopausal women (Mendelsohn and Karas, 1999).

Heart disease is a leading cause of illness and death for women (Benjamin et al., 2019). Previous studies have examined the links between age at natural menopause or surgical menopause separately on the risk of incident CVD (Muka et al., 2016), but few have compared their effects (Dam et al., 2019). The extent that the risk of CVD varies by the type of menopause remains unclear.

Age at menopause (natural or surgical) is an important covariate in the relationship between type of menopause and incident CVD. Earlier age at menopause has been linked to an increased risk of CVD mortality and all-cause mortality (van der Schouw et al., 1996; Muka et al., 2016). In addition, hysterectomy in women aged 50 years or younger is known to increase the risk for CVD later in life, and surgical menopause may further add to the risk of both coronary heart disease (CHD) and stroke (Ingelsson et al., 2011; Yeh et al., 2013; Evans et al., 2016). This suggests that an interaction may exist between the type of menopause and age at menopause on the risk of incident CVD. Also, the association between menopause and risk of CVD might be modified by different HRT status.

The aim of this study is to examine the variation in risk of CVD by type of menopause (natural menopause or surgical menopause) and determine the extent that their effects interact with age at menopause and HRT use. Individual-level data were used from 10 studies that contributed to the International collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE) consortium.

Materials and methods

Study participants

InterLACE has pooled individual-level data on reproductive health and chronic diseases from over 500 000 women from 25 observational studies across 10 countries. Most studies were of prospective longitudinal design and collected survey data on key reproductive, sociodemographic, lifestyle factors and disease outcomes. After the studies had joined InterLACE, a harmonisation process was developed to combine individual-level data. A more detailed description of the InterLACE consortium, including the study recruitment and data harmonisation process, has been published previously (Mishra et al., 2013; Mishra et al., 2016). For the present analyses, we aimed to compare the association of incident CVD for women with natural menopause and those with surgical menopause (i.e. bilateral oophorectomy). Fifteen studies in the InterLACE consortium had collected data on CVD outcomes (including CHD and stroke). Among them, 10 studies have also collected information on the number of ovaries removed for those who had oophorectomy/hysterectomy, and the age at natural menopause for those who did not experience surgery at all. Women with hysterectomy but with ovaries conserved were omitted, as their age at menopause could not be identified for certain. To examine the associations between both types of menopause and incident CVD, we excluded women who had experienced CVD events before menopause ($n = 1784$). Women who had missing data on key covariates were also excluded, including age at last follow-up, race/ethnicity, education level, BMI, smoking status, hypertension status, type 2 diabetes at baseline and HRT status after menopause ($n = 13\ 304$). As a result, this study was based on 10 studies with 203 767 postmenopausal women who reported their type of menopause and age at menopause, and information on CVD events. A flow chart of cohorts selection is shown in [Supplementary Fig. S1](#).

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.

Exposure and outcome variables

The main exposures for this study were two types of menopause, surgical menopause and natural menopause (the reference group). Natural menopause was defined as absence of menstruation over a period of 12 months and no experience of hysterectomy and/or oophorectomy prior to this. Surgical menopause was defined as removal of both ovaries. Age at menopause was categorised as <35, 35–39, 40–44, 45–49, 50–54 and ≥ 55 years.

The study outcome was the first non-fatal CVD event, either self-reported or ascertained from hospital medical records. CVD events were defined as either incident CHD (including heart attack and angina) or stroke (including ischaemic stroke or haemorrhagic stroke). When CVD events were ascertained from hospital records, CHD events were identified using the 10th edition of the International Classification of Diseases (ICD-10) codes I21, I22, I23, I24 and I25, or using the 9th edition (ICD-9) codes 410, 411, 412 and 413. The incidence of stroke was identified using ICD-10 codes I60, I61, I63 and I64, or ICD-9 codes 430, 431, 432, 433 and 434.

Covariates

We included the following factors in the analyses as potential confounders according to evidence from previous studies: (Schoenaker *et al.*, 2014; Zhu *et al.*, 2018a,b) race/ethnicity, years of education, smoking status, BMI, hypertension status, type 2 diabetes, parity and age at menarche. Information collected at baseline was used in the analyses. Furthermore, we adjusted for HRT status in the survey following menopause. Race/ethnicity was grouped into six categories: Caucasian-European, Caucasian-Australian/New Zealand, Caucasian-American/Canadian, Asian, African American/Black and other. Years of education was categorised into ≤ 10 , 11–12 and > 12 years. Smoking status was categorised as current, former, and never smokers. BMI was categorised according to the World Health Organization criteria as < 18.5 kg/m², 18.5–24.9 kg/m², 25–29.9 kg/m² and ≥ 30 kg/m². Hypertension or diabetes status was dichotomised as present or absent based on self-report at baseline. Parity was categorised as 0, 1, 2 and ≥ 3 live births. Age at menarche (self-reported) was divided into five categories as ≤ 11 , 12, 13, 14 and 15 years or more. HRT status after menopause was defined as user or non-user.

Statistical analyses

Baseline characteristics were presented as mean and SD for continuous variables and as percentages (%) for categorical variables. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CI for the study endpoints associated with natural menopause and surgical menopause. We evaluated the proportional hazards assumption by visual inspection of figures of the Schoenfeld residuals plot and it indicated no violation. Study level variability was included in models as a random effect. As the entry age of women in each study of InterLACE varied, women who experienced menopause at a younger age (e.g. < 40 years) will have a longer follow-up time than those who had later menopause. Thus, as a statistical measure to avoid left-truncation bias, the minimum age at surgical menopause (i.e.

28 years) was used as a fixed age for all women to calculate time-to-event. For women with a CVD event, follow-up time was calculated as their age at first CVD event minus 28 years; for women without a CVD event, follow-up time was defined as their age at last follow-up minus 28 years. Women with natural menopause formed the reference category. Because the time between age 28 years and menopause was unexposed person-years, we used time-dependent variable of menopausal status to deal with the issue of immortal time bias. All incident CVD was investigated first, followed by separate analyses for incident CHD and stroke. HRs (95% CI) were estimated using models which included race/ethnicity, education level, BMI, smoking status, hypertension status, type 2 diabetes, parity and HRT status after menopause.

The first analysis was to determine the association between types of menopause (the exposure) and incident CVD using natural menopause as the reference category, then the analyses were stratified by age at menopause using natural menopause at 50–54 years as the reference. In addition, age at menopause was also treated as a continuous variable to estimate the effect of 1-year decrease. HRT status might mediate the association between menopause types and incident CVD, so a further analysis examined the combined effect of types of menopause and HRT status on incident CVD.

We compared the goodness of fit of nested models using values of $-2 \log L$ and the Akaike Information Criterion (where a smaller value indicates a better fit). We also calculated χ^2 statistics between nested models to assess whether the change was statistically significant after adding a parameter to the original model.

Sensitivity analysis

Five sensitivity analyses were completed. First, only those CVD cases ascertained by hospital registry data from the DNC, WHL and UK Biobank studies were included. Second, because the UK Biobank contributed over 50% of the total CVD cases, an analysis was undertaken that excluded this study. Third, the women's characteristics in the complete dataset were compared with those in the dataset with missing values, and an analysis was conducted using data from a 10 times multiple imputation to impute missing covariates. Fourth, as age at menarche was also a potential confounder that could affect the association between menopause and incident CVD (Wilson and Mishra, 2016), it was included in a model using data from nine studies (WHITEHALL study did not collect data on age at menarche). Last, family history of CVD was included in the model using data from four studies (DNC, UKWCS, WHITEHALL and UK Biobank) that had relevant information.

Statistical analyses were performed using SAS (version 9.4, SAS Institute Inc, Cary, NC, USA). The proportional hazards regression procedure was used to perform the Cox proportional hazards regression analyses. All statistical tests were based on the two-sided 5% level of significance corresponding to two-sided 95% CI of the HR.

Results

Study characteristics

Of the 203 767 postmenopausal women in the 10 studies, 87.5% experienced natural menopause and 12.5% experienced surgical

menopause. There were 13 460 CVD events, including 9966 CHD and 4578 stroke events. The mean (SD) age at menopause was 49.7 (5.0) years, and the mean (SD) age at last follow-up was 61.0 (6.9) years (Table I). Nearly 54% of women were born between 1940 and 1949. The median (interquartile range: Q1–Q3) age at menopause for natural menopause and surgical menopause was 50.0 (48.0–53.0) and 47.0 (42.0–52.0) years, respectively. Women with surgical menopause were more likely to be Caucasian-Australian, with lower education level, obese and non-HRT users (Table II).

Types and age of menopause and incident CVD

Compared with natural menopause, the initial analysis (Model 1, Table III) showed that surgical menopause was associated with over 20% higher risk of CVD (HR 1.22, 95% CI 1.16–1.28), with similar results for the incidence of CHD and stroke. After adjusting for age at menopause (Model 2, Table III), the relationship with each outcome was attenuated. Comparison of nested models that included both type of menopause and age at menopause showed that although age at menopause explained much of the association with incident CVD, there was also an interaction between type of menopause and age at menopause ($P < 0.001$, Supplementary Table SI). It was found that compared with natural menopause at age 50–54 years, surgical menopause before age 35 (2.55, 2.22–2.94) and 35–39 years (1.91, 1.71–2.14) was associated with higher risk of CVD than natural menopause at the same age (1.59, 1.23–2.05 and 1.51, 1.33–1.72, respectively) (Table IV). The HRs (95% CIs) were similar between complete case analyses (Table IV) and multiple imputation-based analyses (Table V). When age at menopause was analysed as a continuous variable, each 1-year decrease was associated with an increased risk of incident CVD of 3% (1.03, 1.02–1.04) in natural menopause group, and 5% (1.05, 1.05–1.06) in surgical menopause group.

Examining the joint effect with HRT status, we found the association between surgical menopause and incident CVD was only evident in non-users of HRT (1.12, 1.06–1.19) (Supplementary Table SII, Fig. 1). Women who experienced surgical menopause at earlier age (<50 years) and took HRT had lower risk of incident CVD than those who were not users of HRT, while the effects of natural menopause on risk of CVD varied little by HRT status (Supplementary Table SII, Fig. 1).

Sensitivity analysis

When CVD cases ascertained by hospital records were analysed (Supplementary Table SIII), similar results were produced to those presented in Table V. After excluding the UK Biobank study, associations between surgical menopause and risk of CVD were remained (Supplementary Table SIV). Overall, women's characteristics in the complete and missing datasets were comparable (Supplementary Table SV). Results remained unchanged when models were adjusted for age at menarche or family history of CVD (data not shown).

Discussion

Compared with natural menopause, surgical menopause was associated with a higher risk of incident CVD. Although this was largely

attenuated after adjustment for age at menopause, there was still evidence of an interaction between type of menopause and the age at menopause. Risk of incident CVD increased with earlier age at menopause for both natural and surgical menopause, and surgical menopause was associated with an additional risk compared with women with natural menopause at the same age. For women with early surgical menopause, HRT use reduced but did not eliminate the excess risk of CVD.

Compared with women with average age at natural menopause, our previous research has shown that women with premature and early natural menopause experienced a substantially increased risk of first non-fatal CVD event (either CHD or stroke) before the age of 60 years (Zhu et al., 2019). Our findings here showed that although age at menopause largely attenuated the association of both natural and surgical menopause with incident CVD, there was a graded relationship between earlier age at menopause and incident CVD across both types of menopause. Our findings are consistent with a recent study that found each 1-year decrease in age at menopause was associated with 2% higher risk of incident CHD (Dam et al., 2019).

In previous research, a Nurses' Health Study (NHS) study showed surgical menopause was significantly associated with incident CHD and stroke compared with women who had hysterectomy with ovarian conservation, especially for women who experienced surgery before age 45 years and those who never used HRT (Colditz et al., 1987; Parker et al., 2009). In contrast, the Women's Health Initiative (WHI) study observed no association, even after stratifying the analysis by age at menopause (<40, 40–49, 50 years and above) (Jacoby et al., 2011). Both of these studies adjusted for age at surgical menopause in the models. Their conflicting findings may be related to different ages at enrolment (mean age was 63 years for WHI versus 51 years for NHS) and different cut-points for age at menopause used for analyses. As both studies used women with hysterectomy and ovaries conserved as the reference group, the comparison with natural menopause was not considered. Using women with natural menopause as the reference and stratifying the analysis by age at menopause, we found the highest risks with incident CVD were in the earlier age at surgical menopause group. Guidelines already suggest that surgical menopause for risk reduction of diseases, such as cancer, should be balanced with the consequences of loss of ovarian hormones (American College of Obstetricians and Gynecologists (ACOG), 2008; The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2017). Findings on CVD from our study lend some support to the position that elective bilateral oophorectomy (surgical menopause) at hysterectomy for benign diseases should be discouraged based on an increased risk of CVD (Matthews, 2016).

There are several possible reasons why surgical menopause had a stronger association with incident CVD than natural menopause. First, oophorectomy is often part of a hysterectomy, and about 90% of hysterectomies were caused by benign disease, such as fibroids and endometriosis (Hammer et al., 2015). These benign indications might coexist with some metabolic conditions, which may increase the risk of CVD, or they might increase the risk of CVD directly. The association between uterine fibroids and serum lipids is mixed. Some studies found that women with uterine fibroids had unfavourable lipid profile (Melo et al., 2010; Uimari et al., 2016), while more studies found that women with uterine fibroids had a higher high-density lipoprotein-C level, lower low-density lipoprotein-C level and lower total cholesterol

Table 1 Characteristics of individual studies in the InterLACE consortium.

Study	Country	N	Number of CVD event	Baseline survey year	Last survey year used	Age at menopause, 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	8 183	957	1996	2013	50.1 (5.3)	62.7 (4.0)		74.8		25.2			
Melbourne Collaborative Cohort Study (MCCS)	Australia	13 387	1525	1990–1994	2003–2006	48.8 (5.5)	67.1 (7.9)	30.2	41.0	25.2	3.6			
Danish Nurse Cohort Study (DNC)	Denmark	9719	1484	1993	1999	49.0 (4.4)	69.2 (9.0)	26.6	48.8	24.6				
Women's Lifestyle and Health Study (WLH)	Sweden	10 467	759	1991–1992	2003–2004	50.1 (4.1)	55.6 (4.0)		72.5	26.7	0.8			
MRC National Survey of Health and Development (NSHD)	UK	638	63	1993	2000	49.4 (4.3)	53.9 (0.3)		100					
National Child Development Study (NCDS)	UK	307	13	2008	2013	48.3 (4.5)	54.7 (1.2)			100				
English Longitudinal Study of Ageing (ELSA)	UK	1906	517	2002	2010–2011	49.2 (5.8)	70.3 (9.8)	21.0	28.1	37.8	12.9			0.2
UK Women's Cohort Study (UKWCS)	UK	7923	462	1995–1998	1999–2004	48.8 (5.2)	60.3 (7.5)	11.4	39.2	41.5	7.9			0.1
Whitehall II study (WHITEHALL)	UK	1732	309	1985–1988	2006	49.5 (4.7)	64 (6.6)	0.1	49.5	44.4	6.0			
UK Biobank (UK)	UK	149 505	7371	2006–2010	2013*	49.8 (5.0)	60.1 (5.8)		4.3	56.5	35.5			3.8
All cohorts combined		203 767	13 460			49.7 (5.0)	61.0 (6.9)	4.0	10.3	53.7	29.2			2.8

*There were 20 000–25 000 people included in the repeated assessment. CVD, cardiovascular disease; InterLACE, International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events.

Table II Baseline characteristics of women by type of menopause (*n* = 203 767 women).

	Natural menopause, 178 304 (87.5%)	Surgical menopause, 25 463 (12.5%)
Age at baseline (years), mean (SD)	58.1 (7.1)	57.5 (7.5)
Age at menopause (years), median (Q1–Q3)	50.0 (48.0–53.0)	47.0 (42.0–52.0)
Age in years at last follow-up		
<55	28 956 (16.2)	5 178 (20.3)
55–60	44 009 (24.7)	5 111 (20.1)
≥60	105 329 (59.1)	15 174 (59.6)
Race/ethnicity		
Caucasian-Australian	12 812 (7.2)	3061 (12.0)
Caucasian-European	159 478 (89.4)	21 479 (84.4)
Caucasian-American	541 (0.3)	61 (0.2)
Asian	2609 (1.5)	333 (1.3)
Black	1660 (0.9)	330 (1.3)
Others	1194 (0.7)	199 (0.8)
Educational attainment		
≤10 years	86 812 (48.7)	14 278 (56.1)
11–12 years	21 119 (11.8)	2897 (11.4)
>12 years	70 363 (39.5)	8288 (32.5)
BMI (kg/m ²)		
Underweight, <18.5	1896 (1.1)	173 (0.7)
Normal, 18.5–24.9	77 971 (43.7)	9060 (35.6)
Overweight, 25.0–29.9	63 358 (35.5)	9433 (37.0)
Obese, ≥30	35 069 (19.7)	6797 (26.7)
Smoking status		
Never	100 693 (56.5)	14 323 (56.3)
Past	57 858 (32.5)	8186 (32.1)
Current	19 743 (11.1)	2954 (11.6)
Hypertension status		
Yes	133 201 (74.7)	17 454 (68.5)
No	45 093 (25.3)	8009 (31.5)
Type 2 diabetes		
Yes	170 296 (95.5)	23 824 (93.6)
No	7998 (4.49)	1639 (6.4)
HRT use		
Yes	106 094 (59.5)	6571 (25.8)
No	72 200 (40.5)	18 892 (74.2)
Number of children		
0	28 905 (16.2)	4579 (18.0)
1	22 063 (12.4)	3374 (13.3)
2	76 890 (43.1)	11 392 (44.7)
3+	49 411 (27.7)	7708 (30.3)

Q1, first quartiles; Q3, third quartiles.

level (Sadlonova et al., 2008; Sersam, 2012; Hussam and Zwain, 2016). A recent prospective study found that the presence of fibroids was not associated with subclinical CVD (Laughlin-Tommaso et al., 2019). Thus, the presence of uterine fibroids might not explain the difference with risk of CVD between surgical menopause and natural menopause. Evidence has shown endometriosis was associated with increased risk of CHD (Mu et al., 2016; Tan et al., 2019). The strong

association observed between surgical menopause and incident CVD might be confounded by endometriosis. To the best of our knowledge, however, no studies have compared the effect of surgical and natural menopause on the risk of CVD by adjusting for endometriosis. Atsma et al. (2006) compared the effect of premature menopause (<40 years) versus menopause >45 years on risk of CVD in surgical menopausal women and natural menopausal women separately, and

Table III The hazard ratio (95% CI) between type of menopause and incident CVD.*

	CVD		CHD		Stroke	
	Model 1	Model 2=Model 1+ age	Model 1	Model 2=Model 1+ age	Model 1	Model 2=Model 1+ age
Menopause types						
Natural menopause	Reference	Reference	Reference	Reference	Reference	Reference
Surgical menopause	1.22 (1.16, 1.28)	1.05 (1.00, 1.11)	1.26 (1.19, 1.33)	1.08 (1.02, 1.14)	1.21 (1.11, 1.31)	1.03 (0.94, 1.13)

*Cox proportional-hazards models were used to estimate hazard ratios (HR) and 95% CI. Model 1 adjusted: race/ethnicity, education, BMI, smoking status, hypertension status, diabetes status, parity at baseline and postmenopausal hormone therapy status. Model 2 adjusted: Model 1 + age at menopause. CVD, cardiovascular disease; CHD, coronary heart disease.

Table IV The associations between type of menopause and incident CVD by age at menopause (based on complete dataset).*

By age at menopause, years	CVD			CHD			Stroke		
	No. of CVD events	No. of cases per 1000 person-years	Adjusted hazard ratio (95% CI)	No. of CHD events	No. of cases per 1000 person-years	Adjusted hazard ratio (95% CI)	No. of stroke events	No. of cases per 1000 person-years	Adjusted hazard ratio (95% CI)
Natural menopause									
<35	59	3.2	1.59 (1.23, 2.05)	46	2.5	1.59 (1.18, 2.13)	18	1.0	1.41 (0.87, 2.27)
35-39	242	3.1	1.51 (1.33, 1.72)	179	2.3	1.49 (1.28, 1.73)	97	1.2	1.77 (1.43, 2.18)
40-44	1054	2.6	1.32 (1.24, 1.41)	780	1.9	1.32 (1.23, 1.43)	359	0.9	1.31 (1.17, 1.47)
45-59	2887	2.1	1.13 (1.08, 1.18)	2122	1.6	1.13 (1.07, 1.20)	963	0.7	1.11 (1.03, 1.20)
50-54	5424	1.9	Reference	3953	1.3	Reference	1847	0.6	Reference
≥55	1790	1.9	0.97 (0.92, 1.02)	1304	1.4	0.96 (0.90, 1.03)	616	0.7	0.98 (0.89, 1.08)
Surgical menopause									
<35	204	5.4	2.55 (2.22, 2.94)	162	4.2	2.55 (2.17, 2.99)	69	1.8	2.60 (2.03, 3.33)
35-39	322	3.9	1.91 (1.71, 2.14)	249	3.0	1.92 (1.69, 2.19)	108	1.3	1.91 (1.56, 2.33)
40-44	473	3.2	1.58 (1.44, 1.74)	373	2.5	1.63 (1.46, 1.81)	150	1.0	1.54 (1.30, 1.82)
45-59	558	2.4	1.20 (1.10, 1.31)	424	1.8	1.23 (1.11, 1.36)	190	0.8	1.21 (1.04, 1.41)
50-54	362	1.9	0.91 (0.82, 1.01)	278	1.5	0.92 (0.81, 1.05)	125	0.7	0.93 (0.78, 1.12)
≥55	126	1.5	0.73 (0.61, 0.87)	96	1.1	0.76 (0.62, 0.93)	36	0.4	0.61 (0.44, 0.85)

*Cox proportional-hazards models were used to estimate HR and 95% CI. All HRs were adjusted for race/ethnicity, education, BMI, smoking status, hypertension status, parity and menopausal hormone therapy status.

they found the effect in surgical menopause group was higher than that in natural menopause group. This might indicate that the effect of early surgical menopause on the risk of CVD was stronger than the effect of early natural menopause. Second, endogenous oestrogen is protective against heart disease (Mendelsohn and Karas, 1999). In a review, Korse *et al.* concluded that oestrogen level in surgical menopausal women was lower than in women with natural menopause (Korse *et al.*, 2009). Women with surgical menopause experience acute hormonal decline and this may have a severe impact on the vascular system. Last, genetic variations of the oestrogen receptor gene in women with hysterectomy may also be related to risk of CHD (Weel *et al.*, 1999; Shearman *et al.*, 2003).

HRT is recommended for women with earlier menopause to manage menopausal symptoms (Thurston and Joffe, 2011; The North American Menopause Society Hormone Therapy Position

Statement Advisory Panel, 2017). The current evidence suggests that HRT is not indicated for primary or secondary prevention of CHD and it increases the risk of stroke (Boardman *et al.*, 2015). Nevertheless, there is a 'timing' hypothesis, i.e. women who started HRT less than 10 years after menopause had the most favourable effects (Manson *et al.*, 2013). We found that women who had surgical menopause before age 45 years and took HRT had a lower risk of CHD than non-users of HRT. Our findings support the evidence that for women who experienced early surgical menopause, taking HRT might reduce their risk of CHD. Several studies have shown that HRT was associated with less coronary atherosclerosis and lower mortality, while less favourable to risk of stroke (Boardman *et al.*, 2015; Arnsen *et al.*, 2017). The North American Menopause Society has suggested that for women with early surgical menopause or primary ovarian insufficiency, HRT is recommended until at least

Table V The associations (adjusted HR, 95% CI) between type, age of menopause and incident CVD after missing covariates were imputed.*

	CVD			CHD			Stroke		
	No. of CVD events	No. of cases per 1000 person-years	Adjusted HR (95% CI)	No. of CHD events	No. of cases per 1000 person-years	Adjusted HR (95% CI)	No. of stroke events	No. of cases per 1000 person-years	Adjusted HR (95% CI)
Type of menopause [†]									
Natural menopause	12646	1.8	Reference	9116	1.3	Reference	4425	0.6	Reference
Surgical menopause	2131	2.7	1.05 (1.03, 1.06)	1653	2.1	1.07 (1.05, 1.09)	717	0.9	1.05 (1.02, 1.08)
By age at menopause, years									
Natural menopause									
<35	59	3.2	1.54 (1.19, 1.99)	46	2.5	1.55 (1.15, 2.07)	18	1.0	1.37 (0.85, 2.21)
35-39	240	3.1	1.47 (1.29, 1.68)	178	2.3	1.46 (1.26, 1.7)	96	1.2	1.69 (1.37, 2.08)
40-44	2287	1.4	1.50 (1.42, 1.58)	1544	0.9	1.47 (1.38, 1.56)	901	0.5	1.57 (1.43, 1.71)
45-49	2877	2.1	1.12 (1.07, 1.17)	2116	1.6	1.12 (1.06, 1.19)	959	0.7	1.1 (1.01, 1.19)
50-54	5394	1.8	Reference	3929	1.3	Reference	1835	0.6	Reference
≥55	1789	1.9	0.98 (0.93, 1.03)	1303	1.4	0.97 (0.91, 1.03)	616	0.7	1 (0.91, 1.09)
Surgical menopause									
<35	308	5.7	2.65 (2.36, 2.97)	249	4.6	2.69 (2.36, 3.07)	111	2.0	2.83 (2.32, 3.45)
35-39	323	3.9	1.83 (1.63, 2.05)	250	3.0	1.84 (1.62, 2.10)	108	1.3	1.84 (1.50, 2.24)
40-44	476	3.2	1.52 (1.38, 1.67)	376	2.5	1.56 (1.40, 1.74)	150	1.0	1.47 (1.24, 1.74)
45-49	556	2.3	1.14 (1.04, 1.25)	422	1.8	1.17 (1.05, 1.29)	189	0.8	1.16 (1.00, 1.36)
50-54	354	1.9	0.88 (0.79, 0.98)	270	1.5	0.88 (0.78, 1.00)	124	0.7	0.93 (0.77, 1.11)
≥55	114	1.5	0.72 (0.60, 0.87)	86	1.1	0.75 (0.61, 0.93)	35	0.4	0.63 (0.45, 0.89)

*Cox proportional-hazards models were used to estimate HR and 95% CI All HRs were adjusted for race/ethnicity, education, BMI, smoking status, hypertension status, diabetes status, parity and menopausal hormone therapy status.

[†]Age at menopause was further adjusted.

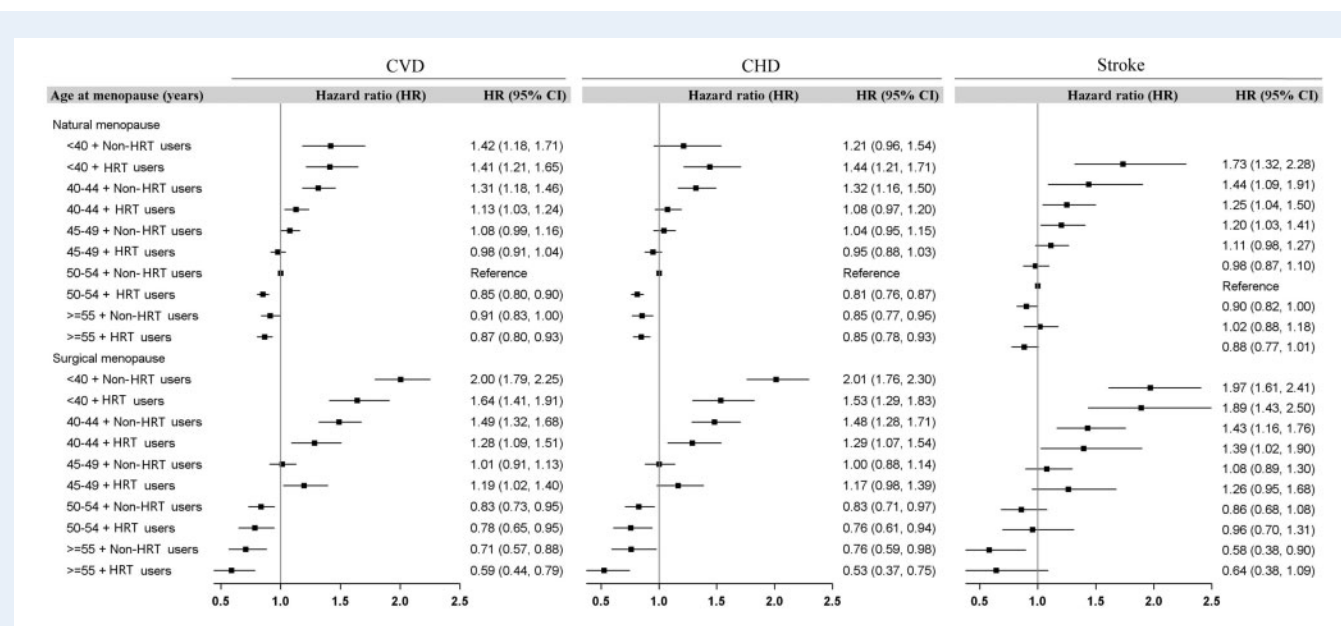


Figure 1. The associations between types of menopause and incident CVD by age at menopause and HRT status. Cox proportional-hazards models were used to estimate HRs and 95% CI. All HRs were adjusted for race/ethnicity, education, BMI, smoking status, hypertension status, diabetes status, and parity. CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio.

the median age of menopause (i.e. 50–52 years) ([The North American Menopause Society Hormone Therapy Position Statement Advisory Panel, 2017](#)).

Strengths and limitations

The main strength of this study was the use of pooled individual-level data from 10 studies across different geographic regions and populations. This provided a large sample size and sufficient statistical power to quantify the association between natural and surgical menopause, age at menopause and specific types of incident CVD. The participant-level data in InterLACE has enabled the harmonisation of variables using common definitions, coding and cut points, which is not usually possible with meta-analyses of published results. This has also enabled the investigation of associations of surgical menopause compared with those of natural menopause, while taking into account a wide range of covariates.

Several limitations need to be acknowledged. First, self-reported oophorectomy status and age at menopause in this study may lead to some misclassifications of the exposure groups, e.g. some women who reported bilateral oophorectomy (surgical menopause) might be unilateral oophorectomy. However, previous studies found self-reported oophorectomy were in high concordance with the assessment of the surgical record ([Colditz et al., 1987](#); [Phipps and Buist, 2009](#)), and misclassification would only make the effect of surgical menopause underestimated. Second, around 38% of postmenopausal CVD events were self-reported, but consistent findings were observed in the sensitivity analysis confined to CVD events ascertained through medical records. Third, we used variables reported at baseline (mid age) or postmenopausal single time of HRT status as covariates rather than treating them as time-varying covariates, which may lead to some bias. Nonetheless, in studies of InterLACE that included women who reported smoking status and BMI levels both before and after menopause (i.e. UK Biobank, NSHD, NCDS), the concordance was approximately 83%. In addition, for around 80% of women using HRT, the treatment would last over 6 years ([Karim et al., 2011](#)). Thus, we conclude that the bias caused by time-varying covariates is limited. Fourth, we lacked information on type (oestrogen-only or oestrogen plus progestin) and route (oral or transdermal) of HRT use, thus whether the risk for CVD varied by type and route of HRT use could not be examined in this study. Last, as the outcome of this study was non-fatal CVD events, the exclusion of fatal CVD events may bias our results. However, given that only 7.2% of individuals have a fatal event as their first CVD event ([Jorstad et al., 2016](#)) and that earlier menopause has been associated with higher CVD mortality ([Muka et al., 2016](#)), the inclusion of fatal events in the analyses would only strengthen the association between earlier age at menopause and incident CVD.

In summary, earlier surgical menopause (e.g. <45 years) poses additionally increased risk of incident CVD events, compared with women with natural menopause at the same age, and this risk increased with lower age at menopause. Although HRT use reduced the risk of CVD in women with early surgical menopause, it did not eliminate the excess risk.

Our findings may have important public health implications. First, prophylactic bilateral oophorectomy at the time of hysterectomy should be undertaken with great caution, especially in women with

benign conditions and younger than 50 years. Second, in women with early surgical menopause or primary ovarian insufficiency, taking HRT might reduce their excess risk of CVD. Third, in clinical practice, women who experienced natural menopause or had surgical menopause at an earlier age need close monitoring and engagement for preventive health measures and early diagnosis of CVD. Last, our findings suggested that timing of menopause should be considered as an important factor in risk assessment of CVD for women. Further research is needed to assess the added value of these female-specific predictors to existing CVD models for women.

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Authors' roles

DZ conducted the literature review, statistical analyses and drafted the manuscript. HFC and NP harmonised the data and contributed to the interpretation of the results. AJD contributed to the statistical analyses and interpretation of the results. EJB, DCG, DK, RH, JEC, GGG, FB, PD, MKS, SS and EW provided study data. GDM conceived the study design and contributed to interpretation of the results. All authors contributed to critical revision of the manuscript.

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Conflict of interest

The authors have declared that no competing interests exist.

Disclaimer

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