Article:
Zhu, D, Chung, H-F, Dobson, AJ et al. (13 more authors) (2020) Type of menopause, age of menopause and variations in the risk of incident cardiovascular disease: pooled analysis of individual data from 10 international studies. Human Reproduction. ISSN 0268-1161

https://doi.org/10.1093/humrep/deaa124

Original Research

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

Running title: Natural, surgical menopause and cardiovascular disease

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Word count: main text, 3103 (not include abstract, acknowledgement and reference)

Abstract

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 with women with natural menopause at the same age, and MHT 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 MHT use 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.

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. The study outcome was the first non-fatal CVD (defined as either incident CHD or stroke) event ascertained from hospital medical records or self-reported. We used Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals (HR, 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 age 50-54 years, women with surgical menopause before age 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 MHT had lower risk of incident CHD than those who were not users of MHT.

Limitations, reasons for caution: Most of the studies (except birth cohorts) relied on self-reported data on type and age of menopause which may have led to some degree of bias.

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.

Study funding/competing interest(s): InterLACE project is funded by the Australian National Health and Medical Research Council project grant (APP1027196). GDM is supported by Australian National Health and Medical Research Council Principal Research Fellowship (APP1121844). There is no competing interests.

Keywords: natural menopause, surgical menopause, cardiovascular disease, menopausal hormone therapy, hazard ratio

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 (Muka *et al.*, 2016; van der Schouw *et al.*, 1996). 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 (Evans *et al.*, 2016; Ingelsson *et al.*, 2011; Yeh *et al.*, 2013). 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 menopausal hormone therapy (MHT) 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 MHT 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 ten 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, ten 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, body mass index (BMI), smoking status, hypertension status, type 2 diabetes at baseline, and menopausal hormone therapy (MHT) 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 was shown in Figure 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 ischemic 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.*, 2018; Zhu *et al.*, 2018) race/ethnicity, years of education, smoking status, body mass index (BMI), hypertension status, type 2 diabetes, parity, and age at menarche. Information collected at baseline was used in the analyses. Further, we adjusted for MHT 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 (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. 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 was divided into 5 categories as ≤11, 12, 13, 14, and 15 years or more. MHT status after menopause was defined as user or non-user.

Statistical analyses

Baseline characteristics were presented as means and standard deviation (SD) for continuous variables and as percentages (%) for categorical variables. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence

intervals (HR, 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 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 MHT 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. MHT status might mediate the association between menopause types and incident CVD, so a further analysis

examined the combined effect of types of menopause and MHT status on incident CVD.

We compared the goodness of fit of nested models using values of -2logL and Akaike Information Criterion (AIC) (where a smaller value indicates a better fit). We also calculated Chi-Square 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). The PHREG 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% confidence intervals 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 1). Nearly 40% 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-MHT users (Table 2).

Types and age of menopause and incident CVD

Compared with natural menopause, the initial analysis (Model 1, table 3) 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 3), 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 (Table S1), there was also an interaction between type of menopause and age at menopause ($p<0.001$, Table S1). 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 4, Figure 1). The HRs (95% CIs) were similar between complete case analyses (Table 4) and multiple imputation-based analyses (Table 5). 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 MHT status, we found the association between surgical menopause and incident CVD was only evident in non-users of MHT (1.12, 1.06-1.19) (Table S2, Figure 2). Women who experienced surgical menopause at earlier age (<50 years) and took MHT had lower risk of incident CVD than those who were not users of MHT, while the effects of natural menopause on risk of CVD varied little by MHT status (Table S2, Figure 2).

Sensitivity analysis

When CVD cases ascertained by hospital records were analysed (Table S3), similar results were produced to those presented in Table 5. After excluding the UK Biobank study, associations between surgical menopause and risk of CVD were remained (Table S4). Overall, women's characteristics in the complete and missing datasets were comparable (Table S5). Results remained unchanged when models were adjusted for age at menarche or family history of CVD (data not shown).

Discussion

Summary of results

Compared with natural menopause, surgical menopause was associated with 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, MHT 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 (Dongshan Zhu, 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, an 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 MHT (Colditz *et al.*, 1987; Parker *et al.*, 2009). In contrast, the 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 due to different ages at enrolment (mean age was 63 years for WHI vs. 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, thus 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 hormone (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 HDL-C level, lower LDL-C level and lower total cholesterol level (Hussam and Zwain, 2016; Sadlonova *et al.*, 2008; Sersam, 2012). 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 compared the effect of premature menopause (<40 years) vs menopause >45 years on risk of CVD in surgical menopausal women and natural menopausal women separately, and they found the effect in surgical menopause group was higher than that in natural menopause group (Atsma *et al.*, 2006). 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, Susan 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 (Shearman *et al.*, 2003; Weel *et al.*, 1999).

MHT is recommended for women with earlier menopause to manage menopausal symptoms (The North American Menopause Society Hormone Therapy Position Statement Advisory Panel, 2017; Thurston and Joffe, 2011). The current evidence suggests that MHT 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 MHT 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 MHT had lower risk of CHD than non-users of MHT. Our findings support the evidence that for women who experienced early surgical menopause, taking MHT might reduce their risk of CHD. Several studies have shown that MHT was associated with less coronary

atherosclerosis and lower mortality, while less favourable to risk of stroke (Arnson *et al.*, 2017; Boardman *et al.*, 2015). The North American Menopause Society has suggested that for women with early surgical menopause or primary ovarian insufficiency, MHT is recommended until at least the median age of menopause (i.e., 50-52 years) (The North American Menopause Society Hormone Therapy Position Statement Advisory Panel, 2017).

Strength and limitation

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 harmonization 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 MHT 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 MHT, 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 MHT use, thus whether the risk for CVD varied by type and route of MHT 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 MHT 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 MHT 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.

Acknowledgements

The data on which this research is based were drawn from 10 observational studies. The research included data from the ALSWH, the University of Newcastle, Australia, and the University of Queensland, Australia. We are grateful to the Australian Government Department of Health for funding and to the women who provided the survey data. The MCCS cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further augmented by Australian National Health and Medical Research Council grants 209057, 396414 and 1074383 and by infrastructure provided by Cancer Council Victoria. Cases and their vital status were ascertained through the Victorian Cancer Registry and the Australian Institute of Health and Welfare, including the National Death Index and the Australian Cancer Database. DNC was supported by the National Institute of Public Health, Copenhagen, Denmark. WLH was funded by a grant from the Swedish Research Council (Grant number 521-2011-2955). NSHD has core funding from the UK Medical Research Council (MC UU 12019/1). NCDS is funded by the Economic and Social Research Council. ELSA is funded by the National Institute on Aging (Grants 2RO1AG7644 and 2RO1AG017644-01A1) and a consortium of UK government departments. UKWCS was funded by the World Cancer Research Fund. The Whitehall II study has been supported by grants from the Medical Research Council (K013351) and British Heart Foundation (RG/16/11/32334). This research has been conducted using the UK Biobank resource under application 26629. All studies would like to thank the participants for volunteering their time to be involved in the respective studies. The findings and views in this paper are not necessarily those of the original studies or their respective funding agencies.

Authors' roles

D.Z. conducted the literature review, statistical analyses and drafted the manuscript. H.F.C. and N.P. harmonised the data and contributed to the interpretation of the results. A.J.D. contributed to the statistical analyses and interpretation of the results. E.J.B., D.C.G., D.K., R.H., J.E.C., G.G.G., F.B., P.D., M.K.S., S.S. and E.W. provided study data. G.D.M. conceived the study design and contributed to interpretation of the results. All authors contributed to critical revision of the manuscript.

Funding

InterLACE project is funded by the Australian National Health and Medical Research Council project grant (APP1027196). GDM is supported by Australian National Health and Medical Research Council Principal Research Fellowship (APP1121844). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

The authors have declared that no competing interests exist.

Disclaimer

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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	8183	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 were included in the repeated assessment.

Abbreviations: InterLACE, International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events; SD, standard deviation. UK: United Kingdom.

Table 2. 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, mean (SD)	58.1 (7.1)	57.5 (7.5)
Age at menopause, median (Q1, Q3)	50.0 (48.0, 53.0)	47.0 (42.0, 52.0)
Age at last follow-up		
<55	28956 (16.2)	5178 (20.3)
55-60	44009 (24.7)	5111 (20.1)
≥60	105329 (59.1)	15174 (59.6)
Race/ethnicity		
Caucasian-Australian	12812 (7.2)	3061 (12.0)
Caucasian-European	159478 (89.4)	21479 (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	86812 (48.7)	14278 (56.1)
11-12 years	21119 (11.8)	2897 (11.4)
>12 years	70363 (39.5)	8288 (32.5)
Body mass index (kg/m^2)		
Underweight, <18.5	1896 (1.1)	173 (0.7)
Normal, 18.5-24.9	77971 (43.7)	9060 (35.6)
Overweight, 25.0-29.9	63358 (35.5)	9433 (37.0)
Obese, ≥30	35069 (19.7)	6797 (26.7)
Smoking status		
Never	100693 (56.5)	14323 (56.3)
Past	57858 (32.5)	8186 (32.1)
Current	19743 (11.1)	2954 (11.6)
Hypertension status		
Yes	133201 (74.7)	17454 (68.5)
No	45093 (25.3)	8009 (31.5)
Type 2 diabetes		
Yes	170296 (95.5)	23824 (93.6)
No	7998 (4.49)	1639 (6.4)
MHT use		
Yes	106094 (59.5)	6571 (25.8)
No	72200 (40.5)	18892 (74.2)
Number of children		
0	28905 (16.2)	4579 (18.0)
1	22063 (12.4)	3374 (13.3)
2	76890 (43.1)	11392 (44.7)
3+	49411 (27.7)	7708 (30.3)

Abbreviations: SD, standard deviation; Q1, first quartiles; Q3, third quartiles; MHT, menopausal hormone therapy.

Table 3. 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	Ref	Ref	Ref	Ref	Ref	Ref
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% confidence interval (95% CI).
Model 1 adjusted: race/ethnicity, education, body mass index, smoking status, hypertension status, diabetes status, parity at baseline and postmenopausal hormone therapy status.
Model 2 adjusted: Model 1 + age at menopause.
Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.

Table 4. 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	Ref	3953	1.3	Ref	1847	0.6	Ref
≥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 hazard ratios (HR) and 95% confidence interval (95% CI). All HRs were adjusted for race/ethnicity, education, body mass index, smoking status, hypertension status, parity and menopausal hormone therapy status.
Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.

Table 5. 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 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)
Type of menopause[†]									
Natural menopause	12646	1.8	Ref	9116	1.3	Ref	4425	0.6	Ref
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	Ref	3929	1.3	Ref	1835	0.6	Ref
≥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 hazard ratios (HR) and 95% confidence interval (95% CI). All HRs were adjusted for race/ethnicity, education, body mass index, smoking status, hypertension status, diabetes status, parity and menopausal hormone therapy status. Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.
[†] Age at menopause was further adjusted.