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The association between reproductive lifespan and incident nonfatal cardiovascular disease: a pooled analysis of individual patient data from 12 studies

Short title: Reproductive lifespan and incident CVD

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Key Points

Question: Is the length of reproductive lifespan associated with future risk of CVD events?

Findings: In a pooled analysis of 307,855 women from 12 studies participating in the International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE), we found that short reproductive lifespan (<33 years) was associated with an increased risk of CVD events in midlife. Women who had both short reproductive lifespan and early menarche (≤11 years) had the most pronounced risk of CVD events.

Meaning: These findings highlight reproductive lifespan as a potential marker of women's risk of CVD events in midlife.

Tweet: "A pooled analysis of 12 observational studies found that short reproductive lifespan (<33 years) was associated with an increased risk of non-fatal CVD events in midlife, and the risk was higher for women with early menarche (≤11 years)."

ABSTRACT

Importance

Early menarche and early menopause are associated with increased risk of cardiovascular disease (CVD) in mid-life, but little is known about the association between reproductive lifespan and the risk of CVD.

Objective

We aimed to investigate the association between the length of reproductive lifespan and risk of incident CVD events, while also considering the timing of menarche and menopause.

Design, setting and participants

Individual-level data were pooled from 12 studies participating in the International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE). Altogether 307,855 women provided complete information on the timing of menarche and menopause, non-fatal CVD events, and covariates. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95%CI), adjusted for covariates. The association between reproductive lifespan and CVD was adjusted for age at menarche and age at menopause separately.

Exposures

Reproductive lifespan was calculated by subtracting age at menarche from age at menopause and categorised as <30, 30-32, 33-35, 36-38 (reference), 39-41, 42-44, and ≥45 years.

Main outcomes and measures

First non-fatal CVD event, including coronary heart disease and stroke events.

Results

Pooled analyses showed that women with very short reproductive lifespans (<30 years) were at 1.71 (HR 95%CI 1.58, 1.84) times higher risk of incident CVD events than women with reproductive lifespans of 36-38 years after adjustment for covariates. This association remained unchanged when adjusted for age at menarche, but was attenuated to 1.26 (1.09, 1.46) when adjusted for age at menopause. There was a significant interaction between reproductive lifespan and age at menarche associated with CVD risk (P <0.001). Women who had both short reproductive lifespans (<33 years) and early menarche (≤11 years) had the highest risk of CVD (HR 2.06, 95%CI 1.76-2.41) compared with those with reproductive lifespans of 36-38 years and menarche at 13 years.

Conclusions and relevance

Short reproductive lifespan was associated with an increased risk of non-fatal CVD events in midlife, and the risk was significantly higher for women with early age at menarche.

Keywords: cardiovascular disease, coronary heart disease, stroke, menarche, menopause, reproductive lifespan

INTRODUCTION

Globally, cardiovascular disease (CVD) contributes to a high burden of mortality and morbidity for women.[1,2] Women who experience early menarche [3,4] and early menopause [3,5] are at increased risk of CVD, which suggests a potential role for the female reproductive lifespan in the risk of CVD in later life.[2,6,7]

Two systematic review and meta-analysis studies have shown that early menarche and early menopause are associated with higher risk of all-cause mortality, while the associations with cardiovascular mortality and non-fatal cardiovascular outcomes were less conclusive.[8,9] Subsequently, three large studies have shown fairly consistent evidence for links of early menarche and early menopause with CVD events.[3-5] Besides the timing of menarche and menopause, recent interest has emerged in the association between CVD risk and reproductive lifespan (defined by age at menopause minus age at menarche). The Nurses' Health Study (NHS) reported that a shorter reproductive lifespan (<30 years) was associated with a 1.32 (95% confidence interval [CI] 1.16-1.49) times higher risk of CVD events compared with a reproductive lifespan of ≥42 years.[3] Further, the association with long reproductive lifespan was either null[10,11] or mixed.[3,12,13] These findings suggest that the association between reproductive lifespan and CVD is not entirely clear and requires further investigation. Additionally, our previous study showed that women with early menarche were at increased risk of experiencing premature and early menopause,[14] which may consequently lead to a shorter reproductive lifespan compared with those with normal ages at menarche and menopause. To date, no study has examined whether the timing of menarche or menopause affects the association between reproductive lifespan and risk of CVD events.

For the present study, individual-level data pooled from 12 studies participating in the International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE) consortium[15] were used to examine the association between

reproductive lifespan and risk of incident CVD events, whilst considering the timing of menarche and menopause.

METHODS

Ethics

Each study participating in InterLACE received ethics approval from the Institutional Review Board or Human Research Ethics Committee at each participating institution, and all the participants provided informed consent.

Study participants

The InterLACE consortium consists of over 20 observational studies across ten countries. Briefly, each study collected prospective or retrospective survey data on women's reproductive health across the lifespan, socio-demographic and lifestyle factors, and chronic disease events. Key variables were harmonised into the simplest level of detail that would incorporate information from as many studies as possible. The eligibility criteria for participating studies and data harmonisation procedures have been published elsewhere. [15,16]

In this study, we pooled data from 12 studies which had collected information on ages at menarche and menopause and CVD events (Table 1). A total of 484,870 women were included at analytic baseline. In our analyses, we first excluded women who had missing data on CVD events (n=4,544) and age at onset of CVD events (n=8,794). Women who did not report their age at menarche and their menopause status was unknown (n=56,232), and those who were using menopausal hormone therapy before menopause, and who had undergone a hysterectomy or oophorectomy were excluded from this study (n=70,597). Further, women who had missing data on covariates (n=36,848) were also excluded, leaving 307,855 women for the complete case analysis (**eSupplementary figure 1).**

Assessment of reproductive markers

The main exposure variables were reproductive lifespan, age at menarche, and age at menopause. Age at menarche was collected retrospectively by most studies except for the two British birth cohort studies,[17,18] and was categorized as age ≤10, 11, 12, 13 (reference), 14, 15, and ≥16 years.[4] Women who experienced CVD events before menopause or who were still premenopausal (menstrual cycle in past 3 months with no change in regularity over past 12 months) or perimenopausal (who had a menstrual cycle in past 12 months with change in regularity) were categorized as premenopausal or perimenopausal, and were included in the analyses as a separate group. Age at natural menopause (amenorrhea for at least 12 months without an intervention such as hysterectomy or bilateral oophorectomy) was categorized as <40, 40-44, 45-49, 50-51 (reference), 52-53, 54-55, and ≥56 years.[14] Reproductive lifespan was calculated by subtracting age at menarche from age at natural menopause (using actual ages) and was categorized into seven categories with 3-year increments: <30, 30-32, 33-35, 36-38 (reference), 39-41, 42-44, and ≥45 years.

Case ascertainment

A CVD event was defined as the first event of non-fatal CVD reported in survey questionnaires, including coronary heart disease (CHD; heart attack and angina) and stroke (ischaemic stroke and haemorrhagic stroke). Three studies (UK Biobank, WLH, and DNC) also provided hospital admission data.[15] Thus, both the self-reported physician-diagnoses and hospital admissions were used to define non-fatal CVD events in these studies. Incident CHD events were classified by International Classification of Diseases 10th Edition (ICD-10) codes I21- I25, or classified by ICD-9 codes 410 - 413. Stroke was classified by ICD-10 codes I60, I61, I63, and I64, or ICD-9 codes 430- 434.[19]

Covariates

We included following factors as covariates: women's year of birth (<1940, 1940-49, and ≥1950), age at last follow-up (<60, 60-64, and ≥65 years), education (≤10, 11-12, and >12 years), smoking status at baseline (never, past, and current), body mass index (BMI) at baseline (<18.5, 18.5-22.9, 23-24.9, 25-29.9, and ≥30 kg/m^2), age at first birth (no children, ≤20, 21-25, 26-30, and >30 years), number of children (no children, 1, 2, 3, and ≥4 children), and use of menopausal hormone therapy (never, past, and current). Participant self-reported their specific race/ethnicity. In the studies where this information was not available, race/ethnicity was defined based on country of birth, language spoken at home, or the country of residence. This pooled study included data from 12 studies across six countries. Thus, we categorised race/ethnicity (region) as follows: Caucasian–Australian/NZ, Caucasian–European, Caucasian–American, Asian (including Japanese, Chinese, South Asian, and Southeast Asian), and Other.

Statistical analyses

First, tests for associations between demographic variables and CVD events by reproductive lifespan were examined using chi-square tests for categorical variables. Cox proportional hazards models were used to examine the association of reproductive lifespan, age at menarche, and age at menopause with the incidence of CVD events (i.e. three separate regression models), providing estimates of hazard ratios and 95% confidence intervals (HR, 95%CI). The proportional hazards assumption was checked using log cumulative hazard plots and found to be reasonable. We adjusted for within study correlation by treating the study-level as a random effect in all models. For women with CVD, the total follow-up time was calculated as age at first CVD event. For women without CVD, the total follow-up time was calculated as age at last follow-up. For post-menopausal women, the time leading up to menopause was classified as the unexposed period and was included in the survival analyses to account for immortal time bias. First, we built two models: i) 'partially adjusted model' was adjusted for women's years of birth, race/ethnicity, education, smoking status at baseline and baseline BMI, and ii) 'fully

adjusted model' was additionally adjusted for other reproductive factors: age at first birth, number of children, menopausal hormone therapy (MHT) according to evidence from prior studies.[3 13 14]

Excluding 127,648 women who were pre- or peri-menopausal, we examined which combination of exposures provided the model with the best fit. Separate nested models for each reproductive marker were adjusted for women's years of birth, race/ethnicity, education, smoking status at baseline, BMI at baseline, age at first birth, number of children, menopausal hormone therapy (MHT) use (model 1-3). Model 4 included both reproductive lifespan and age at menarche and the covariates. Model 5 included both reproductive lifespan and age at menopause and the covariates. Model 6 included both age at menarche and age at menopause and the covariates. The -log likelihood (-logL) value was used in two ways. For nested models (e.g. models 1 or 2 compared to model 4) it was used to calculate the deviance (-2×difference in logL values) and test the statistical significance of inclusion of the additional factor. Also, as the factors all had the same number of categories (seven), it was used to compare goodness of fit between models 4, 5 and 6 (as the Akaike Information Criterion = constant – 2logL, in this case). Separate analyses were undertaken for CHD and stroke events. For the model including reproductive lifespan and age at menarche, we further examined the combined association of reproductive lifespan (<33, 33-35, 36-38, 39-41, ≥42 years) with different ages at menarche (≤11, 12, 13, 14, ≥15 years) – using a 5×5 heat map.

In addition, a sensitivity analysis was conducted by restricting the sample to women who experienced CVD events at least 5 years (n=136,267), 7 years (n=116,305), and 10 years (n=87,832) after menopause to minimise the possible influence of subclinical CVD causing earlier age at menopause. A further sensitivity analysis was undertaken using the three studies (DNC, WLH, and UK Biobank; n=142,763) which provided hospital admission data on non-fatal CVD events to check the robustness of findings.

The primary analyses were conducted by using PHREG procedure following a sequential Cox proportional hazards models in SAS version 9.4 (SAS Institute Inc, Cary, NC), also taking into account study-level as random effects.[20] All statistical analyses were based on two-sided 5% level of significance.

RESULTS

Study characteristics

Altogether, 307,855 women were included in this pooled analysis (**eSupplementary figure 1**). The data were predominantly from Caucasian populations from the UK, USA, Australia, Denmark, and Sweden (**Table 1**). Overall, the mean (SD) ages at menarche, menopause, and reproductive lifespan were 13.0 (1.5) years, 50.2 (4.4) years, and 37.2 (4.6) years, respectively. The incidence of non-fatal CVD, CHD, and stroke events after menopause were 3.3% (10,235 cases), 2.5% (7,610 cases), and 1.0% (3,161 cases), respectively. Baseline characteristics according to reproductive lifespan and occurrence of CVD events were shown in **eSupplementary table 1**.

Reproductive lifespan, age at menarche, and age at menopause and non-fatal CVD events

Women who had reached menopause showed an inverse relationship between increasing reproductive lifespan and non-fatal CVD events (P <0.001 for trend) (**Table 2**). After adjusting for covariates (fully adjusted model), women with <30 years of reproductive lifespan had 71% higher risk of CVD (HR 1.71, 95% CI 1.58-1.84) compared with those with a reproductive lifespan of 36-38 years. Similar results were also observed for non-fatal CHD (HR 1.66, 95% CI 1.52-1.82) and stroke (HR 1.75, 95% CI 1.52-2.01) (**eSupplementary table 2**). Having a reproductive lifespan of 30-32 years and 33-35 years was also associated with higher risk of CVD, CHD, and stroke but to a lesser extent.

A U-shaped relationship was evident between age at menarche and CVD events (**Figure 1**). Compared with women with menarche at age 13 years, those with early menarche (≤11 years) had almost 16% increased risk of CVD, and those with late menarche (≥15 years) had 4 to 15% increased risk of CVD (fully adjusted model). A similar U-shaped relationship was observed for CHD and stroke events (**eSupplementary figure 2**).

Premature (<40 years) and early menopause (40-44 years) were strongly associated with the incidence of non-fatal CVD, CHD and stroke events. Compared with women aged 50-51 years at menopause, those with premature menopause had 92% (HR 1.92, 95%CI 1.69-2.18) higher risk of incident CVD events, and those with early menopause had 57% (HR 1.57, 95% CI 1.45-1.70) higher risk of CVD. In contrast, those with late menopause ≥56 years had a 28% lower risk of CVD (HR 0.72, 95% CI 0.65-0.79). Similar findings were found for CHD and stroke events.

Association of reproductive lifespan adjusted for age at menarche or age at menopause

For the combined associations, the model included reproductive lifespan and age at menarche (Model 4) had the best fit (**Table 3**). The association of very short reproductive lifespans (<30 years) with CVD risk remained unchanged after adjusting for age at menarche (HR 1.70, 95% CI 1.57-1.84), while the association of early menarche was strengthened and the association of late menarche disappeared. In contrast, after adjusting for age at menopause, the association of short reproductive lifespan on CVD was attenuated, from a HR of 1.69 (1.57-1.83) to 1.25 (1.08-1.45) for duration of <30 years but it still remained statistically significant (Model 5). In the model of age at menarche and age at menopause (Model 6), the association of premature menopause (<40 years) remained unaffected after adjusting for age at menarche. Similar patterns of results were evident for CHD and stroke events (**eSupplementary table 3**).

An interaction was detected between reproductive lifespan and age at menarche (P value for interaction <0.001). Compared with women with menarche at age 13 years and a reproductive

lifespan of 36-38 years, those with menarche at 13 years and short reproductive lifespan <33 years had almost 50% higher risk (HR 1.48, 95% CI 1.30-1.69) of CVD events. Early menarche (≤11 years) strengthened the association, with the risk of CVD even higher for women with early age at menarche and a short reproductive lifespan (HR 2.06, 95% CI 1.76-2.41), while late age at menarche (≥15 years) did not influence the association (Figure 2). The estimates used in the Figure 2 are shown in **eSupplementary table 4**.

Sensitivity analysis

A sensitivity analysis was performed to examine the estimates restricted to the onset of CVD at least five years after menopause. The findings for the association between reproductive lifespan, age at menarche, age at menopause, and risk of CVD events were increased with longer follow-up after menopause (**eSupplementary table 5 A:C**). Furthermore, when the analysis was restricted to the three studies with hospital data on CVD events (n=142,763), the results remained unchanged (**eSupplementary table 6**).

DISCUSSION

This large pooled analysis of data from 307,855 women provides robust evidence for the relationship between a shorter reproductive lifespan and the first non-fatal CVD event. Having a short reproductive lifespan (<30 years) was associated with 71% higher risk of CVD after adjusting for covariates. A U-shaped relationship was found between age at menarche and CVD, with a higher risk of CVD for both early menarche (≤11 years) and late menarche (≥15 years). Premature (<40 years) and early menopause (40-44 years) were strongly associated with higher risk of nonfatal CVD events. The association of short reproductive lifespan with incident CVD remained unchanged after adjusting for age at menarche but was attenuated substantially after adjusting for age at menopause, showing the strong association between premature and early menopause and short reproductive lifespan. Additionally, there was an interaction between

reproductive lifespan and age at menarche. We found the risk of nonfatal CVD was highest for women with early menarche and a short reproductive lifespan (over two-fold increased risk). Women in this group had an average age at menopause of 40 years.

Our findings are consistent with earlier studies that suggested a shorter reproductive lifespan is associated with a higher risk of CVD[3,11], CHD[3,12] and stroke.[3,12] Our study further expanded these findings by showing whether the association between reproductive lifespan and risk of CVD is affected by the timing of menarche or menopause. Previous studies have suggested that menarche at age 12-14 years was optimal in terms of future CVD risk [3,4]; but our study has demonstrated that this does not capture the increased risk for women with a short reproductive lifespan who have an average age at menarche. A previous study which looked at the combined association of age at menarche with different lengths of reproductive lifespan included a small sample of stroke cases (189 cases and 192 controls).[10] Women with later age at menarche (>15 years) and short reproductive lifespan (≤36 years) had a higher risk of stroke compared with those with menarche at ≤15 years and reproductive lifespan >36 years. No evidence of an association for early age at menarche (≤15 years) and short reproductive lifespan (≤36 years) was reported.[10] Our study showed that both combinations, early menarche (≤11 years) and short reproductive lifespan (<33 years), and late menarche (≥15 years) and short reproductive lifespan (<33 years), were associated with increased risk of CVD events compared with menarche at age 13 years and reproductive lifespan at 36-38 years.

Our finding of a lower risk of non-fatal CVD events for women who had a long reproductive lifespan (≥42 years), is consistent with the cardio-protective effect of endogenous oestrogen in blood-vascular systems by regulating the levels of metabolic markers such as lipids, inflammatory markers, and coagulants.[2,7] On the other hand, a short reproductive lifespan may indicate accelerated ageing in midlife. The end of the reproductive lifespan serves as a marker for a range of biological mechanisms linked with progressive damage to tissues and organs

(aging) increasing the risk not only for CVD, but also for Parkinson's disease, dementia, depression, and osteoporosis.[9,21] Some shared genetic and environmental factors also contribute to risk, along with the timing of menarche and menopause that together explain the risk of CVD for women in the middle-age.[22] Further, some evidence suggest a possible link between socio-economic factors (e.g. higher education, being employed and having better self-reported health) [23] and risk of later menopause, and exposure to persistent organic pollutants (e.g., polyfluoroalkyl chemicals) and risk of early menopause.[24] Given the inter-relationship between timing of menarche and menopause [14], we suggest that for women in midlife, CVD risk assessment should take into account the timing of both menarche and menopause.

The strengths of our study include its large sample size, the diverse sample of women from multiple racial/ethnic groups, and the availability of information on other reproductive variables. By adjusting for age at menarche or menopause, we were able to compare women at same timing of either menarche or menopause relative to their reproductive lifespan. Further, this pooled study had sufficient power to detect the association at extreme age ranges of menarche, menopause, and reproductive lifespan to allow replication of findings from earlier studies.[3-5,13]

Our study also had some limitations. First, information on reproductive markers was mostly collected based on retrospective recall (except for data collected from the longitudinal cohorts), which could have introduced measurement errors due to recall bias. Second, the non-fatal CVD events were based on self-report of physician diagnosis in most studies, which may have resulted in misclassification of CVD outcomes. However, three large studies -- UK Biobank, WLH (UK) and DNC (Denmark) – also provided hospital admissions data and a sensitivity analysis using only these data confirmed the main results. Third, we could not adjust for genetic factors, early life factors, diet, physical activity and comorbidities (e.g. diabetes, cancer, chronic obstructive pulmonary disease) which might be related to both the exposure and outcomes

variables but earlier estimates from the Nurses' Health Study were unchanged after adjusting for history of diabetes, hypertension, and hypercholesterolemia.[3]

CONCLUSIONS

Short reproductive lifespan was associated with higher risk of non-fatal CVD events in midlife. Early age at menarche and menopause were also associated with a higher risk of non-fatal CVD events. Women who had both short reproductive lifespan and early menarche had the most pronounced risk of non-fatal CVD events. These findings highlight reproductive lifespan as a potential marker of women's risk of CVD events in midlife, however further research is needed on the underlying mechanisms linking fertility, reproductive ageing, with CVD risk across the lifespan.

FINANCIAL DISCLOSURE

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CONFLICT OF INTEREST: The authors have declared that no competing interests exist.

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Figure 1. Hazard ratio and 95% confidence interval (CI) of incident cardiovascular disease (CVD) by age at menarche. The estimates used in the figure are shown in **Table 2**. The hazard ratios were fully adjusted for women's year at birth, race/ethnicity, education, smoking status at baseline, BMI at baseline, number of children, age at first birth, and MHT use. Reference category was menarche at 13 years of age. The area of the square was inversely proportional to the variance of log hazard ratio.

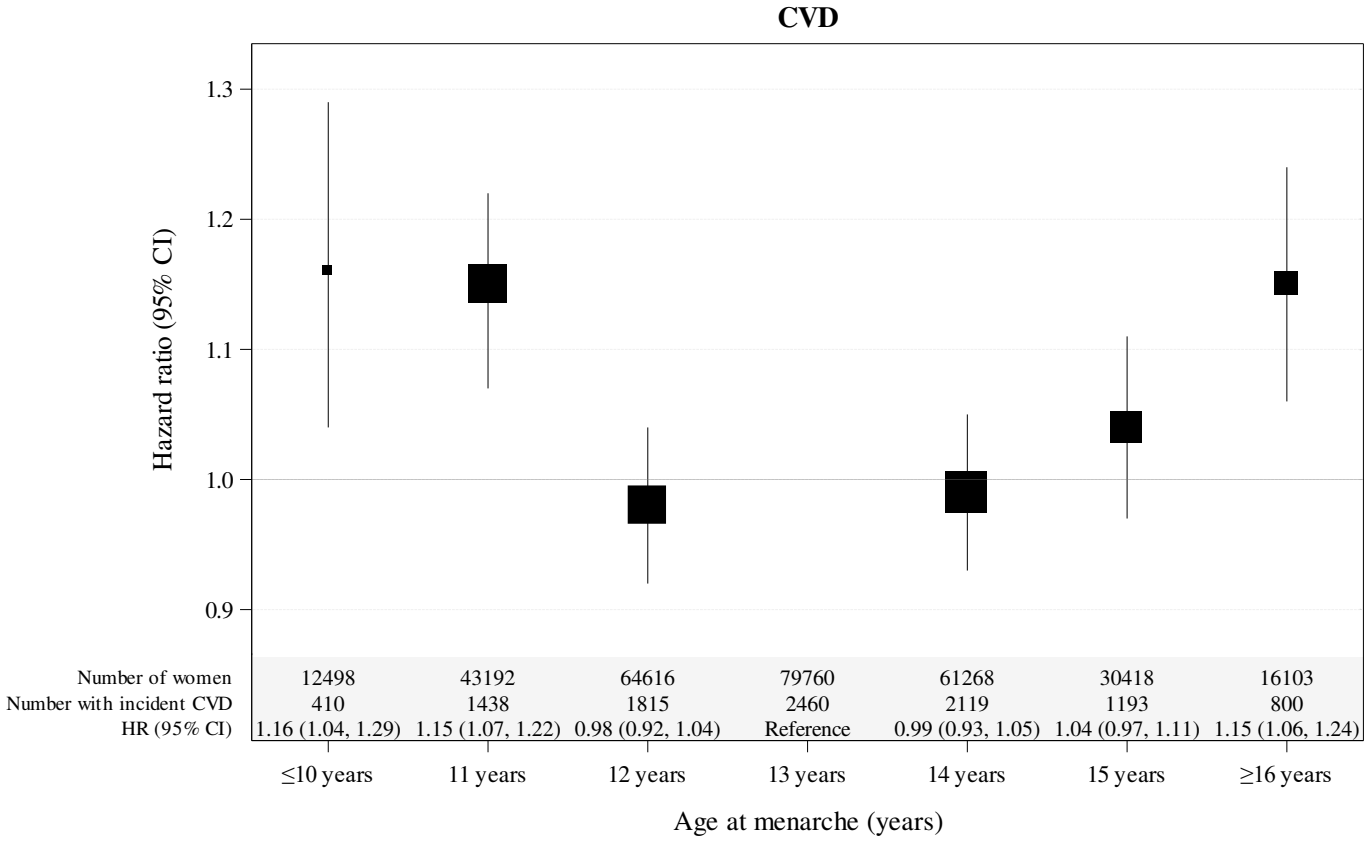

Figure 2. Heat-map for association between reproductive lifespan and age at menarche. The figure shows the association (hazard ratios and 95% CI) between the combination of reproductive lifespan (<33, 33-35, 36-38, 39-41, ≥42 years) and age at menarche (≤11, 12, 13, 14, ≥15 years) with non-fatal CVD events. The hazard ratios were fully adjusted for women's year at birth, race/ethnicity, education, smoking status at baseline, BMI at baseline, number of children, age at first birth, and MHT use. The number above each hazard ratio show the mean age at menopause for that combination. A darker colour (in a gradient from green to red) shows increasing risk of nonfatal CVD. The estimates for Figure 2 are shown in **eSupplementary table 4 in Supplement**.

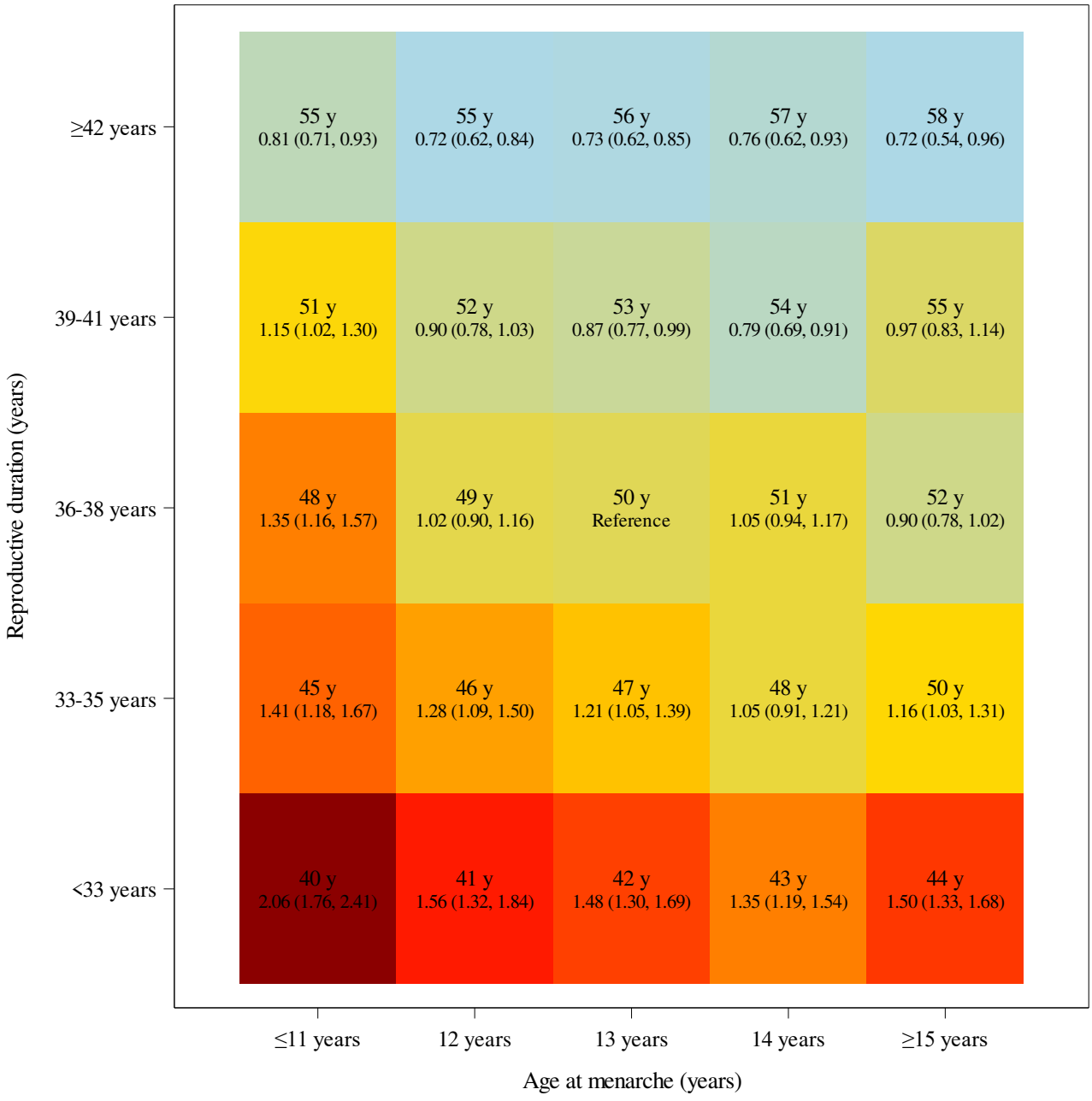

Table 1: Characteristics of 12 individual studies of a subset of women having information on reproductive lifespan and CVD events in the InterLACE consortium.

Study	**Country**	**N**	**Age in years at baseline Median (Q1, Q3)**	**Age in years at last follow-up Median (Q1, Q3)**
Australian Longitudinal Study on Women's Health (ALSWH)	Australia	6516	47.6 (46.3, 48.9)	63.8 (62.4, 65.4)
Melbourne Collaborative Cohort Study (MCCS)	Australia	14394	56.7 (48.0, 63.4)	65.6 (57.4, 72.1)
Danish Nurse Cohort Study (DNC)	Denmark	16098	50.0 (47.0, 59.0)	61.0 (47.0, 71.0)
Women's Lifestyle and Health Study (WLH)	Sweden	26216	38.0 (34.0, 42.0)	47.0 (42.0, 53.0)
Japan Nurses' Health Study (JNHS)	Japan	39889	41.0 (35.0, 47.0)	41.0 (35.0, 47.0)
Hilo Women's Health Study (HILO)	USA	614	50.4 (45.6, 55.1)	50.4 (45.6, 55.1)
Study of Women's Health Across the Nation (SWAN)	USA	2717	46.0 (44.0, 48.0)	54.0 (52.0, 57.0)
MRC National Survey of Health and Development (NSHD)*	UK	573	47.0 (47.0, 47.0)	54.0 (54.0, 54.0)
National Child Development Study (NCDS)*	UK	2454	50.0 (50.0, 50.0)	55.0 (55.0, 55.0)
English Longitudinal Study of Ageing (ELSA)	UK	2621	57.0 (51.0, 66.0)	67.0 (61.0, 76.0)
UK Women's Cohort Study (UKWCS)	UK	15768	48.6 (43.1, 56.5)	50.9 (45.2, 59.1)
UK Biobank (UKB)	UK	179995	57.0 (49.0, 62.0)	57.0 (50.0, 63.0)
Total		307855	51.0 (44.0, 60.0)	54.0 (46.0, 62.0)

* 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.

Abbreviations: CVD: cardiovascular disease; InterLACE: International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events; Q1: first quartile; Q3: third quartile.

Table 2. Association between each of reproductive lifespan, age at menarche, age at menopause (separately), and risk of non-fatal CVD events (N=307,855).

	Number of women	Number. of CVD events	Person years at risk	No. of events per 10,000 person-years	**Partially adjusted model[ϕ]** HR (95%CI)	**Fully adjusted model[§]** HR (95%CI)
Reproductive lifespan (years)						
pre- or peri-menopause	127648	2019	5685573	3.6	0.28 (0.25,0.30)	0.25 (0.23,0.27)
<30	11442	906	677722	13.4	1.73 (1.60,1.87)	1.71 (1.58,1.84)
30-32	14075	875	844714	10.4	1.32 (1.22,1.43)	1.31 (1.21,1.42)
33-35	29046	1475	1737737	8.5	1.16 (1.08,1.24)	1.16 (1.08,1.24)
36-38	51552	2221	3114752	7.1	**ref**	**ref**
39-41	45647	1752	2781965	6.3	0.90 (0.85,0.96)	0.91 (0.85,0.96)
42-44	21901	776	1359193	5.7	0.77 (0.71,0.84)	0.78 (0.72,0.85)
≥45	6544	211	416146	5.1	0.61 (0.53,0.70)	0.62 (0.54,0.72)
Trend P value[δ]					<0.001	<0.001
Age at menarche (years)						
≤10	12498	410	658174	6.2	1.16 (1.05,1.29)	1.16 (1.04,1.29)
11	43192	1438	2302984	6.2	1.16 (1.08,1.24)	1.15 (1.07,1.22)
12	64616	1815	3401406	5.3	0.99 (0.93,1.05)	0.98 (0.92,1.04)
13	79760	2460	4288161	5.7	**ref**	**ref**
14	61268	2119	3356786	6.3	1.00 (0.94,1.06)	0.99 (0.93,1.05)
15	30418	1193	1698551	7.0	1.05 (0.98,1.13)	1.04 (0.97,1.11)
≥16	16103	800	911741	8.8	1.16 (1.07,1.26)	1.15 (1.06,1.24)
Age at menopause (years)						
pre- or peri-menopause	127648	2019	5685573	3.6	0.27 (0.21,0.29)	0.25 (0.23,0.27)
<40	3366	272	193608	14.0	1.97 (1.73,2.23)	1.92 (1.69,2.18)
40-44	13184	921	783746	11.8	1.58 (1.46,1.71)	1.57 (1.45,1.70)
45-49	45112	2298	2681408	8.6	1.21 (1.13,1.28)	1.21 (1.14,1.29)
50-51	44072	1904	2671383	7.1	**ref**	**ref**
52-53	35737	1407	2179906	6.5	0.91 (0.85,0.97)	0.92 (0.86,0.98)
54-55	24196	892	1500466	5.9	0.79 (0.73,0.85)	0.80 (0.73,0.86)
≥56	14540	522	921714	5.7	0.71 (0.64,0.78)	0.72 (0.65,0.79)
Trend P value[δ]					<0.001	<0.001

Abbreviations: CVD: cardiovascular disease. [ϕ]Adjusted for women's year at birth, race/ethnicity, education, smoking status at baseline, and baseline BMI. [§]Additionally adjusted for number of children, age at first birth, and menopausal hormone therapy (MHT) use.

Table 3: Nested models between reproductive lifespan, age at menarche, age at menopause, and risk of non-fatal CVD events (N=180,207).

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
–*log likelihood*	87117	87317	87102	87078	87092	87086
Reproductive lifespan (years)						
<30	1.69 (1.57,1.83)			1.70 (1.57,1.84)	1.25 (1.08,1.45)	
30-32	1.31 (1.21,1.42)			1.31 (1.21,1.42)	1.09 (0.98,1.20)	
33-35	1.16 (1.09,1.24)			1.16 (1.09,1.24)	1.04 (0.96,1.12)	
36-38	**ref**			**ref**	**ref**	
39-41	0.90 (0.84,0.96)			0.86 (0.81,0.92)	1.01 (0.94,1.09)	
42-44	0.76 (0.70,0.83)			0.71 (0.66,0.78)	0.95 (0.84,1.07)	
≥45	0.58 (0.50,0.67)			0.52 (0.45,0.60)	0.75 (0.61,0.91)	
Age at menarche (years)						
≤10		1.13 (1.00,1.27)		1.34 (1.19,1.52)		1.12 (1.00,1.27)
11		1.16 (1.07,1.24)		1.27 (1.18,1.37)		1.14 (1.06,1.23)
12		0.98 (0.91,1.05)		1.03 (0.96,1.10)		0.98 (0.91,1.05)
13		**ref**		**ref**		**ref**
14		1.00 (0.93,1.06)		0.95 (0.89,1.01)		1.00 (0.94,1.07)
15		1.07 (0.99,1.15)		0.97 (0.89,1.04)		1.07 (0.99,1.16)
≥16		1.17 (1.07,1.28)		0.98 (0.90,1.08)		1.16 (1.07,1.27)
Age at menopause (years)						
<40			1.92 (1.69,2.18)		1.54 (1.27,1.87)	1.90 (1.67,2.15)
40-44			1.55 (1.44,1.68)		1.33 (1.16,1.52)	1.55 (1.43,1.68)
45-49			1.22 (1.15,1.29)		1.18 (1.09,1.27)	1.22 (1.14,1.29)
50-51			**ref**		**ref**	**ref**
52-53			0.92 (0.85,0.98)		0.92 (0.85,0.99)	0.92 (0.86,0.98)
54-55			0.78 (0.72,0.85)		0.81 (0.73,0.90)	0.78 (0.72,0.85)
≥56			0.68 (0.62,0.75)		0.79 (0.68,0.92)	0.68 (0.62,0.75)

Abbreviations: CVD: cardiovascular disease.

Model 1-3 (three separate models) was adjusted for women's year at birth, race/ethnicity, education, smoking status at baseline, baseline BMI, number of children, age at first birth, and menopausal hormone therapy (MHT) use.

Model 4 (one model) included both reproductive lifespan and age at menarche, and the covariates.
Model 5 (one model) included both reproductive lifespan and age at menopause, and the covariates.
Model 6 (one model) included both reproductive lifespan, age at menarche and age at menopause and the covariates.