Association Between Reproductive Life Span and Incident Nonfatal Cardiovascular Disease
A Pooled Analysis of Individual Patient Data From 12 Studies

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

OBJECTIVE To investigate the association between the length of reproductive life span 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 consortium. Women provided complete information on the timing of menarche and menopause, nonfatal CVD events, and covariates. Cox proportional hazards models were used to estimate hazard ratios and 95% CIs, adjusted for covariates. The association between reproductive life span and CVD was adjusted for age at menarche and age at menopause separately. Analysis began March 2018 and ended December 2019.

EXPOSURES Reproductive life span was calculated by subtracting age at menarche from age at menopause and categorized as younger than 30, 30 to 32, 33 to 35, 36 to 38 (reference group), 39 to 41, 42 to 44, and 45 years or older.

MAIN OUTCOMES AND MEASURES First nonfatal CVD event, including coronary heart disease and stroke events.

RESULTS A total of 307,855 women were included. Overall, the mean (SD) ages at menarche, menopause, and reproductive life span were 13.0 (1.5) years, 50.2 (4.4) years, and 37.2 (4.6) years, respectively. Pooled analyses showed that women with a very short reproductive life span (<30 years) were at 1.71 (95% CI, 1.58-1.84) times higher risk of incident CVD events than women with a reproductive life span of 36 to 38 years after adjustment for covariates. This association remained unchanged when adjusted for age at menarche but was attenuated to 1.26 (95% CI, 1.09-1.46) when adjusted for age at menopause. There was a significant interaction between reproductive life span and age at menarche associated with CVD risk (P < .001). Women who had both short reproductive life span (<33 years) and early menarche (age ≤11 years) had the highest risk of CVD (hazard ratio, 2.06; 95% CI, 1.76-2.41) compared with those with a reproductive life span of 36 to 38 years and menarche at age 13 years.

CONCLUSIONS AND RELEVANCE Short reproductive life span was associated with an increased risk of nonfatal CVD events in midlife, and the risk was significantly higher for women with early age at menarche.

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lobally, cardiovascular disease (CVD) contributes to a high burden of mortality and morbidity for women.1,2 Women who experience early menarche3,4 and early menopause3,5 are at increased risk of CVD, which suggests a potential role for the female reproductive life span 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 nonfatal cardiovascular outcomes were less conclusive.8,9 Subsequently, 3 large studies have shown fairly consistent evidence for links of early menarche and early menopause with CVD events.3,4,5 Besides the timing of menarche and menopause, recent interest has emerged in the association between CVD risk and reproductive life span (defined by age at menopause – age at menarche). The Nurses’ Health Study9 reported that a shorter reproductive life span (<30 years) was associated with a 1.32 (95% CI, 1.16-1.49) times higher risk of CVD events compared with a reproductive life span of 42 years or longer. Further, the association with long reproductive life span was either null10,11 or mixed.3,12,13 These findings suggest that the association between reproductive life span and CVD is not entirely clear and requires further investigation. Additionally, our previous study showed that women with early menarche were associated with increased risk of experiencing premature and early menopause,14 which may consequently lead to a shorter reproductive life span compared with those with normal ages at menarche and menopause. To date and to our knowledge, no study has examined whether the timing of menarche or menopause affects the association between reproductive life span and risk of CVD events.

For the present study, individual-level data pooled from 12 studies15-26 participating in the International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE) consortium27 were used to examine the association between reproductive life span and risk of incident CVD events, while 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. All the participants provided informed consent.

Study Participants

The InterLACE consortium consists of more than 20 observational studies across 10 countries. Briefly, each study collected prospective or retrospective survey data on women’s reproductive health across the life span, sociodemographic and lifestyle factors, and chronic disease events. Key variables were harmonized into the simplest level of detail that would incorporate information from as many studies as possible. The eligibility criteria for participating studies and data harmonization procedures have been published elsewhere.27,28

In this study, we pooled data from 12 studies15-26 that 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 = 4544) and age at onset of CVD events (n = 8794). Women who did not report their age at menarche and whose 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 (eFigure 1 in the Supplement).

Assessment of Reproductive Markers

The main exposure variables were reproductive life span, age at menarche, and age at menopause. Age at menarche was collected retrospectively by most studies except for the 2 British birth cohort studies15,16 and was categorized as age 10 or younger, 11, 12, 13 (reference group), 14, 15, and 16 years or older.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 younger than 40, 40 to 44, 45 to 49, 50 to 51 (reference group), 52 to 53, 54 to 55, and 56 years or older.14 Reproductive life span was calculated by subtracting age at menarche from age at natural menopause (using actual ages) and was categorized into 7 categories with 3-year increments: younger than 30, 30 to 32, 33 to 35, 36 to 38 (reference group), 39 to 41, 42 to 44, and 45 years or older.

Case Ascertainment

A CVD event was defined as the first event of nonfatal CVD reported in survey questionnaires, including coronary heart disease (CHD); myocardial infarction and angina) and stroke (ischemic stroke and hemorrhagic stroke). Three studies (UK
First, tests for associations between demographic variables and CVD events by reproductive life span were examined using \( \chi^2 \) tests for categorical variables. Cox proportional hazards models were used to examine the association of reproductive life span, age at menarche, and age at menopause with the incidence of CVD events (ie, 3 separate regression models), providing estimates of hazard ratios (HRs) and 95% CIs. 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 postmenopausal 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 2 models: (1) the partially adjusted model was adjusted for women's years of birth, race/ethnicity, education, smoking status at baseline, and baseline BMI and (2) the fully adjusted model was additionally adjusted for other reproductive factors: age at first birth, number of children, and menopausal hormone therapy according to evidence from prior studies.3,13,14

Excluding 127 648 women who were premenopausal or perimenopausal, we examined which combination of exposures provided the model with the best fit. Separate models for reproductive life span (model 1), age at menarche (model 2), and age at menopause (model 3) 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, and menopausal hormone therapy use. Model 4 included both reproductive life span and age at menarche in addition to the covariates. Model 5 included both reproductive life span and age at menopause in addition to the covariates. Model 6 included both age at menarche and age at menopause in addition to the covariates. The \(-\log\) likelihood \((-\log L)\) value was used in 2 ways. For nested models (eg, models 1 or

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**Table 1. Characteristics of 12 Individual Studies of a Subset of Women With Information on Reproductive Life Span and Cardiovascular Disease Events in the InterLACE Consortium**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>No. of individuals</th>
<th>Age, median (IQR), y At baseline</th>
<th>At last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian Longitudinal Study on Women's Health, 2015 (Australia)</td>
<td>Australia</td>
<td>6516</td>
<td>47.6 (46.3-48.9)</td>
<td>63.8 (62.4-65.4)</td>
</tr>
<tr>
<td>Melbourne Collaborative Cohort Study, 2002-2010 (Australia)</td>
<td>Australia</td>
<td>14 394</td>
<td>56.7 (48.0-63.4)</td>
<td>65.6 (57.4-72.1)</td>
</tr>
<tr>
<td>Danish Nurse Cohort Study, 2012-2010 (Denmark)</td>
<td>Denmark</td>
<td>16 098</td>
<td>50.0 (47.0-59.0)</td>
<td>61.0 (47.0-71.0)</td>
</tr>
<tr>
<td>Women's Lifestyle and Health Study, 2017 (Sweden)</td>
<td>Sweden</td>
<td>26 216</td>
<td>38.0 (34.0-42.0)</td>
<td>47.0 (42.0-53.0)</td>
</tr>
<tr>
<td>Japan Nurses' Health Study, 2007 (Japan)</td>
<td>Japan</td>
<td>39 889</td>
<td>41.0 (35.0-47.0)</td>
<td>41.0 (35.0-47.0)</td>
</tr>
<tr>
<td>Hilo Women's Health Study, 2007-2013 (United States)</td>
<td>United States</td>
<td>614</td>
<td>50.4 (45.6-55.1)</td>
<td>50.4 (45.6-55.1)</td>
</tr>
<tr>
<td>Study of Women's Health Across the Nation, 2000-2010 (United States)</td>
<td>United States</td>
<td>2717</td>
<td>46.0 (44.0-48.0)</td>
<td>54.0 (52.0-57.0)</td>
</tr>
<tr>
<td>MRC National Survey of Health and Development, 2006-2010 (United Kingdom)</td>
<td>United Kingdom</td>
<td>573</td>
<td>47.0 (47.0-47.0)</td>
<td>54.0 (54.0-54.0)</td>
</tr>
<tr>
<td>National Child Development Study, 2006-2010 (United Kingdom)</td>
<td>United Kingdom</td>
<td>2454</td>
<td>50.0 (50.0-50.0)</td>
<td>55.0 (55.0-55.0)</td>
</tr>
<tr>
<td>English Longitudinal Study of Aging, 2013 (United Kingdom)</td>
<td>United Kingdom</td>
<td>2621</td>
<td>57.0 (51.0-66.0)</td>
<td>67.0 (61.0-76.0)</td>
</tr>
<tr>
<td>UK Women's Cohort Study, 2017-2010 (United Kingdom)</td>
<td>United Kingdom</td>
<td>15 768</td>
<td>48.6 (43.1-56.5)</td>
<td>50.9 (45.2-59.1)</td>
</tr>
<tr>
<td>UK Biobank, 2015 (United Kingdom)</td>
<td>United Kingdom</td>
<td>179 995</td>
<td>57.0 (49.0-62.0)</td>
<td>57.0 (50.0-63.0)</td>
</tr>
<tr>
<td>Total</td>
<td>NA</td>
<td>307 855</td>
<td>51.0 (44.0-60.0)</td>
<td>54.0 (46.0-62.0)</td>
</tr>
</tbody>
</table>

Abbreviations: InterLACE, International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events; IQR, interquartile range; MRC, Medical Research Council; NA, not applicable.

* National Survey of Health and Development (1946 British Birth Cohort) and National Child Development Study (1958 British Birth Cohort) first collected information on women's health in 1993 (age 47 years) and 2008 (age 50 years), respectively.

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Biobank, Women's Lifestyle and Health Study, and Danish Nurse Cohort Study also provided hospital admission data. Thus, both the self-reported physician diagnoses and hospital admissions were used to define nonfatal CVD events in these studies. Incident CHD events were classified by *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes I21-I25, or classified by ICD-9 codes 410-413. Strokewasclassifiedby codes I60, I61, I62, I63, and I64, or classified by codes I61, I62, I63, and I64, or ICD-9 codes 430-434.
2 compared with 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, because the factors all had the same number of categories (7), 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 life span and age at menarche, we further examined the combined association of reproductive life span (<33, 33-35, 36-38, 39-41, ≥42 years) with different ages at menarche (<11, 12, 13, 14, ≥15 years) using a 5 × 5 heatmap.

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 minimize the possible influence of subclinical CVD causing earlier age at menopause. A further sensitivity analysis was undertaken using the 3 studies (UK Biobank, Women’s Lifestyle and Health Study, Danish Nurse Cohort Study; n = 142,763) that provided hospital admission data on nonfatal CVD events to check the robustness of findings.

The primary analyses were conducted by using PHREG procedure (SAS Enterprise Guide, version 9.4 [SAS Institute Inc]) following a sequential Cox proportional hazards models in SAS version 9.4 (SAS Institute Inc), also taking into account study characteristics (UK Biobank, Women’s Lifestyle and Health Study, Danish Nurse Cohort Study; n = 142,763) that provided hospital admission data on nonfatal CVD events to check the robustness of findings.  

Sensitivity Analysis

A sensitivity analysis was performed to examine the estimates restricted to the onset of CVD at least 5 years after menopause. The findings for the association between reproductive life span and age at menarche 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 menopause disappeared. In contrast, after adjusting for age at menopause, the association of short reproductive life span with CVD was attenuated, from an HR of 1.69 (95% CI, 1.57-1.83) to 1.25 (95% CI, 1.08-1.45) for duration of less than 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 (eTable 3 in the Supplement).

Association of Reproductive Life Span Adjusted for Age at Menarche or Age at Menopause With CVD Risk

For the combined associations, the model that included reproductive life span and age at menarche (model 4) had the best fit (Table 3). The association of very short reproductive life span (<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 menopause disappeared. In contrast, after adjusting for age at menopause, the association of short reproductive life span with CVD was attenuated, from an HR of 1.69 (95% CI, 1.57-1.83) to 1.25 (95% CI, 1.08-1.45) for duration of less than 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 (eTable 3 in the Supplement).

An interaction was detected between reproductive life span and age at menarche (P for interaction <.001). Compared with women with menarche at age 13 years and a reproductive life span of 36 to 38 years, those with menarche at 13 years and short reproductive life span less than 33 years had almost 50% higher risk (HR, 1.48; 95% CI, 1.30-1.69) of CVD events. Early menarche (age ≤11 years) strengthened the association, with the risk of CVD even higher for women with early age at menarche and a short reproductive life span (HR, 2.06; 95% CI, 1.76-2.41), while late age at menarche (age ≥15 years) did not influence the association (Figure 2). The estimates used in the Figure 2 are shown in eTable 4 in the Supplement.
life span, age at menarche, age at menopause, and risk of CVD events were increased with longer follow-up after menopause (eTables 5, 6, and 7 in the Supplement). Furthermore, when the analysis was restricted to the 3 studies with hospital data on CVD events (n = 142,763), the results remained unchanged (eTable 8 in the Supplement).

**Discussion**

This large pooled analysis of data from 307,855 women provides robust evidence for the association between a shorter reproductive life span and the first nonfatal CVD event. Having
A short reproductive life span (<30 years) was associated with a 71% higher risk of CVD after adjusting for covariates. A U-shaped association was found between age at menarche and CVD, with a higher risk of CVD for both early menarche (age ≤11 years) and late menarche (age ≥15 years). Premature (age <40 years) and early menopause (age 40-44 years) were

Table 3. Nested Models Between Reproductive Life Span, Age at Menarche, Age at Menopause, and Risk of Nonfatal Cardiovascular Disease Events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard ratio (95% CI)</th>
<th>Model 1a</th>
<th>Model 2a</th>
<th>Model 3a</th>
<th>Model 4b</th>
<th>Model 5c</th>
<th>Model 6d</th>
</tr>
</thead>
<tbody>
<tr>
<td>-log Likelihood</td>
<td></td>
<td>87 117</td>
<td>87 317</td>
<td>87 102</td>
<td>87 078</td>
<td>87 092</td>
<td>87 086</td>
</tr>
<tr>
<td>Reproductive life span, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>1.69 (1.57-1.83)</td>
<td>NA</td>
<td>NA</td>
<td>1.70 (1.57-1.84)</td>
<td>1.25 (1.08-1.45)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>30-32</td>
<td>1.31 (1.21-1.42)</td>
<td>NA</td>
<td>NA</td>
<td>1.31 (1.21-1.42)</td>
<td>1.09 (0.98-1.20)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>33-35</td>
<td>1.16 (1.09-1.24)</td>
<td>NA</td>
<td>NA</td>
<td>1.16 (1.09-1.24)</td>
<td>1.04 (0.96-1.12)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>36-38</td>
<td>1 (Reference)</td>
<td>NA</td>
<td>NA</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>39-41</td>
<td>0.90 (0.84-0.96)</td>
<td>NA</td>
<td>NA</td>
<td>0.86 (0.81-0.92)</td>
<td>1.01 (0.94-1.09)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>42-44</td>
<td>0.76 (0.70-0.83)</td>
<td>NA</td>
<td>NA</td>
<td>0.71 (0.66-0.78)</td>
<td>0.95 (0.84-1.07)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>≥45</td>
<td>0.58 (0.50-0.67)</td>
<td>NA</td>
<td>NA</td>
<td>0.52 (0.45-0.60)</td>
<td>0.75 (0.61-0.91)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Age at menarche, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>NA</td>
<td>1.13 (1.00-1.27)</td>
<td>NA</td>
<td>1.34 (1.19-1.52)</td>
<td>NA</td>
<td>1.12 (1.00-1.27)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>NA</td>
<td>1.16 (1.07-1.24)</td>
<td>NA</td>
<td>1.27 (1.18-1.37)</td>
<td>NA</td>
<td>1.14 (1.06-1.23)</td>
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</tr>
<tr>
<td>12</td>
<td>NA</td>
<td>0.98 (0.91-1.05)</td>
<td>NA</td>
<td>1.03 (0.96-1.10)</td>
<td>NA</td>
<td>0.98 (0.91-1.05)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>NA</td>
<td>1 (Reference)</td>
<td>NA</td>
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<td>NA</td>
<td>1 (Reference)</td>
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<tr>
<td>14</td>
<td>NA</td>
<td>1.00 (0.93-1.06)</td>
<td>NA</td>
<td>0.95 (0.89-1.01)</td>
<td>NA</td>
<td>1.00 (0.94-1.07)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>NA</td>
<td>1.07 (0.99-1.15)</td>
<td>NA</td>
<td>0.97 (0.89-1.04)</td>
<td>NA</td>
<td>1.07 (0.99-1.16)</td>
<td></td>
</tr>
<tr>
<td>≥16</td>
<td>NA</td>
<td>1.17 (1.07-1.28)</td>
<td>NA</td>
<td>0.98 (0.90-1.08)</td>
<td>NA</td>
<td>1.16 (1.07-1.27)</td>
<td></td>
</tr>
<tr>
<td>Age at menopause, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>NA</td>
<td>NA</td>
<td>1.92 (1.69-2.18)</td>
<td>NA</td>
<td>1.54 (1.27-1.87)</td>
<td>1.90 (1.67-2.15)</td>
<td></td>
</tr>
<tr>
<td>40-44</td>
<td>NA</td>
<td>NA</td>
<td>1.55 (1.44-1.68)</td>
<td>NA</td>
<td>1.33 (1.16-1.52)</td>
<td>1.55 (1.43-1.68)</td>
<td></td>
</tr>
<tr>
<td>45-49</td>
<td>NA</td>
<td>NA</td>
<td>1.22 (1.15-1.29)</td>
<td>NA</td>
<td>1.18 (1.09-1.27)</td>
<td>1.22 (1.14-1.29)</td>
<td></td>
</tr>
<tr>
<td>50-51</td>
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<td>1 (Reference)</td>
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<td>1 (Reference)</td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>52-53</td>
<td>NA</td>
<td>NA</td>
<td>0.92 (0.85-0.98)</td>
<td>NA</td>
<td>0.92 (0.85-0.99)</td>
<td>0.92 (0.86-0.98)</td>
<td></td>
</tr>
<tr>
<td>54-55</td>
<td>NA</td>
<td>NA</td>
<td>0.78 (0.72-0.85)</td>
<td>NA</td>
<td>0.81 (0.73-0.90)</td>
<td>0.78 (0.72-0.85)</td>
<td></td>
</tr>
<tr>
<td>≥56</td>
<td>NA</td>
<td>NA</td>
<td>0.68 (0.62-0.75)</td>
<td>NA</td>
<td>0.79 (0.68-0.92)</td>
<td>0.68 (0.62-0.75)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

a Models 1 to 3 were adjusted for women's year at birth, race/ethnicity, education, smoking status at baseline, baseline body mass index, number of children, age at first birth, and menopausal hormone therapy use.
b Model 4 included both reproductive life span and age at menarche in addition to the covariates.
c Model 5 included both reproductive life span and age at menopause in addition to the covariates.
d Model 6 included both age at menarche and age at menopause in addition to the covariates.

Figure 2. Heat Map for the Association Between Reproductive Life Span and Age at Menarche

The association (hazard ratios and 95% CI) between the combination of reproductive life span (<33, 33-35, 36-38, 39-41, ≥42 years) and age at menarche (≤11, 12, 13, 14, ≥15 years) with nonfatal cardiovascular disease events is displayed. The hazard ratios were fully adjusted for women's year at birth, race/ethnicity, education, smoking status at baseline, body mass index at baseline, number of children, age at first birth, and menopausal hormone therapy use. The number above each hazard ratio shows the mean age at menopause for that combination. A darker color (in a gradient from green to red) shows increasing risk of nonfatal cardiovascular disease. The estimates are shown in eTable 4 in the Supplement.
strongly associated with higher risk of nonfatal CVD events. The association of short reproductive life span 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 life span. Additionally, there was an interaction between reproductive life span and age at menarche. We found the risk of nonfatal CVD was highest for women with early menarche and a short reproductive life span (more than 2-fold increased risk). Women in this group had a mean age at menopause of 40 years.

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

Our finding of a lower risk of nonfatal CVD events for women who had a long reproductive life span (≥42 years) is consistent with the cardioprotective effect of endogenous estrogen in blood-vascular systems by regulating the levels of metabolic markers such as lipids, inflammatory markers, and coagulants. On the other hand, a short reproductive life span may indicate accelerated aging in midlife. The end of the reproductive life span serves as a marker for a range of biologic mechanisms linked with progressive damage to tissues and organs (aging) increasing the risk not only for CVD, but also for Parkinson disease, dementia, depression, and osteoporosis. 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. Further, some evidence suggests a possible link between socioeconomic factors (eg, higher education, being employed, and having better self-reported health) and risk of later menopause as well as exposure to persistent organic pollutants (eg, polyfluoroalkyl chemicals) and risk of early menopause. Given the interrelationship between timing of menarche and menopause, we suggest that for women in midlife, CVD risk assessment should take into account the timing of both menarche and menopause.

Strengths and Limitations
The strengths of our study include its large sample size from 6 countries 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 life span. Further, this pooled study had sufficient power to detect the association at extreme age ranges of menarche, menopause, and reproductive life span to allow replication of findings from earlier studies.

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 nonfatal CVD events were based on self-report of physician diagnosis in most studies, which may have resulted in misclassification of CVD outcomes. However, 3 large studies, UK Biobank, Women’s Lifestyle and Health Study (UK), and Danish Nurse Cohort Study (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 (eg, 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.

Conclusions
Short reproductive life span was associated with higher risk of nonfatal CVD events in midlife. Early age at menarche and menopause were also associated with a higher risk of nonfatal CVD events. Women who had both short reproductive life span and early menarche had the most pronounced risk of nonfatal CVD events. These findings highlight reproductive life span 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 aging, with CVD risk across the life span.

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