Age at Menarche and Risks of Coronary Heart and Other Vascular Diseases in a Large UK Cohort

Running title: Canoy et al.; Age at menarche, CHD and other vascular diseases

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Abstract

Background—Early menarche has been associated with increased risk of coronary heart disease (CHD) but most studies were relatively small and could not assess risk across a wide range of menarcheal ages; few have examined associations with other vascular diseases. We examined coronary, cerebrovascular and hypertensive disease risks by age at menarche in a large prospective study of UK women.

Methods and Results—In 1.2 million women (mean age=56 [SD5] years) without prior heart disease, stroke, or cancer, menarcheal age was reported to be 13 years by 25%; ≤10 years by 4%; and ≥17 years by 1%. After 11.6 years of follow-up, 73,378 women had first hospitalization or death for CHD; 25,426 for cerebrovascular disease; and 249,426 for hypertensive disease. Using Cox regression, we calculated relative risks for each vascular outcome by single year of menarcheal age. The relationship was U-shaped for CHD: compared to women with menarche at 13 years, the adjusted relative risk for CHD for menarche at ≤10 years was 1.27 (95% CI 1.22 to 1.31; P<0.0001); and for menarche at ≥17 years was 1.23 (95% CI 1.16 to 1.30; P<0.0001). U-shaped relationships were also seen for cerebrovascular and hypertensive disease, although the magnitudes of these risks for early and late menarche were smaller than those for CHD.

Conclusions—In this cohort, the relation of age at menarche to vascular disease risk was U-shaped, with both early and late menarche being associated with increased risk. Associations were weaker for cerebrovascular and hypertensive disease than for CHD.

Key words: women, coronary heart disease, epidemiology, cerebrovascular disease/stroke, hypertension, menarche
Introduction

Menarche is a marker of puberty and the onset of ovarian and other endocrine functions relating to reproduction.\textsuperscript{1} The timing of menarche has been reported to influence cardiovascular and metabolic health in adolescence and young adulthood,\textsuperscript{2-4} but its long-term impact on vascular health in middle-age is unclear. Several studies have suggested that early menarche is associated with increased risk of coronary heart disease\textsuperscript{5-11} or stroke,\textsuperscript{7} but findings have been inconsistent.\textsuperscript{11-13} Some studies have shown associations between early menarche and coronary heart disease only among non-smokers,\textsuperscript{9-11} while others have not adequately accounted for adult adiposity\textsuperscript{6, 7, 9, 12} which is known to be associated with early menarche.\textsuperscript{14-17} Some suggested a non-linear association between menarcheal age and coronary heart disease risk\textsuperscript{6, 7} but these studies could not examine variation in risk of coronary heart disease, or of other vascular diseases, over a wide range of menarcheal ages, as numbers of events were generally small.\textsuperscript{11} It is also unclear if the relation with coronary heart disease is modified by smoking and low socioeconomic status, factors which are associated with both vascular disease\textsuperscript{18, 19} and late menarche.\textsuperscript{6, 14} In a cohort of over a million middle-aged UK women, we investigated the relation of age at menarche with incident coronary heart disease and examined the relationship separately by subgroups as defined by their adult body mass index, smoking and socioeconomic status. We also investigated the associations of menarcheal age with other vascular diseases, in particular, cerebrovascular and hypertensive disease.

Methods

The Million Women Study is a UK population-based cohort study which recruited 1.3 million women aged 50 to 64 years who had been invited for routine breast cancer screening by the
National Health Service (NHS) screening programmes of England and Scotland between 1996 and 2001. Details of the study design and recruitment have been previously described in detail (www.millionwomenstudy.org). Around 70% of women invited to attend the national breast cancer screening programme participated in the study, and our cohort members represented 1 in 4 women in the UK in the target age range at the time of recruitment. All participants gave their written consent to take part in the study. The Oxford and Anglia Multi-Centre Research Ethics Committee approved the conduct of the study.

At recruitment, participants completed a questionnaire, which included questions on reproductive and medical history, weight, height, socio-demographic details and lifestyle habits. We obtained information on deaths and hospitalization through linkage with NHS databases for hospital admissions and mortality. Hospital admissions data for in-patients and day-patients are available from the Hospital Episode Statistics for participants in England (from 1 April 1997), and the Scottish Morbidity Records for participants in Scotland (from 1 January 1981). Hospital diagnoses and causes of death are coded using the International Classification of Diseases, Tenth Revision (ICD-10).

Women reported their age at menarche in single years, and were classified for this study as having an age at menarche of \( \leq 10, 11, 12, 13, 14, 15, 16 \) or \( \geq 17 \) years. In a subset comprising 394 participants who were also included in a nationally representative birth cohort study (National Survey of Health and Development), age at menarche reported in middle age was correlated with that reported at the time of puberty (\( r=0.6 \)), and the mean ages at menarche reported in middle age (13.0 years) and at puberty (12.9 years) were not significantly different (\( p=0.09 \)). The regression dilution ratio, which estimates the relative attenuation of relative risks due to measurement error, was 0.44.
We defined incident coronary heart disease as the first hospital admission with a diagnosis of coronary heart disease (ICD-10 I20 to I25), or death with coronary heart disease as the underlying cause. Similarly, incident cerebrovascular disease (ICD-10 I60 to I69) and incident hypertensive disease (ICD-10 I10 to I15) were defined as first hospital admission or death with these conditions. Virtually all UK residents are registered with general practitioners, and general practice records are a comprehensive source of information about an individual’s health and medical care.27 In a study to assess reliability of vascular outcomes recorded in hospital admissions data, there was generally excellent agreement between vascular diagnoses recorded in hospital records and those reported by general practitioners.27

Nine years after recruitment, non-fasting blood samples were collected at local general practice clinics for 16,954 randomly selected cohort participants. We assayed plasma concentrations of total cholesterol, high-density lipoprotein cholesterol, apolipoprotein B and apolipoprotein A1 for this subgroup of women (details of laboratory methods in Methods supplement).

Statistical analysis

Our analysis is based on the 1,217,840 women who reported their age at menarche and, at baseline, had no reported or prior hospitalization for heart disease, cerebrovascular disease/stroke or cancer (except non-melanoma skin cancer). We used Cox regression to calculate hazard ratio, hereafter referred to as ‘relative risk’, for each year of menarcheal age (categorized into ≤10, 11, 12, 14, 15, 16 and ≥17 years) with age 13 years as the reference group. Relative risks were calculated separately for each vascular disease outcome. Person-years were calculated from date of recruitment to date of first hospitalization for the relevant outcome, death, loss to follow-up or the end of study (31 March 2011 in England and 31 December 2008 in Scotland), whichever
came first. Around 5% of participants in England were recruited before 1 April 1997, the start of English hospital admissions data, and their person-years were calculated from this date. We used age as the underlying time-to-event variable in our Cox regression. Therefore, time at risk began for each woman at their age at recruitment, and continued until their age at first hospitalization for the outcome of interest, death, other loss to follow-up, or end of follow-up. The regression models were stratified by geographical region of recruitment within the UK (10 regions), and adjusted for year of birth, body mass index, height, smoking (never, past and current smokers with consumptions of <5, 5 to 9, 10 to 14, 15 to 19, 20 to 24 and ≥25 cigarettes per day), weekly alcohol consumption (0, 1 to 6, 7 to 14 and ≥15 units), frequency of strenuous exercise (rarely/never, once a week or less, and more than once a week), and socioeconomic status (fifths of Townsend index of deprivation28). For each adjustment variable, women with missing values were assigned to a separate category (proportion of missing values for body mass index, exercise and all other covariates were <5%, <3% and <1%, respectively).

We further investigated the associations by additionally adjusting for reproductive factors (parity [0, 1, 2 and >2 full-term pregnancies], past use of oral contraceptive pill [yes or no], menopausal status [pre/perimenopausal, natural menopause at age <50 years, natural menopause at age ≥50 years and others with undetermined status], and ever use of menopausal hormone replacement therapy [yes or no]), as well as for mediating factors including hypertension (ever had or being treated for hypertension [yes or no]), diabetes (ever had or being treated for diabetes [yes or no]) and hypercholesterolemia (ever had or being treated for high blood cholesterol [yes or no]). We also examined the risk of incident coronary heart disease by age at menarche in subgroups of women defined by their body mass index, smoking habit and socioeconomic status.

To examine heterogeneity in the association of coronary heart disease across categories
of body mass index, smoking and socioeconomic status, we used likelihood ratio tests to
compare multivariate Cox regression models with and without the interaction term for age at
menarche and the relevant risk factor (both treated as categorical variables). In an additional
sensitivity analysis, we evaluated the effects of reporting errors in menarcheal age on vascular
disease risks by plotting the relative risks against estimated mean menarcheal ages as they would
have been reported at puberty, within each category of menarcheal age reported in middle age.

We also report on the plasma concentrations of cholesterol and lipid subfractions by age
at menarche. To test the heterogeneity of mean lipid concentration across menarcheal age
categories, we compared linear regression models with and without the categorical term for
menarcheal age in the model using likelihood ratio tests.

When comparing two groups, as described in the text, we report relative risks with their
conventional 95% confidence interval (95% CI). When relative risks for multiple groups are
presented, as in the figures and tables, we report relative risks with their 95% group-specific CIs,
to allow direct comparison of risks between any two categories of menarcheal age even if neither
of them is the reference group.29 We used Stata 13.0 (StataCorp, College Station, USA)30 to
conduct our analyses.

Results

The mean age of study participants at recruitment was 56 (SD=4.8) years (25th and 75th
percentile: 52 and 60) and the mean reported age at menarche was 13.0 (SD=1.6) years (25th and
75th percentile: 12 and 14). The proportions reporting menarche at age ≤10, 13 and ≥17 years
were 3.9%, 24.5% and 1.4%, respectively. Mean ages at menarche for women born in the years
<1930, 1930 – 1939, and ≥1940 were 13.3 (SD=1.6), 13.2 (SD=1.6), and 12.9 (SD=1.6) years,
respectively. At baseline, women with earlier menarche were, on average, slightly younger, had a higher body mass index and were slightly shorter than women with later menarche (Table). The proportions of women in the lowest third of socioeconomic status or who were current smokers were lower among women with menarcheal age 12, 13 and 14 years than among women with earlier or later menarche. Women with earlier menarche were more likely to have reported hypertension, diabetes and hypercholesterolemia than those with later menarche at recruitment. Women with late menarche were also least likely to engage in weekly strenuous exercise.

During an average follow-up of 11.6 years per woman (14.1 million person-years), 73,378 women had incident coronary heart disease (68,744 hospitalisations and 4,634 deaths). Moreover, 25,362 women had incident cerebrovascular disease and 249,426 women had incident hypertensive disease (Table).

Figure 1 (further details in Supplementary Table 1) shows the relative risks of incident coronary heart disease by single year of age at menarche (≤10, 11 to 16, and ≥17 years). Women with menarche at age 13 years had the lowest risk. Compared to this group of women, the risks of incident coronary heart disease were significantly increased at both earlier and later ages at menarche. The highest risks were seen with menarche at ages ≤10 and ≥17 years, with relative risks of 1.27 (95% CI 1.22 to 1.31; P<0.0001) and 1.23 (95% CI 1.16 to 1.30; P<0.0001), respectively, after adjustment for birth year, body mass index, height, smoking, alcohol consumption, exercise, and socioeconomic status. Further adjustment for reproductive factors and known mediating factors slightly attenuated the risk for early (but not late) menarche, but the risk estimates remained significant (Supplementary Table 1). Excluding women with unusually early (<10 years) or late (≥18 years) menarche did not materially alter our results, with relative risks of 1.18 (95% CI 1.13 to 1.23; P<0.0001) and 1.20 (95% CI 1.12 to 1.28; P<0.0001)
respectively for exact menarcheal ages of 10 and 17 years compared to menarche at age 13 years.

We then investigated the association between age at menarche and incident coronary disease separately within subgroups of women defined by their body mass index, smoking, or socioeconomic status (Figure 2, further details in Supplementary Table 2). The U-shape relation between age at menarche and risk of coronary disease was evident in lean, overweight and obese women, among current, past and never smokers, or among low, middle and high socioeconomic groups. Menarche at ages ≤10 years and ≥17 years associated with the highest risks in all the subgroups studied, with no significant heterogeneity across the subgroups (all P>0.05).

We also examined the relation for coronary heart disease mortality. Because the number of deaths were relatively modest (N=4634), we limited the analyses to menarcheal ages ≤11, 12, 13, 14, 15 and ≥16 years. Relative to menarche at age 13 years, the risk of coronary heart disease mortality was 1.12 (1.02 to 1.22; P=0.014) for menarche at age ≤11 years; there was no significant increase in risk of coronary disease death for menarche at age ≥16 years, with relative risk of 1.02 (95% CI 0.90 to 1.15; P=0.8) (Supplementary Table 3).

The risk of incident cerebrovascular disease in relation to menarcheal age is shown in Figure 3 (further details in Supplementary Table 4). Both early and late menarche were associated with increased risk for incident cerebrovascular disease, but the risk estimates were of smaller magnitude than those found for coronary heart disease. Compared with menarche at age 13 years, menarche at age ≤10 and ≥17 years were associated with significant excess risks of 16% (95% CI 9 to 24%) and 13% (95% CI 3 to 24%), respectively. Further adjustment for mediating and other confounding factors only slightly attenuated the risks (Supplementary Table 4). Similarly, we found small but significant increased risk for incident hypertensive
disease for menarche at age ≤10 and ≥17 years compared to menarche at age 13 years (Supplementary Figure 1 and further details in Supplementary Table 4).

In the sensitivity analysis exploring the effects of reporting errors in menarcheal age, the relationship between age at menarche and the vascular outcomes remained U-shaped, but the curve was steeper than estimated by the main analysis (Supplementary Figure 2).

Finally, we examined the lipid profile of a subgroup of women by age at menarche. We found no significant variation in the mean plasma concentrations of cholesterol and other lipid subfractions across categories of menarcheal age (Supplementary Table 5).

Discussion

Coronary heart disease incidence varied significantly by age at menarche in this large cohort of UK women in middle age. The pattern of the association was U-shaped over single ages at menarche, the risk being lowest for menarche at age 13 years, and increasing with younger and older ages at menarche. This pattern did not differ significantly between lean, overweight and obese women, between current, past smokers and never smokers, or between women in low, middle and high socioeconomic groups. We also found similar U-shaped associations for incident cerebrovascular and hypertensive disease, although the magnitude of the risks for early and late menarche was weaker than that observed for coronary heart disease. To our knowledge, our study is the first to demonstrate a significant excess coronary and other vascular disease risk associated with both early and late ages at menarche.

A number of prospective studies have previously investigated the relation of menarcheal age with coronary heart disease (Supplementary Table 6). Some, but not all, have reported that early age at menarche was associated with increased risk of coronary heart disease incidence\textsuperscript{5,6}.
or mortality. Consistent with these reports, we found that early age at menarche was associated with increased risk of incident coronary heart disease. While others have reported an increased coronary disease risk with early menarche among non-smokers only, we found similar associations among smokers and non-smokers alike. Several studies, including ours, have also shown an association between early menarche and higher body mass index in adulthood, but our findings have been adjusted for adult body mass index, and we found that the association of early menarche with coronary heart disease was similar in lean, overweight and obese women.

Previous studies have investigated the association of menarcheal age with cerebrovascular disease (Supplementary Table 7). Most of these studies reported no significant relationship between cerebrovascular disease risk and age at menarche, with only one study suggesting an increased risk of cerebrovascular disease associated with early menarche. In our cohort, we found a significant increase in cerebrovascular disease risk not only with early (≤10 years) but also with late (≥17 years) menarche. Moreover, we also found a similar U-shaped relationship between menarcheal age and hospitalization for hypertensive disease. However, the increasing risks of incident cerebrovascular and hypertensive disease associated with earlier and later menarche were weaker in magnitude than the risks of coronary heart disease.

Early age at menarche has been associated with increased blood pressure, which is consistent with our finding of an increased risk of incident hypertensive disease in women with early menarche. Hypertension may, therefore, partly explain the association of early menarche with coronary heart disease and cerebrovascular disease. Further, in our cohort as well as in others, early menarche is associated with diabetes as well as with a history of hypercholesterolemia. These findings suggest that impaired glucose homeostasis and
dyslipidemia, together with hypertension, are important mediating factors for the relation of early menarche with risks of coronary and cerebrovascular disease. Adjusting for these mediating factors attenuated the results but the risk estimates remained significant (Supplementary Tables 1 and 4). Moreover, the adjustment for reported hypercholesterolemia had little effect on the risk estimates as shown for coronary heart disease (Supplementary Table 1), consistent with our finding of little variation in the lipid profile of women across categories of menarcheal age (see Supplementary Table 5).

While some suggested that the association between age at menarche and coronary heart disease may be non-linear,6,7 none of the previous studies have reported a significant increase in risk with late menarche. As observed in other cohorts,14 the proportion of current smokers among our participants is notably increased at later ages at menarche but we adjusted for smoking, and the U-shaped relationship between menarcheal age and risk of coronary heart disease did not differ significantly across subgroups of women with different smoking patterns. Indeed, the risk estimates associated with late menarche (≥17 years) for every vascular disease outcome that we examined were hardly altered by adjusting for potential mediating factors. Even the risk for incident hypertensive disease associated with late menarche, though significant, was relatively small. In one study, late menarche was associated with increased brachial artery diameter and reduced flow-mediated dilation, suggestive of systemic subclinical atherosclerosis,32 so endothelial dysfunction may play a role in the excess risk of coronary and cerebrovascular disease associated with late menarche.

Our study participants were mostly in their late 50s when recruited, but many of them are still currently in their 60s and 70s. While our findings are likely to apply to such women in contemporary populations, menarcheal age varies within and between populations33,34 and our
findings may not be generalizable to populations with very different distributions of age at menarche. Further, mean age at menarche has been declining over time,\textsuperscript{34, 35} but the fall in mean menarcheal age has been relatively small, and the differences in risk for each single year of menarcheal age in our study are also small. However, the shift towards younger age at menarche over time would mean an increase in the proportion with early menarcheal age in the future.

Although mechanisms underlying the variation in the timing of menarche are unclear, childhood obesity, which is highly prevalent in many populations,\textsuperscript{36} has been consistently associated with early menarche.\textsuperscript{37, 38} Public health strategies to reduce childhood obesity, if successful, could have an added benefit of achieving ages at menarche with favourable vascular health outcomes in the long-term.

The main strengths of this prospective study are its size and virtually complete follow-up for hospital and fatal vascular disease outcomes, allowing us to examine disease risk in detail across a wide range of menarcheal ages. Women were asked in middle-age to recall their age at menarche, but the likely effect of reporting errors would be to attenuate risk estimates so that the observed relationship implies, if anything, even steeper U-shaped relationships than suggested in Figures 1 and 3 as well as in Supplementary Figure 1 (compare Supplementary Figure 2). In addition, while we adjusted for age, adiposity, lifestyle factors, socioeconomic status, reproductive factors, and known clinical vascular risk factors, we cannot rule out residual confounding by factors that we have not measured.

In this large cohort of middle-aged UK women, both early and late ages at menarche are associated with significantly increased risk of incident coronary heart disease. There are similar, but weaker, U-shaped relationships for incident cerebrovascular and hypertensive disease.
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cerebrovascular disease outcome and contributed in revising the manuscript. All authors gave their final approval of the version to be submitted.

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**Conflict of Interest Disclosures:** None.

**References:**


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**Table 1. Characteristics of study participants in the Million Women Study, by age at menarche.**

<table>
<thead>
<tr>
<th>Number of women</th>
<th>≤10 (Mean=9.9)</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>≥17 (Mean=17.4)</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at recruitment, mean (SD)</td>
<td>55.0 (4.5)</td>
<td>55.5 (4.6)</td>
<td>55.8 (4.8)</td>
<td>55.9 (4.8)</td>
<td>56.3 (4.9)</td>
<td>56.6 (4.9)</td>
<td>56.9 (5.0)</td>
<td>57.0 (5.0)</td>
<td>56.0 (4.8)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>28.1 (5.6)</td>
<td>27.2 (5.0)</td>
<td>26.4 (4.6)</td>
<td>25.9 (4.4)</td>
<td>25.6 (4.3)</td>
<td>25.5 (4.3)</td>
<td>25.2 (4.2)</td>
<td>25.3 (4.5)</td>
<td>26.1 (4.6)</td>
</tr>
<tr>
<td>Height (cm), mean (SD)</td>
<td>160.9 (6.7)</td>
<td>161.1 (6.6)</td>
<td>161.9 (6.6)</td>
<td>162.3 (6.6)</td>
<td>162.4 (6.7)</td>
<td>162.4 (6.9)</td>
<td>162.6 (7.0)</td>
<td>162.6 (7.3)</td>
<td>162.0 (6.7)</td>
</tr>
<tr>
<td>Parity, mean (SD)</td>
<td>2.1 (1.2)</td>
<td>2.1 (1.2)</td>
<td>2.1 (1.2)</td>
<td>2.1 (1.2)</td>
<td>2.2 (1.2)</td>
<td>2.2 (1.3)</td>
<td>2.2 (1.3)</td>
<td>2.2 (1.3)</td>
<td>2.1 (1.2)</td>
</tr>
<tr>
<td>% Current smoker</td>
<td>22.2</td>
<td>21.5</td>
<td>18.4</td>
<td>18.2</td>
<td>20.9</td>
<td>23.3</td>
<td>23.3</td>
<td>24.7</td>
<td>20.4 (233,652)</td>
</tr>
<tr>
<td>% Non-drinker of alcoholic beverages</td>
<td>31.2</td>
<td>29.8</td>
<td>27.6</td>
<td>27.1</td>
<td>29.1</td>
<td>31.4</td>
<td>32.7</td>
<td>34.9</td>
<td>71.0 (787,163)</td>
</tr>
<tr>
<td>% Engage in vigorous exercise ≤1 per week</td>
<td>46.2</td>
<td>48.5</td>
<td>46.0</td>
<td>45.9</td>
<td>48.8</td>
<td>50.8</td>
<td>50.6</td>
<td>52.3</td>
<td>47.8 (561,217)</td>
</tr>
<tr>
<td>% Lowest third of socioeconomic status</td>
<td>32.9</td>
<td>32.9</td>
<td>30.0</td>
<td>29.9</td>
<td>33.3</td>
<td>36.2</td>
<td>37.0</td>
<td>40.0</td>
<td>32.4 (391,366)</td>
</tr>
<tr>
<td>% Ever use of hormone replacement therapy</td>
<td>54.2</td>
<td>51.9</td>
<td>49.1</td>
<td>49.4</td>
<td>50.0</td>
<td>50.8</td>
<td>51.6</td>
<td>51.4</td>
<td>50.3 (605,942)</td>
</tr>
<tr>
<td>% Ever use of contraceptive pills</td>
<td>63.0</td>
<td>60.6</td>
<td>59.7</td>
<td>60.3</td>
<td>59.1</td>
<td>58.9</td>
<td>59.1</td>
<td>58.4</td>
<td>59.9 (721,888)</td>
</tr>
<tr>
<td>% Ever had/being treated for hypertension</td>
<td>27.9</td>
<td>25.8</td>
<td>23.7</td>
<td>22.5</td>
<td>21.9</td>
<td>21.7</td>
<td>20.9</td>
<td>21.5</td>
<td>23.2 (282,264)</td>
</tr>
<tr>
<td>% Ever had/being treated for diabetes</td>
<td>3.9</td>
<td>3.0</td>
<td>2.3</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
<td>2.2</td>
<td>2.9</td>
<td>2.4 (28,727)</td>
</tr>
<tr>
<td>% Ever had/being treated for hypercholesterolemia</td>
<td>10.6</td>
<td>10.3</td>
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<td>9.3</td>
<td>9.5</td>
<td>9.5</td>
<td>9.3</td>
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<td>9.6 (117,009)</td>
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</tbody>
</table>

**Follow-up details**

<table>
<thead>
<tr>
<th></th>
<th>No. with incident coronary heart disease</th>
<th>Person-years (1000s)</th>
<th>No. with incident cerebrovascular disease</th>
<th>Person-years (1000s)</th>
<th>No. with incident hypertensive disease</th>
<th>Person-years (1000s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3477</td>
<td>12,759</td>
<td>12,121</td>
<td>16,199</td>
<td>15,064</td>
<td>8784</td>
</tr>
<tr>
<td></td>
<td>561</td>
<td>2286</td>
<td>2513</td>
<td>3464</td>
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<td>4183</td>
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<td>573</td>
<td>2328</td>
<td>2552</td>
<td>3515</td>
<td>2938</td>
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<td></td>
<td>11,695</td>
<td>44,418</td>
<td>43,487</td>
<td>57,483</td>
<td>49,759</td>
<td>27,712</td>
</tr>
</tbody>
</table>

Percentages are calculated based on women with complete information for that specific variable; SD – standard deviation.
Figure Legends

Figure 1. Relative risk (RR) (95% confidence interval [CI]) of incident coronary heart disease (CHD), by age at menarche (further details in Supplementary Table 1). RRs (hazard ratios) stratified by region of recruitment, and adjusted for year of birth, body mass index, height, smoking, alcohol consumption, exercise, and socioeconomic status; Reference category = menarche at age 13 years; Area of square is inversely proportional to the variance of the log risk; ICD-10 – International Classification of Diseases 10th Revision.

Figure 2. Relative risk (RR) (95% confidence interval [CI]) of incident coronary heart disease (CHD), by age at menarche and risk factors for CHD (further details in Supplementary Table 2). RRs (hazard ratios) stratified by region of recruitment, and adjusted for year of birth, body mass index, height, smoking, alcohol consumption, exercise, and socioeconomic status except when this is the factor under consideration; Reference category = menarche at age 13 years; Area of square is inversely proportional to the variance of the log risk.

Figure 3. Relative risk (RR) (95% confidence interval [CI]) of incident cerebrovascular disease, by age at menarche (further details in Supplementary Table 4). RRs (hazard ratios) stratified by region of recruitment, and adjusted for year of birth, body mass index, height, smoking, alcohol consumption, exercise, and socioeconomic status; Reference category = menarche at age 13 years; Area of square is inversely proportional to the variance of the log risk; ICD-10 – International Classification of Diseases 10th Revision.
Coronary heart disease (ICD–10: I20 to I25)

Mean age at menarche (years) | Number with incident CHD | RR (95% CI)
--- | --- | ---
9.9 | 3477 | 1.27 (1.22, 1.31)
11 | 12,759 | 1.12 (1.10, 1.14)
12 | 12,121 | 1.02 (1.01, 1.04)
13 | 16,199 | 1.00 (0.98, 1.02)
14 | 15,064 | 1.04 (1.02, 1.06)
15 | 8784 | 1.06 (1.04, 1.08)
16 | 3614 | 1.10 (1.07, 1.14)
17.4 | 1360 | 1.23 (1.16, 1.29)
A. By body mass index (BMI) in kg/m² (P for heterogeneity=0.4)

BMI < 25 kg/m²

BMI 25–29 kg/m²

BMI ≥ 30 kg/m²

B. By smoking (P for heterogeneity=0.3)

Never smoker

Past smoker

Current smoker

C. By socioeconomic status (SES) (P for heterogeneity=0.08)

High SES

Middle SES

Low SES
Cerebrovascular disease (ICD–10: I60 to I69)

Mean age at menarche (years) | Number with incident CeVD | RR (95% CI)
---|---|---
9.9 | 1068 | 1.16 (1.09, 1.23)
11 | 4093 | 1.04 (1.01, 1.07)
12 | 4183 | 1.00 (0.97, 1.03)
13 | 5845 | 1.00 (0.97, 1.03)
14 | 5288 | 1.00 (0.97, 1.02)
15 | 3096 | 1.01 (0.97, 1.05)
16 | 1311 | 1.06 (1.00, 1.12)
17.4 | 478 | 1.13 (1.03, 1.24)
Age at Menarche and Risks of Coronary Heart and Other Vascular Diseases in a Large UK Cohort
Dexter Canoy, Valerie Beral, Angela Balkwill, F. Lucy Wright, Mary E. Kroll, Gillian K. Reeves, Jane Green and Benjamin J. Cairns

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Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2014/12/10/CIRCULATIONAHA.114.010070.DC1
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METHODS SUPPLEMENT

Laboratory methods

In subsequent resurvey of the Million Women Study cohort members at around 9 years after recruitment, study participants provided information on their health and lifestyle. A randomly selected subgroup of women in the cohort gave non-fasting blood samples collected at their local general practice clinics between 2006 and 2008 which were transported overnight at ambient temperature and processed at the Cancer Epidemiology Unit laboratory at University of Oxford (Oxford, UK). Plasma samples were then stored at -80°C. Using Beckman Synchron CX autoanalyzers (Beckman Coulter, High Wycombe, UK), we measured total cholesterol by enzymatic assay in EDTA plasma and apolipoprotein B (ApoB) and A1 (ApoA1) by immunoturbimetric assay but we measured high-density lipoprotein cholesterol (HDL-cholesterol) directly. The coefficients of variation were as follows: for total cholesterol = 1.6% and 1.5% at a mean value of 3.5 mmol/L and 6.7 mmol/L, respectively; for HDL-cholesterol = 2.6% and 2.1% at a mean value of 0.76 mmol/L and 1.82 mmol/L, respectively; for ApoB = 2.9% and 3.6% at a mean value of 0.88 g/L and 1.12 g/L, respectively; and for ApoA1 = 3.1% and 2.9% at a mean value of 1.24 g/L and 1.50 g/L, respectively.
Supplementary table 1. Relative risk (95% confidence interval [CI]) of incident coronary heart disease (ICD-10: I20 to I25), by age at menarche (years).

<table>
<thead>
<tr>
<th>No. of women</th>
<th>≤10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>≥17</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events (rate/1000s)</td>
<td>48,552</td>
<td>197,666</td>
<td>217,097</td>
<td>298,341</td>
<td>250,609</td>
<td>135,214</td>
<td>52,987</td>
<td>17,374</td>
</tr>
<tr>
<td>No. of events (rate/1000s)</td>
<td>3477 (6.2)</td>
<td>12,759 (5.6)</td>
<td>12,121 (4.8)</td>
<td>16,199 (4.7)</td>
<td>15,064 (5.2)</td>
<td>8784 (5.6)</td>
<td>3614 (6.0)</td>
<td>1360 (6.9)</td>
</tr>
</tbody>
</table>

Adjusting for: Year of birth, body mass index, height, smoking, alcohol consumption, exercise and socioeconomic status

| RR (95% CI) | 1.27 (1.22 to 1.31) | 1.12 (1.10 to 1.14) | 1.02 (1.01 to 1.04) | 1.00 (0.98 to 1.02) | 1.04 (1.02 to 1.06) | 1.06 (1.04 to 1.08) | 1.10 (1.07 to 1.14) | 1.23 (1.16 to 1.29) |

Additionally adjusting for:

Parity, oral contraceptive use, menopausal status and hormone replacement therapy use

| RR (95% CI) | 1.24 (1.20 to 1.29) | 1.11 (1.09 to 1.13) | 1.02 (1.01 to 1.04) | 1.00 (0.98 to 1.02) | 1.04 (1.02 to 1.06) | 1.06 (1.03 to 1.08) | 1.10 (1.06 to 1.13) | 1.22 (1.16 to 1.29) |

Ever had/being treated for hypertension

| RR (95% CI) | 1.24 (1.20 to 1.29) | 1.10 (1.08 to 1.12) | 1.02 (1.00 to 1.04) | 1.00 (0.98 to 1.02) | 1.05 (1.03 to 1.06) | 1.07 (1.05 to 1.09) | 1.12 (1.08 to 1.15) | 1.24 (1.17 to 1.31) |

Ever had/being treated for diabetes

| RR (95% CI) | 1.24 (1.20 to 1.28) | 1.10 (1.09 to 1.12) | 1.02 (1.00 to 1.04) | 1.00 (0.98 to 1.02) | 1.04 (1.02 to 1.06) | 1.06 (1.04 to 1.09) | 1.10 (1.07 to 1.14) | 1.22 (1.15 to 1.28) |

Ever had/being treated for hypercholesterolemia

| RR (95% CI) | 1.26 (1.22 to 1.30) | 1.11 (1.09 to 1.13) | 1.02 (1.00 to 1.04) | 1.00 (0.98 to 1.02) | 1.04 (1.02 to 1.06) | 1.06 (1.04 to 1.09) | 1.11 (1.07 to 1.14) | 1.23 (1.17 to 1.30) |

Adjusting for: All of the above factors

| RR (95% CI) | 1.20 (1.16 to 1.24) | 1.08 (1.07 to 1.10) | 1.02 (1.00 to 1.04) | 1.00 (0.98 to 1.02) | 1.04 (1.02 to 1.06) | 1.06 (1.04 to 1.08) | 1.10 (1.07 to 1.14) | 1.22 (1.15 to 1.28) |

RR – relative risk (hazard ratio); ICD-10 – International Classification of Diseases 10th Revision; All RRs stratified by region; Reference category = menarche at age 13 years; Rate in person-years.
### Supplementary Table 2 (supplement to Figure 2). Relative risk (95% CI) of incident coronary heart disease (CHD), by age at menarche (years) and risk factors of CHD.

<table>
<thead>
<tr>
<th>No. of women</th>
<th>≤10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>≥17</th>
</tr>
</thead>
<tbody>
<tr>
<td>All, RR (95% CI)</td>
<td>1.27 (1.22 to 1.31)</td>
<td>1.12 (1.10 to 1.14)</td>
<td>1.02 (1.01 to 1.04)</td>
<td>1.00 (0.98 to 1.02)</td>
<td>1.04 (1.02 to 1.06)</td>
<td>1.06 (1.04 to 1.08)</td>
<td>1.10 (1.07 to 1.14)</td>
<td>1.23 (1.16 to 1.29)</td>
</tr>
</tbody>
</table>

#### 1. Body mass index <25 kg/m²
- **RR (95% CI)**
  - No. with CHD 738: 1.20 (1.12 to 1.29)
  - No. with CHD 3923: 1.00 (0.97 to 1.03)
  - No. with CHD 5972: 1.00 (0.97 to 1.03)
  - No. with CHD 5774: 1.02 (0.99 to 1.04)
  - No. with CHD 3586: 1.05 (1.02 to 1.09)
  - No. with CHD 1521: 1.10 (1.07 to 1.13)
  - No. with CHD 564: 1.16 (1.07 to 1.26)

#### 2. Smoking
- **Never smokers**
  - RR (95% CI) 1.23 (1.17 to 1.31)
  - No. with CHD 1239: 1.13 (1.10 to 1.16)
  - No. with CHD 4972: 1.03 (1.00 to 1.06)
  - No. with CHD 6628: 1.00 (0.98 to 1.02)
  - No. with CHD 5646: 1.03 (1.01 to 1.06)
  - No. with CHD 3070: 1.05 (1.01 to 1.09)
  - No. with CHD 1279: 1.10 (1.04 to 1.16)
  - No. with CHD 487: 1.26 (1.16 to 1.38)

- **Past smokers**
  - RR (95% CI) 1.33 (1.25 to 1.42)
  - No. with CHD 970: 1.11 (1.07 to 1.15)
  - No. with CHD 3234: 1.03 (1.00 to 1.07)
  - No. with CHD 4318: 1.00 (0.97 to 1.03)
  - No. with CHD 4060: 1.06 (1.03 to 1.09)
  - No. with CHD 2370: 1.09 (1.05 to 1.14)
  - No. with CHD 984: 1.16 (1.09 to 1.23)
  - No. with CHD 364: 1.30 (1.17 to 1.44)

- **Current smokers**
  - RR (95% CI) 1.25 (1.18 to 1.32)
  - No. with CHD 1076: 1.11 (1.07 to 1.14)
  - No. with CHD 3276: 1.03 (0.99 to 1.06)
  - No. with CHD 4322: 1.00 (0.97 to 1.03)
  - No. with CHD 4426: 1.03 (1.00 to 1.06)
  - No. with CHD 2789: 1.05 (1.01 to 1.09)
  - No. with CHD 1116: 1.07 (1.01 to 1.14)
  - No. with CHD 407: 1.12 (1.01 to 1.23)

#### 3. Socioeconomic status (SES)

- **Least deprived third**
  - RR (95% CI) 1.26 (1.18 to 1.35)
  - No. with CHD 922: 1.08 (1.04 to 1.12)
  - No. with CHD 3243: 0.98 (0.95 to 1.02)
  - No. with CHD 3365: 1.00 (0.97 to 1.03)
  - No. with CHD 4705: 1.03 (1.00 to 1.07)
  - No. with CHD 3937: 1.02 (0.97 to 1.06)
  - No. with CHD 2049: 1.07 (1.00 to 1.15)
  - No. with CHD 835: 1.24 (1.10 to 1.38)

- **Middle third**
  - RR (95% CI) 1.23 (1.16 to 1.31)
  - No. with CHD 1034: 1.15 (1.12 to 1.19)
  - No. with CHD 4059: 1.03 (1.00 to 1.07)
  - No. with CHD 3891: 1.00 (0.97 to 1.03)
  - No. with CHD 5124: 1.04 (1.01 to 1.07)
  - No. with CHD 4565: 1.08 (1.03 to 1.12)
  - No. with CHD 2606: 1.03 (0.97 to 1.10)
  - No. with CHD 989: 1.25 (1.13 to 1.38)

- **Most deprived third**
  - RR (95% CI) 1.30 (1.23 to 1.37)
  - No. with CHD 1500: 1.11 (1.08 to 1.14)
  - No. with CHD 5353: 1.04 (1.01 to 1.07)
  - No. with CHD 4777: 1.00 (0.98 to 1.03)
  - No. with CHD 6252: 1.05 (1.02 to 1.07)
  - No. with CHD 6444: 1.08 (1.05 to 1.12)
  - No. with CHD 4071: 1.17 (1.12 to 1.23)
  - No. with CHD 1760: 1.23 (1.14 to 1.32)

RR = relative risk (hazard ratio); CI = confidence interval; All RRs stratified by region and adjusted for year of birth, body mass index, height, smoking, alcohol consumption, exercise and SES except when it is the factor under consideration; Reference category = menarche at age 13 years; P for heterogeneity: BMI=0.4, smoking=0.3 and SES=0.08.
Supplementary table 3. Relative risk (95% confidence interval [CI]) of coronary heart disease (ICD-10: I20 to I25) mortality, by age at menarche.

<table>
<thead>
<tr>
<th>Age at menarche (years)</th>
<th>No. of women</th>
<th>No. of CHD deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤11</td>
<td>246,218</td>
<td>1014</td>
</tr>
<tr>
<td>12</td>
<td>217,097</td>
<td>777</td>
</tr>
<tr>
<td>13</td>
<td>298,341</td>
<td>1010</td>
</tr>
<tr>
<td>14</td>
<td>250,609</td>
<td>943</td>
</tr>
<tr>
<td>15</td>
<td>135,214</td>
<td>576</td>
</tr>
<tr>
<td>≥16</td>
<td>70,361</td>
<td>314</td>
</tr>
</tbody>
</table>

Relative risk (95% CI) for each age category:
- ≤11: 1.12 (1.05 to 1.19)
- 12: 1.06 (0.98 to 1.13)
- 13: 1.00 (0.94 to 1.06)
- 14: 0.99 (0.93 to 1.06)
- 15: 1.02 (0.94 to 1.11)
- ≥16: 1.02 (0.91 to 1.14)

CHD – coronary heart disease; ICD-10 – International Classification of Diseases 10th Revision; Total number of CHD deaths = 4634; All relative risks (hazard ratios) stratified by region and adjusted for year of birth, body mass index, height, smoking, alcohol consumption, exercise and socioeconomic status; Reference category = menarche at age 13 years.
**Supplementary table 4** (supplement to Figure 3 and *Supplementary figure 4*). Relative risk (95% confidence interval [CI]) of incident cerebrovascular and hypertensive disease, by age at menarche (years).

<table>
<thead>
<tr>
<th>No. of women</th>
<th>≤10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>≥17</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events</td>
<td>48,552</td>
<td>197,666</td>
<td>217,097</td>
<td>298,341</td>
<td>250,609</td>
<td>135,214</td>
<td>52,987</td>
<td>17,374</td>
</tr>
<tr>
<td>Incident cerebrovascular disease (ICD-10: I60 to I69)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusting for year of birth, body mass index, height, smoking, alcohol consumption, exercise and socioeconomic status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.16 (1.09 to 1.23)</td>
<td>1.04 (1.01 to 1.07)</td>
<td>1.00 (0.97 to 1.03)</td>
<td>1.00 (0.97 to 1.02)</td>
<td>1.01 (0.97 to 1.05)</td>
<td>1.06 (1.00 to 1.12)</td>
<td>1.13 (1.03 to 1.24)</td>
<td></td>
</tr>
<tr>
<td>Additionally adjusting for reproductive and mediating factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.11 (1.05 to 1.18)</td>
<td>1.01 (0.98 to 1.05)</td>
<td>0.99 (0.96 to 1.02)</td>
<td>1.00 (0.97 to 1.03)</td>
<td>1.00 (0.97 to 1.03)</td>
<td>1.07 (1.01 to 1.13)</td>
<td>1.13 (1.04 to 1.24)</td>
<td></td>
</tr>
<tr>
<td>Incident hypertensive disease (ICD-10: I10 to I15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusting for year of birth, body mass index, height, smoking, alcohol consumption, exercise and socioeconomic status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.20 (1.18 to 1.22)</td>
<td>1.11 (1.10 to 1.12)</td>
<td>1.03 (1.02 to 1.04)</td>
<td>1.00 (0.99 to 1.01)</td>
<td>1.01 (1.00 to 1.02)</td>
<td>1.01 (1.00 to 1.02)</td>
<td>1.03 (1.01 to 1.05)</td>
<td>1.07 (1.04 to 1.11)</td>
</tr>
<tr>
<td>Additionally adjusting for reproductive and mediating factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.14 (1.12 to 1.16)</td>
<td>1.07 (1.06 to 1.08)</td>
<td>1.02 (1.01 to 1.03)</td>
<td>1.00 (0.99 to 1.01)</td>
<td>1.02 (1.01 to 1.03)</td>
<td>1.02 (1.01 to 1.04)</td>
<td>1.05 (1.03 to 1.07)</td>
<td>1.08 (1.04 to 1.11)</td>
</tr>
</tbody>
</table>

ICD-10 – *International Classification of Diseases 10th* Revision; All relative risks (hazard ratios) stratified by region; Reference category = menarche at age 13 years; Reproductive factors are parity, oral contraceptive use, menopausal status and hormone replacement therapy use; Mediating factors are reported (ever had or being treated for) hypertension, diabetes and hypercholesterolemia.
Supplementary table 5. Mean (95% confidence interval) plasma concentrations of cholesterol and other lipid fractions in 16,954 women, by age at menarche

<table>
<thead>
<tr>
<th>Age at menarche, years</th>
<th>Number of women</th>
<th>&lt;10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>≥17</th>
<th>P for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td></td>
<td>691</td>
<td>2632</td>
<td>3233</td>
<td>4531</td>
<td>3498</td>
<td>1592</td>
<td>583</td>
<td>194</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td></td>
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<td>Apolipoprotein B (mg/dL)</td>
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<td>Apolipoprotein A1 (mg/dL)</td>
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<tr>
<td>Apolipoprotein B to A1 ratio</td>
<td></td>
<td>0.65</td>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
<td>0.8</td>
</tr>
</tbody>
</table>

HDL – high-density lipoprotein; Information limited only to women with lipid fraction measurements; Means were adjusted for age at blood sample collection, year of birth, body mass index, height, smoking, alcohol consumption, exercise and socioeconomic status, and stratified by region.
Supplementary table 6. Prospective studies on age at menarche and coronary heart disease risk.

<table>
<thead>
<tr>
<th>Author &amp; publication year</th>
<th>Country</th>
<th>Study population</th>
<th>Baseline age, years</th>
<th>Study period (follow-up duration)</th>
<th>No. of events</th>
<th>Relative risk (95% confidence interval)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CORONARY HEART DISEASE MORTALITY</strong></td>
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<tr>
<td>Mueller (2012)</td>
<td>Singapore</td>
<td>Singapore Chinese Health Study participants, without invasive cancer</td>
<td>45 to 74</td>
<td>From 1993-1998 to 2009</td>
<td>998</td>
<td>≤12=1.04 (0.80 to 1.34), 13-14=Reference, 15-16=0.76 (0.65 to 0.90), ≥17=0.72 (0.58 to 0.88); P for trend per higher age category&lt;0.001 and 0.01 with further adjustment for diabetes and hypertension</td>
<td>Results adjusted for adiposity; Excluding those with pre-existing heart disease and stroke showed similar results (not shown); significant interaction with smoking (no significant association in ever smokers); results shown here for never smokers only</td>
</tr>
<tr>
<td>Gallagher (2011)</td>
<td>China</td>
<td>Textile workers enrolled in a breast self-exam randomized trial, non-smokers</td>
<td>30 to 60 (median=43)</td>
<td>From 1989-1991 to 2000</td>
<td>442</td>
<td>≤13=1.44 (1.00 to 2.05), 14=1.06 (0.76 to 1.47), 15=Reference, 16=1.09 (0.82 to 1.45), ≥17=0.85 (0.65 to 1.12); P for trend per higher age category=0.007</td>
<td>No adjustment for adiposity; Exclusion of pre-existing cardiovascular disease not mentioned</td>
</tr>
<tr>
<td>Chang (2011)</td>
<td>Korea</td>
<td>Kangwa Cohort Study participants</td>
<td>≥55 (mean=66)</td>
<td>From 1985 to 2005 (up to 20 years)</td>
<td>47</td>
<td>10-16= Reference, 17-18=0.49 (0.25 to 0.98), ≥19=0.65 (0.31 to 1.35); P for trend per higher age category=0.24</td>
<td>Results adjusted for adiposity and hypertension; Excluded oral contraceptive pill users; no exclusion of pre-existing cardiovascular disease but excluded early deaths (around first 6 months of follow-up)</td>
</tr>
<tr>
<td>Jacobsen (2009)</td>
<td>US</td>
<td>Seventh Day Adventists Health Study participants</td>
<td>26 to 101 (mean=55)</td>
<td>From 1976 to 1988 (up to 11 years)</td>
<td>809</td>
<td>&lt;12=1.37 (1.09 to 1.73), 12=1.20 (0.98 to 1.48), 13=Reference, 14=0.93 (0.76 to 1.14), 15=0.95 (0.74 to 1.23), ≥15=1.14 (0.88 to 1.49); P for trend per higher age category=0.01 and 0.3 before after adjusting for adiposity, respectively</td>
<td>No adjustment for adiposity except in trend analysis (limited to subgroup of postmenopausal women with body mass index data); Menarcheal age 2nd order term in regression model was significant (P&lt;0.001), suggesting non-linear association</td>
</tr>
<tr>
<td>Cui (2006)</td>
<td>Japan</td>
<td>Japan Collaborative Cohort Study participants, without pre-existing cardiovascular disease</td>
<td>40 to 79</td>
<td>From 1988-1990 to 1999 (up to 10 years)</td>
<td>178</td>
<td>≤13=Reference, 14=0.77 (0.41 to 1.45), 15=1.22 (0.70 to 2.11), 16=0.98 (0.55 to 1.73), ≥17=1.28 (0.75 to 2.20)</td>
<td>Results adjusted for adiposity</td>
</tr>
<tr>
<td><strong>INCIDENT CORONARY HEART DISEASE</strong></td>
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<tr>
<td>Lakshman (2009)</td>
<td>UK</td>
<td>EPIC-Norfolk study participants, without pre-existing cardiovascular disease</td>
<td>40 to 79</td>
<td>From 1993-1997 to 2008 (median=10.6 years)</td>
<td>1323</td>
<td>8-11=Reference, 12=0.84 (0.70 to 1.01), 13=0.75 (0.63 to 0.89), 14=0.77 (0.65 to 0.92), 15-18=0.83 (0.70 to 0.99); &lt;12=1.26 (1.10 to 1.49); Adjustment for adiposity shown only for age at menarche dichotomised as &lt;12 versus ≥12 years; Menarcheal age quadratic term in regression model was significant (P&lt;0.001), suggesting non-linear association; earlier age at menarche was related to a more adverse</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Name and Participants</td>
<td>Age at Menarche</td>
<td>Number of Participants</td>
<td>Menarche Age Range</td>
<td>Cardio-Metabolic Profile</td>
<td>Adiposity Adjustment</td>
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<tr>
<td>Cooper (1999)</td>
<td>US</td>
<td>Menstruation &amp; Reproductive History Study participants</td>
<td>&lt;25</td>
<td>45</td>
<td>8-11 = 1.32 (0.71 to 2.48), 12-16 = Reference, 14-18 = 0.42 (0.15 to 1.20); Per higher age category between ages 8 to 18 years = 0.76 (0.60 to 0.95) and 0.79 (0.61 to 1.01) before and after adjustment for adiposity, respectively</td>
<td>cardio-metabolic profile although later age at menarche had higher proportion of manual social class</td>
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</tr>
<tr>
<td>Colditz (1987)</td>
<td>US</td>
<td>Nurses' Health Study participants, without pre-existing coronary heart disease</td>
<td>30 to 55</td>
<td>302</td>
<td>≤10 = 1.3 (0.8 to 2.1), 11 = 1.0 (0.7 to 1.3), 12 = 0.8 (0.6 to 1.1), 13 = Reference, 14 = 1.0 (0.7 to 1.4), 15 = 0.6 (0.3 to 1.1), ≥16 = 0.8 (0.5 to 1.5); After adjusting for adiposity: ≤10 = 1.0 (0.6 to 1.7), 13 = Reference, ≥16 = 0.8 (0.4 to 1.6)</td>
<td>adiposity adjustment shown only for analyses using age at menarche as a continuous variable; coronary heart disease defined as self-reported myocardial infarction or coronary heart disease mortality</td>
<td></td>
</tr>
</tbody>
</table>

All studies assessed information on age at menarche based on medical history obtained via single questionnaire except for studies of Colditz (1987), which was based on repeated assessments by questionnaire, Mueller (2012), which was based on interview, and Cooper (1999), which was based on annual menstrual diary over 5 years during their reproductive years; Body mass index is the usual measure for adiposity; A meta-analysis (Charalamopoulos 2014) was conducted based on 2526 coronary heart disease deaths from studies already listed herein with significant heterogeneity and no combined data for each single year of age at menarche was reported.
## Supplementary table 7. Prospective studies on age at menarche and cerebrovascular disease risk.

<table>
<thead>
<tr>
<th>Author &amp; publication year</th>
<th>Country</th>
<th>Study population</th>
<th>Baseline age, years</th>
<th>Study period (follow-up duration)</th>
<th>No. of events</th>
<th>Relative risk (95% confidence interval)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CEREBROVASCULAR DISEASE MORTALITY</strong></td>
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<tr>
<td>Mueller (2012)</td>
<td>Singapore</td>
<td>Singapore Chinese Health Study participants, without invasive cancer</td>
<td>45 to 74</td>
<td>From 1993-1998 to 2009</td>
<td>998</td>
<td>≤12=1.22 (0.86 to 1.74), 13-14=Reference, 15-16=1.07 (0.86 to 1.32), ≥17=0.89 (0.68 to 1.18); P for trend per higher age category=0.27 and 0.6 with further adjustment for diabetes and hypertension</td>
<td>Results adjusted for adiposity; Excluding those with pre-existing heart disease &amp; stroke showed similar results (not shown); significant interaction with smoking (no significant association in ever smokers); results shown here for never smokers only; Ischemic and hemorrhagic stroke not separately reported</td>
</tr>
<tr>
<td>Gallagher (2011)</td>
<td>China</td>
<td>Textile workers enrolled in a breast self-exam randomized trial, non-smokers</td>
<td>30 to 60 (median=43)</td>
<td>From 1989-1991 to 2000</td>
<td>442</td>
<td>Ischemic stroke ≤13=1.05 (0.75 to 1.45), 14=0.82 (0.61 to 1.09), 15= Reference, 16=0.97 (0.76 to 1.23), ≥17=0.87 (0.70 to 1.09); P for trend per higher age category=0.49 Hemorrhagic stroke ≤13=0.97 (0.79 to 1.19), 14=1.03 (0.88 to 1.22), 15= Reference, 16=0.92 (0.79 to 1.07), ≥17=0.90 (0.79 to 1.03); P for trend per higher age category=0.06</td>
<td>No adjustment for adiposity; Exclusion of pre-existing cardiovascular disease not mentioned</td>
</tr>
<tr>
<td>Chang (2011)</td>
<td>Korea</td>
<td>Kangwa Cohort Study participants</td>
<td>≥55 (mean=66)</td>
<td>From 1985 to 2005 (up to 20 years)</td>
<td>297</td>
<td>10-16= Reference, 17-18=0.98 (0.74 to 1.29), ≥19=0.91 (0.66 to 1.25); P for trend per higher age category=0.56</td>
<td>Results adjusted for adiposity and hypertension; Excluded oral contraceptive pill users; no exclusion of pre-existing cardiovascular disease but excluded early deaths (first 6 months of follow-up); Ischemic and hemorrhagic stroke not separately reported</td>
</tr>
<tr>
<td>Jacobsen (2009)</td>
<td>US</td>
<td>Seventh Day Adventists Health Study participants</td>
<td>26 to 101 (mean=55)</td>
<td>From 1976 to 1988 (up to 11 years)</td>
<td>378</td>
<td>&lt;12=1.43 (1.02 to 2.01), 12=1.17 (0.86 to 1.59), 13=Reference, 14=1.14 (0.86 to 1.52), 15=0.78 (0.52 to 1.17), &gt;15=0.90 (0.59 to 1.37); P for trend per higher age category=0.02 and 0.06 before and after adjusting for adiposity, respectively</td>
<td>No adjustment for adiposity except in trend analysis (limited to subgroup of postmenopausal women with body mass index data); Ischemic and hemorrhagic stroke not separately reported</td>
</tr>
<tr>
<td>Cui (2006)</td>
<td>Japan</td>
<td>Japan Collaborative Cohort Study</td>
<td>40 to 79</td>
<td>From 1988-1990 to 1999 (up to 10)</td>
<td>487</td>
<td>≤13=Reference, 14=1.29 (0.89 to 1.88),</td>
<td>Results adjusted for adiposity; Risk estimates for separately for ischemic and hemorrhagic</td>
</tr>
<tr>
<td>STUDY</td>
<td>COUNTRY</td>
<td>DESIGN</td>
<td>AGE RANGE</td>
<td>FEMALE AGE AT MENARCHE</td>
<td>NUMBER</td>
<td>SEXUAL DIFFERENCE</td>
<td>ADJUSTMENTS</td>
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<tr>
<td>Lakshman (2009)</td>
<td>UK</td>
<td>EPIC-Norfolk study participants, without pre-existing cardiovascular disease</td>
<td>40 to 79</td>
<td>From 1993-1997 to 2008 (median=10.6 years)</td>
<td>602</td>
<td>&lt;12=1.13 (0.89 to 1.44), ≥12=Reference</td>
<td>Adjustment for adiposity shown only for age at menarche dichotomised as &lt;12 versus ≥12 years; Earlier age at menarche was related to a more adverse cardio-metabolic profile although later age at menarche had higher proportion of manual social class; Ischemic and hemorrhagic stroke not separately reported.</td>
</tr>
</tbody>
</table>

All studies assessed information on age at menarche based on medical history obtained via single questionnaire except for studies Mueller (2012), which was based on interview; Body mass index is the usual measure for adiposity; All studies did not present results for specific stroke subtypes except for Gallagher (2011); A meta-analysis (Charalampopoulos 2014) was conducted based on 4733 cerebrovascular deaths from studies already listed herein with no combined data for each single year of age at menarche was reported.
Supplementary figure 1. Relative risk (RR) (95% confidence interval [CI]) of incident hypertensive disease, by age at menarche (further details in Supplementary table 4). RRs (hazard ratios) stratified by region of recruitment, and adjusted for year of birth, body mass index, height, smoking, alcohol consumption, exercise, and socioeconomic status; Reference category = menarche at age 13 years; Area of square is inversely proportional to the variance of the log risk; ICD-10 – International Classification of Diseases 10th Revision.
Supplementary figure 2. Relative risk (RR) (95% confidence interval [CI]) of vascular diseases after reporting error correction, by age at menarche. RRs (hazard ratios) from the main analysis (Figures 1 and 3, and Supplementary figure 1) are plotted against the estimated actual mean age at menarche; All RRs are stratified by region of recruitment, and adjusted for year of birth, body mass index, height, smoking, alcohol consumption, exercise, and socioeconomic status; Reporting error correction is based on the regression dilution ratio of 0.44 (Cairns 2011) applied to mean ages within each self-reported category; Reference category=menarche at age 13 years.
SUPPLEMENTARY REFERENCES


