Early Age at Menarche Associated with Cardiovascular Disease and Mortality

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Context: The relationship between age at menarche and cardiovascular disease remains unclear. Two recent studies found an inverse association between age at menarche and all-cause mortality.

Objective: The aim of this study was to examine the relationship between age at menarche and cardiovascular disease risk factors, events, and mortality.

Design, Setting, and Participants: A population-based prospective study involving 15,807 women, aged 40–79 yr in 1993–1997 and followed up to March 2007 for cardiovascular disease events (median follow-up 10.6 yr) and February 2008 for mortality (median follow-up 12.0 yr) was used.

Main Outcome Measures: Odds ratios for cardiovascular disease risk factors and hazard ratios for incident cardiovascular disease and mortality were calculated.

Results: There were 3888 incident cardiovascular disease events (1323 coronary heart disease, 602 stroke, and 1963 other) and 1903 deaths (640 cardiovascular disease, 782 cancer, and 481 other) during follow-up. Compared with other women, those who had early menarche (<12 yr) had higher risks of hypertension [1.13 (1.02–1.24)], incident cardiovascular disease [1.17 (1.07–1.27)], incident coronary heart disease [1.23 (1.06–1.43)], all-cause mortality [1.22 (1.07–1.39)], cardiovascular disease mortality [1.28 (1.02–1.62)], and cancer mortality [1.25 (1.03–1.51)], adjusted for age, physical activity, smoking, alcohol, educational level, occupational social class, oral contraceptive use, hormone replacement therapy, parity, body mass index, and waist circumference.

Conclusions: Early age at menarche (before age 12 yr) was associated with increased risk of cardiovascular disease events, cardiovascular disease mortality, and overall mortality in women, and this association appeared to be only partly mediated by increased adiposity. **(*J Clin Endocrinol Metab* 94: 4953–4960, 2009)**

Menarche signals the end of puberty and the start of reproductive life. Obese girls tend to enter puberty earlier than other girls, and in turn, early menarche has been associated with increased adult body mass index (BMI) (1–4). Earlier menarche has also been associated with increased metabolic syndrome and cardiovascular disease (CVD) risk factors in adolescent girls and in young women studied up to age 40 yr (5–8). In Chinese women aged 25–64 yr, compared with women with average age at menarche, women with early menarche had a 32% higher risk of metabolic syndrome (9). However, the effects of early menarche in older women and on actual CVD events and mortality remain unclear (10–14). Two recent studies have found a 4.5 and 2.4% reduced risk of overall mortality per year later menarche (15, 16). In the European Prospective Investigation into Cancer (EPIC)-Norfolk, co-

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Abbreviations: BMI, Body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer.

hort we previously reported an inverse association between age at menarche and diabetes risk (odds ratio = 0.91 per year later menarche), which appeared to be completely explained by increased BMI (17). Hence we hypothesized that earlier age at menarche would also predict CVD events and CVD mortality.

Subjects and Methods

Study design and population

The EPIC-Norfolk is a population based cohort study of 25,639 Caucasian men and women (women n = 16,716) living in Norfolk, United Kingdom, aged 40–79 yr at recruitment in 1993–1997 (18). The study was approved by the local research ethics committee, and participants gave signed informed consent. At baseline, participants attended for a health check at which anthropometry and blood pressure were measured using standard protocols (19), and a nonfasting blood sample was collected for lipids and glycated hemoglobin (in a subset). Details of these measurements have been described previously (20, 21). Participants also completed a detailed health and lifestyle questionnaire at baseline and at three follow-up assessments (two postal questionnaires at 3 and 10 yr and one repeat health check visit) until 2005. Data to 2007 (for CVD events) and 2008 (for mortality) were obtained by record linkage.

Age at menarche in completed whole years was ascertained by recall in the baseline questionnaire. For the purpose of this study, we excluded women who did not provide information on age at menarche (n = 878) or reported age at menarche as less than 8 yr (n = 2) or more than 18 yr (n = 29) because this was likely to be due to recall error or nonphysiological conditions (22).

Information about prevalent hypertension, hyperlipidemia, and diabetes was based on self-reported medication use at baseline (or self-reported physician diagnosis of diabetes or diabetic diet). Prevalent CVD was based on the answer to the question, "Has a doctor ever told you that you had a heart attack or stroke?" From the baseline questionnaire, we also obtained family history of stroke, heart attack, cancer, and diabetes. Smoking status (current, former, or never), alcohol use (units per week), oral contraceptive use (current, former, or never), hormone replacement therapy use (current, former or never), parity (number of pregnancies), physical activity level (level 1, sedentary, to level 4, most active) (23), occupational social class (professional, managerial and technical, skilled nonmanual, skilled manual, partly skilled manual, or unskilled) and highest educational qualifications (no qualifications, O-level or equivalent, A-level or equivalent, degree level) were recorded at baseline.

Ascertainment of CVD events and risk factors at follow-up

Data on nonfatal incident CVD events were obtained from ENCORE, which is the East Norfolk database recording in-patient episodes from all hospital contacts to Norfolk residents, using record linkage to the EPIC-Norfolk database until March 31, 2007. We used the hospital codes for CVD admissions, which were clinically defined by the attending consultant. Participants were identified as having incident CVD if they had a hospital admission and/or died with CVD mentioned as cause of death anywhere on the death certificate. Follow-up for incident CVD ended either on the date of first disease event (diagnosis or death) or on March 31, 2007 for the remaining cohort. Incident hypertension and hyperlipidemia were identified from nurse interviews at the second health check or from self-reports of medication use on follow-up questionnaires.

Mortality endpoints

All participants were flagged for death certification at the Office of National Statistics, and trained nosologists coded all death certificates up to February 29, 2008. Follow-up time for mortality was calculated for each participant from time of entry to the study to time of death or until February 29, 2008. Main outcomes of interest were all-cause mortality (defined as death from any cause) or cause-specific mortality, which was defined by underlying cause of death using both the International Classification of Diseases, ninth edition ICD-9 or tenth edition ICD-10 codes: CVD mortality (ICD-9 401–448, or ICD-10 I10–I79), coronary heart disease (CHD) mortality (ICD-9 410–414 or ICD-10 I20–I25), stroke mortality (ICD-9 430–438 or ICD-10 I60–I69), and cancer mortality (ICD-9 140–208 or ICD-10 C00–C97).

Statistical analysis

Because of the positive correlation between age at menarche and age at baseline assessment, which reflects the recognized secular trend in age at menarche, we examined age-adjusted risk factor distribution by approximately equal categories (quintiles) of age at menarche. To quantify the association between the exposure (age at menarche in categories) and the prevalence of CVD risk factors (hypertension, hyperlipidemia, diabetes, and obesity), we performed multivariable logistic regression analyses. Where there was a linear association between age at menarche and the risk factor (hypertension, BMI, and waist circumference), linear models were fit using age at menarche as a continuous variable. For incident outcomes (CVD events and mortality), Cox proportional hazards regression analyses were used. We used the earliest category of age at menarche (8–11 yr) as the reference category, with indicator variables for the other four categories and adjusted for age, physical activity, smoking, alcohol, occupational social class, educational level, oral contraceptive use, hormone replacement therapy use, and parity. Subsequent models were constructed further adjusting for BMI and waist circumference to assess whether adiposity mediated the associations. Models were fit using category of age at menarche as a continuous variable to assess the evidence for a linear trend (*P* trend) across the categories. Age-adjusted percentages of CVD risk factors and age-standardized rates of cardiovascular events and mortality were calculated within each category of age at menarche. The age-standardized rates were calculated as a weighted average of the rates within 10-yr age strata.

All analyses were performed using STATA statistical software, version 10 (StataCorp, College Station, TX).

Results

Cohort characteristics

For the 15,807 women eligible for analysis, age at menarche showed a normal distribution (mean 13, median 13, SD 1.6 yr).

At baseline, 3256 women (20.6%) were taking medication for hypertension, 247 (1.6%) for hyperlipidemia, and

TABLE 1. Baseline characteristics and cardiovascular risk factors of 15,807 women at age 40–79 yr by categories (approximate quintiles) of age at menarche: the EPIC-Norfolk cohort study (baseline 1993–1997)

	Categories of age at menarche (in completed whole yr)					
	8–11 yr, n = 3365 (21.3%)	**12 yr, n = 2761 (17.5%)**	**13 yr, n = 3751 (23.7%)**	**14 yr, n = 3259 (20.6%)**	**15–18 yr, n = 2671 (16.9%)**	***P* trend**
Age-adjusted means (95% CI)						
Age at baseline (yr)[a]	57.2 (56.9–57.5)	57.8 (57.4–58.2)	58.2 (57.9–58.5)	59.7 (59.4–60.1)	60.3 (59.9–60.6)	<0.001
BMI (kg/m^2)	27.5 (27.3–27.6)	26.4 (26.3–26.6)	26.1 (25.9–26.2)	25.7 (25.5–25.9)	25.4 (25.2–25.6)	<0.001
Waist (cm)	84.3 (83.9–84.7)	82.6 (82.2–83.0)	81.8 (81.5–82.2)	81.2 (80.8–81.6)	80.9 (80.4–81.3)	<0.001
Height (cm)	160.1 (159.8–160.3)	160.8 (160.6–161.0)	161.0 (160.8–161.2)	161.3 (161.1–161.5)	161.6 (161.4–161.9)	<0.001
Systolic BP (mm Hg)	135.4 (134.8–136.0)	134.3 (133.7–135.0)	133.6 (133.0–134.2)	133.7 (133.1–134.3)	132.9 (132.2–133.6)	<0.001
Diastolic BP (mm Hg)	81.9 (81.5–82.3)	81.2 (80.8–81.7)	80.7 (80.3–81.2)	80.7 (80.3–81.2)	80.5 (80.1–81.0)	<0.001
Cholesterol (mmol/liter)	6.35 (6.31–6.40)	6.31 (6.26–6.36)	6.30 (6.26–6.34)	6.32 (6.28–6.36)	6.27 (6.22–6.31)	0.024
LDL-cholesterol (mmol/liter)	4.05 (4.01–4.09)	4.03 (3.98–4.07)	3.99 (3.95–4.03)	4.03 (3.99–4.07)	3.98 (3.94–4.03)	0.101
HDL-cholesterol (mmol/liter)	1.55 (1.54–1.57)	1.55 (1.53–1.57)	1.59 (1.57–1.61)	1.57 (1.55–1.59)	1.57 (1.55–1.59)	0.035
Triglycerides (mmol/liter)	1.70 (1.67–1.74)	1.63 (1.59–1.67)	1.62 (1.59–1.65)	1.60 (1.57–1.64)	1.57 (1.53–1.61)	<0.001
HbA1c (%), n = 5806	5.39 (5.34–5.43)	5.27 (5.23–5.32)	5.29 (5.25–5.33)	5.28 (5.24–5.33)	5.30 (5.25–5.35)	0.011
Alcohol drinking (units/wk)	4.11 (3.92–4.30)	4.24 (4.03–4.45)	4.51 (4.32–4.69)	4.52 (4.32–4.71)	4.06 (3.85–4.28)	0.370
Age-adjusted % (n)						
Current smoker	11.7 (421)	10.7 (311)	11.2 (438)	11.8 (379)	12.1 (311)	0.450
Low physical activity	30.9 (1024)	29.8 (838)	30.1 (1168)	31.4 (1129)	32.1 (962)	0.177
No qualifications	47.8 (1546)	43.1 (1174)	46.8 (1742)	51.9 (1739)	55.4 (1533)	<0.001
Manual social class	40.5 (1336)	38.2 (1033)	38.8 (1427)	39.1 (1244)	42.0 (1081)	0.301
Never used oral contraceptives	60.0 (1760)	57.7 (1451)	55.7 (1965)	58.0 (1906)	57.9 (1614)	0.174
Never used HRT	67.9 (2211)	71.6 (1933)	71.3 (2629)	70.0 (2290)	70.7 (1910)	0.084
Family history of stroke	25.7 (851)	25.0 (686)	25.8 (968)	23.8 (798)	27.2 (751)	0.629
Family history of heart attack	39.9 (1332)	36.3 (999)	36.2 (1355)	36.4 (1198)	36.5 (987)	0.008
Prevalent cardiovascular disease	1.8 (81)	1.6 (65)	1.5 (82)	1.5 (82)	1.7 (80)	0.560
Prevalent hypertension	21.2 (733)	17.4 (527)	17.9 (748)	17.2 (689)	16.5 (559)	<0.001
Prevalent hyperlipidemia	1.7 (62)	1.2 (37)	1.4 (60)	1.3 (52)	1.1 (36)	0.038
BMI ≥30 kg/m^2	24.8 (695)	17.9 (415)	16.0 (508)	13.1 (362)	12.5 (284)	<0.001
Waist circumference ≥80 cm	60.2 (1645)	52.8 (1203)	50.0 (1561)	47.9 (1338)	46.6 (1079)	<0.001

BP, Blood pressure; CI, confidence interval; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HRT, hormone replacement therapy; LDL, low-density lipoprotein.

[a] Unadjusted.

390 (2.5%) reported a myocardial infarction or stroke. During follow-up, an additional 2012 participants (16.0%) were started on medication for hypertension and 950 (6.1%) for hyperlipidemia. Family history of stroke was present in 4054 (25.7%) and heart attack in 5871 (37.1%) women.

A total of 3888 incident fatal and nonfatal CVD events (1323 CHD, 602 stroke, and 1963 other) were recorded during a median 10.6 yr [interquartile range 9.4–12.0 yr (159,199 person-years)] of follow-up until March 2007. A total of 1903 deaths occurred during a median follow-up of 12.0 yr [interquartile range 10.9–13.1 yr (185,220 person-years)] until February 2008. These included 640 CVD deaths (274 CHD, 219 stroke, and 147 other CVD) and 782 cancer deaths.

Age at menarche and CVD risk factors

Table 1 shows that after adjusting for age, women in earlier categories for menarche were shorter and had a higher BMI, waist circumference, arterial blood pressure, glycated hemoglobin, cholesterol, and triglyceride levels at baseline assessment. They were also more likely to have a family history of heart attack and take medication for hypertension and hyperlipidemia (P for trend <0.05).

Across increasing categories of age at menarche, odds of hypertension, diabetes, obesity (BMI $\geq$30 kg/m^2) and central obesity (waist circumference $\geq$80 cm) decreased (P for trend <0.001, Table 2 and Fig. 1A).

In linear models, for each year delay in onset of menarche, odds of hypertension were lower by 5% (95% confidence interval 3–7%), obesity (BMI $\geq$30 kg/m^2) by 18% (16–21%), and central adiposity (waist circumference $\geq$80 cm) by 12% (10–14%), adjusted for age, physical activity, smoking, alcohol, educational level, occupational social class, oral contraceptive use, hormone replacement therapy, and parity. The association with hypertension was attenuated after adjusting for BMI and waist circumference. The magnitude of the association was similar when incident (excluding prevalent cases) and prevalent hypertension cases were considered separately [incident hypertension 5% (1–7%) and prevalent hypertension 5% (3–8%)].

Age at menarche, CVD events, and mortality

Earlier age at menarche was associated with higher incident CVD, incident CHD, all-cause mortality, and cancer mortality (P for trend <0.05, Table 2). Each year delay in onset of menarche was also associated with a lower risk for all-cause mortality [hazard ratio = 0.96 (0.93–0.99), $P = 0.016$] and cancer mortality [0.95 (0.90–1.00), $P = 0.038$], adjusting for age, physical activity, smoking, alcohol, educational level, occupational social class, oral contraceptive use, hormone replacement therapy, parity, BMI, and waist circumference.

TABLE 2. Adjusted odds ratios for CVD risk factors and hazard ratios for CVD events and mortality by categories (approximate quintiles) of age at menarche: the EPIC-Norfolk cohort study (1993–2008)

	Categories of age at menarche (in completed whole yr)					
	8–11 yr	12 yr	13 yr	14 yr	15–18 yr	*P* trend
Odds ratios (prevalent and incident risk factors)						
Hypertension (n = 5268)	1	0.89 (0.79–0.99)[a]	0.80 (0.72–0.89)[c]	0.80 (0.72–0.89)[c]	0.76 (0.67–0.85)[c]	<0.001
Hyperlipidemia (n = 1197)	1	0.87 (0.71–1.06)	0.94 (0.78–1.12)	0.92 (0.76–1.10)	0.94 (0.77–1.13)	0.657
Diabetes (n = 834)	1	0.85 (0.68–1.06)	0.68 (0.55–0.84)[c]	0.69 (0.56–0.86)[b]	0.65 (0.52–0.82)[c]	<0.001
BMI $\geq$30 kg/m^2 (n = 2264)	1	0.66 (0.57–0.76)[c]	0.58 (0.51–0.66)[c]	0.44 (0.38–0.50)[c]	0.40 (0.35–0.47)[c]	<0.001
Waist circumference $\geq$80 cm (n = 6826)	1	0.75 (0.67–0.84)[c]	0.66 (0.59–0.73)[c]	0.59 (0.53–0.66)[c]	0.55 (0.49–0.62)[c]	<0.001
Hazard ratios (incident events)						
Incident CVD[b] (n = 3888)	1	0.83 (0.74–0.92)[c]	0.79 (0.72–0.87)[c]	0.83 (0.75–0.91)[c]	0.84 (0.76–0.93)[b]	0.001
Incident CHD[b] (n = 1323)	1	0.84 (0.70–1.01)	0.75 (0.63–0.89)[b]	0.77 (0.65–0.92)[b]	0.83 (0.70–0.99)[a]	0.022
All-cause mortality (n = 1903)	1	0.81 (0.69–0.95)[b]	0.86 (0.75–0.99)[a]	0.87 (0.75–1.00)[a]	0.82 (0.70–0.95)[b]	0.039
CVD mortality (n = 640)	1	0.83 (0.63–1.09)	0.75 (0.58–0.97)[a]	0.93 (0.73–1.18)	0.79 (0.61–1.03)	0.260
Cancer mortality (n = 782)	1	0.77 (0.61–0.97)[a]	0.82 (0.67–1.02)	0.74 (0.60–0.92)[b]	0.74 (0.59–0.93)[a]	0.010

Odds ratios and hazard ratios are adjusted for age, physical activity, smoking, alcohol, educational level, occupational social class, oral contraceptive use, hormone replacement therapy use, and parity. Incident CVD and CHD (fatal and nonfatal) data include follow-up until March 2007. Mortality data include follow-up until February 2008.

[a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$ for significant odds ratios or hazard ratios compared with the first category for age at menarche.

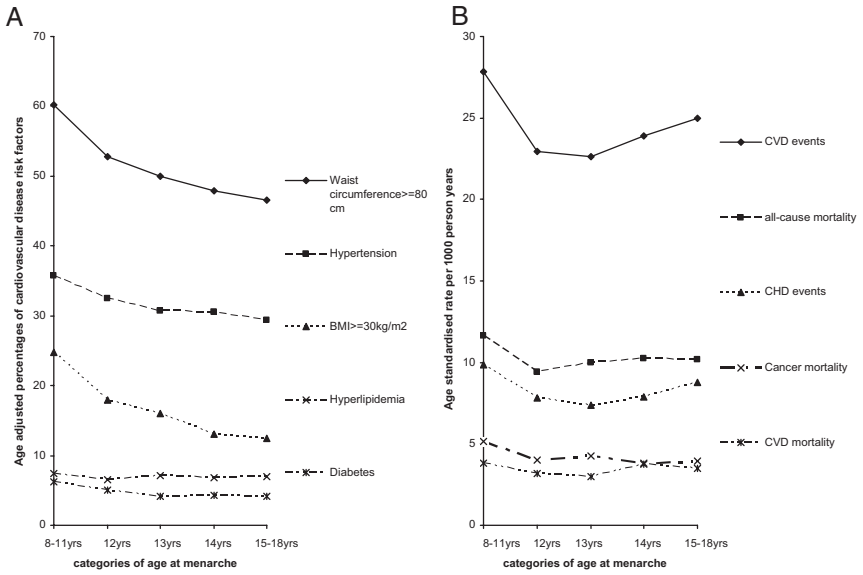

FIG. 1. A, Age-adjusted percentages of CVD risk factors in adulthood by categories (approximate quintiles) of age at menarche; B, age-standardized rates of cardiovascular events and mortality in adulthood by categories (approximate quintiles) of age at menarche.

Early menarche

Figure 1B shows that the age-standardized rates for CVD events, CHD events, all-cause mortality, CVD mortality, and cancer mortality were highest in the earliest category of age at menarche (8–11 yr). Fitting quadratic terms for age at menarche confirmed these apparent nonlinear associations with CVD and CHD events ($P < 0.001$). Women in the earliest category of menarche (8–11 yr) had a higher risk of hypertension, diabetes, obesity, CVD, CHD, and all-cause mortality and cancer mortality than other women (Table 3). Furthermore, these associations were only partially attenuated after adjusting for adult BMI and waist circumference; elevated risks remained for hypertension 13% (2–24%), incident CVD 17% (7–27%), incident CHD 23% (6–43%), all-cause mortality 22% (7–39%), CVD mortality 28% (2–62%), and cancer mortality 25% (3–51%).

Discussion

In this large, prospective, population-based cohort study, we found that women with earlier age at menarche had a higher BMI, waist circumference, blood pressure, and glycated hemoglobin and a worse lipid profile during adulthood. They were also more likely to have a family history of CVD and to take medication for hypertension and hyperlipidemia. Compared with other women, those who had early menarche (8–11 yr) had a higher risk of hypertension, diabetes, CVD and CHD events, and CVD, cancer, and all-cause mortality. Although slightly attenuated, these associations persisted after adjusting for adult BMI and waist circumference.

Comparison with other studies

Our finding of a 4.0% reduced risk of all-cause mortality for each year delay in onset of menarche is consistent with a Norwegian study and a Californian study that found a 2.4 and 4.5% (respectively) reduced risk of mor-

TABLE 3. Early menarche (at age <12 yr) as a risk factor for CVD risk factors, CVD events, and mortality: the EPIC-Norfolk cohort study (1993–2008)

	Model 1		Model 2	
	Odds or hazard ratio (CI)	*P* value	Odds or hazard ratio (CI)	*P* value
CVD risk factors (prevalent and incident)				
Hypertension	1.25 (1.14–1.37)	<0.001	1.13 (1.02–1.24)	0.015
Diabetes	1.41 (1.18–1.68)	<0.001	1.18 (0.98–1.42)	0.081
Obesity (BMI ≥30 kg/m^2)	1.93 (1.74–2.14)	<0.001		
Waist circumference ≥80 cm	1.57 (1.44–1.71)	<0.001		
Events and deaths				
Incident CVD	1.28 (1.13–1.34)	<0.001	1.17 (1.07–1.27)	0.001
Incident CHD	1.26 (1.10–1.49)	0.001	1.23 (1.06–1.43)	0.008
Incident stroke	1.14 (0.89–1.44)	0.297	1.13 (0.89–1.44)	0.317
All-cause mortality	1.21 (1.07–1.38)	0.004	1.22 (1.07–1.39)	0.003
CVD mortality	1.27 (1.01–1.60)	0.065	1.28 (1.02–1.62)	0.035
Cancer mortality	1.28 (1.06–1.57)	0.011	1.25 (1.03–1.51)	0.023

Data for CVD risk factors are odds ratios; data for events and deaths are hazard ratios. Model 1 was adjusted for age, physical activity, smoking, alcohol, educational level, occupational social class, oral contraceptive use, hormone replacement therapy use, and parity. Model 2 was as for model 1 and further adjusted for BMI and waist circumference (both models include 12,902 participants on whom data on all variables were available). Incident CVD, CHD, and stroke (fatal and nonfatal) data include follow-up until March 2007. All-cause mortality data include follow-up until February 2008. CI, Confidence interval.

tality per year later menarche. The Californian study also found a reduced risk of ischemic heart disease (6.0% per category higher menarcheal age) and stroke (8.6%) mortality (15). The Norwegian study recruited approximately 61,000 women from 1956–1959 and followed them for 37 yr (16), whereas the Californian study recruited approximately 20,000 Seventh-Day Adventist women in 1974, and deaths were reported until 1988 (15). The first study did not have data on physical activity or cigarette smoking, and the second study used self-reported anthropometry data; hence, residual confounding could not be ruled out.

A previous review of the literature on reproductive risk factors and CVD events in postmenopausal women concluded that there was no association between age at menarche and CVD risk (12). One prospective study with 119,963 participants (308 cases of CHD) found a nonsignificant association [age-adjusted hazard ratio of 1.3 (0.8–2.1) for menarche before 11 yr compared with menarche at 13 yr] (10), and another with 867 women (45 cases of CHD) found a significant inverse association [age-adjusted hazard ratio 0.76 (0.60–0.95) per year delay in onset of menarche] (11). In our study, 1323 CHD events occurred, and we found a significant increased risk in women with menarche before 12 yr compared with other women. Our positive findings may be explained by the large number of events and potential confounding factors that were included in our study.

In a previous cross-sectional study of 9000 Chinese women aged 25–64 yr and enrolled in 2004–2005, age at menarche was inversely associated with body fatness (BMI, waist circumference, and total and abdominal fat mass), insulin resistance (homeostasis model assessment), and total number of metabolic syndrome components (9). Other studies of younger women and smaller samples have also shown the association between younger age at menarche and increased risk of metabolic syndrome (5, 7, 8, 24). In our study, we found that in older women aged over 40 yr, early age at menarche was associated not only with CVD risk factors but also with elevated risk of CVD events and mortality.

Interestingly, although the associations with CVD risk factors appeared to be linear, we observed significant nonlinear effects of age at menarche on CVD and CHD events. The reasons for this are unclear. It is possible that late age at menarche might also be an independent risk factor. In a Japanese study, women with late menarche at 17 yr or later had a nonsignificant increased risk of stroke mortality and no difference in CHD mortality despite having less hypertension and lower BMI (25). Possible independent effects of late menarche on the development of CVD could include a relatively shorter exposure to the protective effects of endogenous estrogens.

Early age at menarche is an established risk factor for breast cancer incidence and survival, possibly due to hormonal effects (26–29). Although we did not look at site-specific cancer mortality, breast cancer is the most common cancer in women and likely contributed to the increased cancer mortality observed in our study.

Strengths and limitations

The strengths of our study include its large size, population base, and long duration of follow-up from 1993–2008 leading to high numbers of incident events. A comprehensive range of possible confounding and mediating factors were measured and adjusted for in the analyses.

Limitations of our study include the self-recall of age at menarche many years after the event. However, other studies have shown high correlations between age at menarche by recall during middle age and the original childhood data (30, 31). Furthermore, recall bias is unlikely; therefore, any errors would likely attenuate the real strengths of the associations that we observed. Another limitation is that we had only adult measures of BMI and waist circumference. Other more specific measures of adiposity and fat distribution might have mediated the associations we observed with CVD events and CVD mortality. Furthermore, we did not have any information on measures of BMI or waist circumference during childhood, which could help to shed light on the etiology of the associations we observed. Whether higher childhood BMI could be driving the association between age at menarche and adult CVD risk factors, events, or mortality as suggested by some studies (7, 32–35) or independently of childhood BMI as found in other studies (8, 36, 37) remains to be resolved.

Conclusion and implications

Further large prospective studies are needed to understand the mechanisms by which early menarche increases the risk of mortality and CVD in later life. Whether early menarche acts as a marker of childhood obesity, as a risk factor *per se*, or through ongoing sex hormone differences is unclear. It is possible that all of these factors play a role. A higher family risk in women with early age at menarche may suggest a common genetic mechanism.

In conclusion, our study of a large population-based cohort provides evidence that early age of menarche is associated with increased risks of CVD events, CVD mortality, and overall mortality in women, and these associations may be only partly mediated by increased adiposity. History of early menarche (<12 yr) may help to identify women with increased risk of CVD and mortality. These

results highlight the importance of understanding and targeting the childhood antecedents of adult disease.

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