Published in final edited form as:

Ann Epidemiol. 2012 October ; 22(10): 717–722. doi:10.1016/j.annepidem.2012.08.002.

Age at Menarche and Cardiovascular Disease Mortality in Singaporean Chinese Women: The Singapore Chinese Health Study

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Abstract

Purpose—To examine whether menarcheal age was inversely associated with CVD mortality in Singaporean Chinese women.

Methods—34,022 Chinese women aged 45–74 at enrollment (1993–1998), with complete data on study variables, were followed prospectively through 2009 for primary cause of death due to CVD, including coronary heart disease (CHD) and cerebrovascular disease (CERE). Hazard ratios (HRs) for CVD mortality were computed across menarcheal age categories and adjusted for potential confounders and BMI.

Results—Over 460,374 person-years of follow-up, 1,852 women died from CVD; 998 of them from CHD and 557 from CERE. There was a significant interaction between menarcheal age and smoking ($p < 0.05$). In nonsmokers, menarcheal age was inversely associated with risk for CVD and CHD mortality. HRs (and 95% CI) for CVD mortality across menarcheal age categories (12, 13–14, 15–16, 17) were: 1.06 (0.87–1.29), 1 (referent), 0.89 (0.79–1.00), and 0.80 (0.69–0.93), respectively ($p_{trend} < 0.001$); HRs for CHD mortality were: 1.06 (0.80–1.34), 1 (referent), 0.76 (0.65–0.90), and 0.72 (0.58–0.88), respectively ($p_{trend} < 0.001$). In nonsmokers there was no association between menarcheal age and CERE mortality. Among smokers, menarcheal age was not associated with CVD, CHD or CERE mortality.

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Data sharing agreement: Statistical code, and dataset available from the corresponding author at muel0266@umn.edu.

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Author contribution

NTM: Conceptualized, designed and carried out analysis, interpreted data, wrote manuscript, edited manuscript; AOO: Contributed to discussion, reviewed and edited the manuscript; MDG: Reviewed and edited the manuscript; WPK: Reviewed and edited the manuscript; JMY: Reviewed and edited manuscript; MAP: Contributed to design and data interpretation, reviewed and edited manuscript.

Competing interest

None.

Conclusion—Menarcheal age was inversely associated with risk of CVD mortality in nonsmoking Chinese women.

Keywords

Menarche; Cardiovascular Diseases; Coronary Heart Disease; Stroke; Cohort Studies

INTRODUCTION

Identifying markers of cardiovascular disease (CVD) risk early in life provides an opportunity for primordial prevention of CVD morbidity and mortality. Onset of menarche is an important event in the life of a woman and may be a marker for childhood adiposity and related hormonal and metabolic changes (1–3).

Early age at menarche has been shown to be associated with increased adult body mass index (BMI) and cardiometabolic disease risk factors in women from diverse populations (2–7). The impact of menarcheal age on risk of CVD mortality has received little attention and only one study has been conducted in Southeast Asian populations in which CVD is now the leading cause of death (8). Some (9–11) but not all (12) of the prospective studies on this topic have reported an increased risk for CVD mortality with early age at menarche. However, there are a number of methodological inconsistencies across the studies that need to be considered, including limited adjustment for lifestyle CVD risk factors that covary with age at menarche due to secular trends in these variables (9, 11), over adjustment for chronic diseases on the causal pathway (12), and inadequate power to evaluate of effect modification by smoking (9–12), which may have an important impact on sex-steroid hormone levels in women (13). Moreover, only one of these studies evaluated possible mediation by adult adiposity, finding that adult BMI and waist circumference did not mediate the observed association (10).

In the current study we investigated the association between age at menarche and mortality from CVD, including coronary heart disease (CHD) and cerebrovascular disease (CERE), in a population of Singaporean Chinese women. We were able to address methodological problems in previous studies through: 1) evaluation of effect measure modification by cigarette smoking, 2) thorough adjustment of demographic and lifestyle confounding variables, and 3) consideration of adult BMI as a potential mediator. We hypothesized that later age at menarche would be associated with reduced risk of CVD mortality, and that smoking status may modify this association.

METHODS

Study participants

The design of the Singapore Chinese Health Study (SCHS) has been previously described (14). The cohort was drawn from men and women aged 45–74 at enrollment who belonged to one of the major Chinese dialect groups in Singapore, ie, the Hokkien or Cantonese, who originated from the contiguous provinces of Fujian and Guangdong in the southern part of China (15). Between April 1993 and December 1998, 35,303 women completed an in-person interview including questions on demographics, education, height, weight, use of tobacco and alcohol, usual physical activity, menstrual and reproductive history, medical history, family history of cancer, and dietary intake *via* a 165-item validated food frequency questionnaire (FFQ) assessing usual dietary intake of the previous year (14). The Institutional Review Board (IRB) at the National University of Singapore approved this study.

Exposure assessment

Age at menarche was assessed at baseline exam. Women were asked to report when they had their first menstrual period from the following categories: <11, 11–12, 13–14, 15–16, 17 years. Information on menopausal status and age, oral contraceptive use, estrogen use, progesterone use, and parity was also derived from baseline questionnaire data. Enrollment age was defined as age in years at time of the baseline examination. Education was categorized into no formal education, primary school, and secondary school or above. Cigarette smoking was classified as never or ever smoker (former or current smokers) as described previously (15). Physical activity was assessed as the amount (hours) spent doing strenuous sports (eg, jogging, bicycling on hills, tennis, squash, swimming laps, or aerobics), vigorous work (eg, moving heavy furniture, loading or unloading heavy trucks, shoveling, or equivalent manual labor), and moderate activities (eg, brisk walking, bowling, bicycling on level ground, tai chi, and chi kung) in a week. For the present analysis, physical activity levels were categorized into ≥ 2 hours/week of moderate activity or any strenuous activity versus lower levels of activity. Self-reported height and weight were collected at the baseline interview. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

A semi-quantitative FFQ specifically developed for this population assessing 165 commonly consumed food items was administered during the baseline interview. The questionnaire has subsequently been validated against a series of 24-hour dietary recalls, as well as selected biomarkers (16, 17). Dietary patterns were derived for this study population using principal component analysis including all 165 foods and beverages as described previously (18). A vegetable-fruit-soy dietary pattern characterized by high intake of those respective foods and lower intake of meats, dim sum, western fast food and soft drinks was included as a covariate. Frequency of alcohol intake was assessed as the summations of intake of beer, rice wine, other wine and hard liquor.

Assessment of mortality, diabetes, and cardiovascular disease

Date and cause of death was obtained through linkage analysis with the nation-wide registry of birth and death in Singapore. Up to six different *International Classification of Disease Codes Version 9* (ICD-9) were recorded for each death case in the registry. Primary cause of death was used. Vital status for cohort participants was updated through December 31, 2009. Only 27 persons (men and women) were lost to follow-up due to migration out of Singapore, suggesting that emigration of the cohort participants was negligible and that vital statistics follow-up was virtually complete. End points in our cause-specific analyses were deaths from CVD (codes 394.0–459.0), CHD (410.0–414.9, 427.5), and CERE (430.0–438.0).

Diabetes status was assessed by the following question: “Have you been told by a doctor that you have diabetes (high blood sugar)?” If yes: “Please also tell me the age at which you were first diagnosed?” A validation study of the self-report of diabetes mellitus cases used two different methods and was reported in detail in Odegaard et al. (19). Similarly, hypertensive status and heart disease were assessed by the following questions: “Have you been told by a doctor that you have high blood pressure?”; “Have you been told by a doctor that you have had a heart attack or angina (chest pain or exertion that is relieved by medication)?”; and “Have you been told by a doctor that you have had a stroke?” If yes: “Please tell me the age you were first diagnosed.”

Statistical analysis

Of the original 35,303 Singaporean Chinese women, we excluded 1,275 women with a history of invasive cancer (except non-melanoma skin cancer) or superficial, papillary

bladder cancer at baseline interview, as they did not meet the SCHS inclusion criteria. We also excluded six women missing information on menarche age. Thus the present analysis included 34,022 women.

Person-years were counted from date of baseline interview to date of death, date of last contact (for the few participants who migrated out of Singapore), or December 31, 2009, whichever occurred first. The two lowest age at menarche categories (<11 and 11–12) were combined to provide sufficient participants and cases per category for obtaining parameter estimates. The median and mode for age at menarche, 13–14 years, was chosen as the referent group to yield maximum statistical power and to avoid including early and late menarcheal ages. We examined age-adjusted baseline characteristics across menarche age categories to account for the positive association between age at menarche and age at enrollment in the study. We performed multivariable log-binomial regression analyses to estimate prevalence ratios (PRs) and 95% confidence intervals (CIs) for age at menarche and prevalent (*ie*, reported at baseline interview) obesity (Asian cut-off of 27.5 kg/m^2) (20), diabetes, hypertension, heart disease, and stroke.

Proportional hazards (Cox) regression methods were used to estimate the hazard ratios (HRs) and 95% CIs between age at menarche and CVD mortality. There was no evidence that proportional hazards assumptions were violated by lack of significant interaction between menarche age and survival time in the models. The selection of potential confounders was based on prior consideration of their association with both age at menarche, in this population, and CVD. Our final regression models included the following covariates: enrollment age (continuous), year of interview (1993–95 vs. 1996–98), dialect (Hokkien vs. Cantonese), educational level (no formal schooling, primary school, secondary school or above), smoking status (never, former, current), physical activity (≥ 2 hours/week moderate or any strenuous vs. lower levels of activity), alcohol use (none, monthly, weekly, daily), quintiles of vegetable-fruit-soy dietary pattern, total energy intake (kcal), menopausal status/age (pre-menopausal, <50 years, ≥ 50 years), oral contraceptive use (never vs. ever), hormone replacement therapy use (estrogen or progesterone; never vs. ever), parity (0, 1–2, 3–4, ≥ 5), and BMI (kg/m^2 ; <18.5, 18.5–21.4 (referent), 21.5–24.4, 24.5–27.4, ≥ 27.5). In an additional model we assessed potential mediation by including history of physician-diagnosed diabetes and hypertension as covariates. Models were fit using age at menarche as a continuous variable to assess evidence for a linear trend. We evaluated whether the association between age at menarche and risk of CVD mortality was modified by smoking status (ever vs. never), birth cohort (median split), dialect (Hokkien vs. Cantonese), baseline age (median split), physical activity (≥ 2 hours/week moderate or any strenuous vs. lower levels of activity), menopausal status (pre-menopausal, <50 years, ≥ 50 years), or BMI (non-obese vs. obese) using analyses stratified by these variables and by modeling interaction terms. The log-likelihood ratio test was used to evaluate interaction terms. Lastly, to reduce potential information bias or changes in lifestyle and body weight due to pre-existing disease, we completed an analysis excluding subjects with reported history of heart disease, stroke, diabetes or hypertension.

All analyses were performed using SAS v.9.2 software (SAS Institute, Inc., Cary, North Carolina) and all tests of statistical significance were based on 2-sided probability.

RESULTS

The median age at menarche for the 34,022 women eligible for the present analysis was 13.5 years (age 13–14). Baseline characteristics of the study participants according to categories of age at menarche are presented in Table 1. Later age at menarche was associated with later age at enrollment—a result of the well-established secular trend in age at menarche (21).

After adjustment for enrollment age, later menarcheal age was associated with greater parity, lower levels of education, and higher baseline BMI (all p values < 0.05). Women who had a later menarche were also less likely to use oral contraceptives and hormone therapy, engage in physical activity, and consume alcohol and a fruit-, vegetable, and soy-based dietary pattern (all p values < 0.05).

Prevalence ratios for CVD risk factors and events, self-reported at baseline exam, are presented in Table 2. After full multivariate adjustment, later age at menarche was significantly associated, in a graded manner, with lower prevalence of obesity ($p_{trend} < 0.001$), hypertension ($p_{trend} < 0.001$), diabetes ($p_{trend} < 0.001$), and heart disease ($p_{trend} = 0.03$), but not for stroke ($p_{trend} = 0.15$) (Table 2).

The relation between age at menarche and CVD mortality for ever smokers was statistically significantly different from that for nonsmokers ($p_{interaction} < 0.05$). Hence, statistical analyses were conducted for data stratified by smoking status (pooled analyses, for ever and never smokers combined, can be found in the Supplementary Table). In 31,058 nonsmokers, with a mean follow up of 13.6 years, 1,511 women died from CVD including 804 from CHD and 465 from CERE. Later age at menarche was significantly associated with decreased risk for CVD and CHD mortality in a graded fashion (both $p_{trend} < 0.001$) (Table 3a). There was a nonsignificant reduction in risk of death from CERE across later menarche age categories. In 2,964 smokers with a mean follow up of 12.5 years, there were 341 CVD deaths, including 194 from CHD and 92 from CERE. Among smokers, menarche age was not significantly associated with CVD, CHD, or CERE mortality (Table 3b).

There was no evidence that the observed associations differed by baseline age, birth cohort, dialect, physical activity, menopausal status, or BMI. In a potential mediator model, which included baseline self-reported diabetes and hypertension as covariates, HRs for CVD mortality in nonsmokers across increasing categories of age at menarche were modestly attenuated (Table 3a). Results from sensitivity analyses, in which we excluded subjects who reported history of heart disease, stroke, diabetes or hypertension at baseline, were not materially different (data not shown).

DISCUSSION

In this large cohort study of Chinese women, the association between age at menarche and CVD mortality differed significantly between smokers and nonsmokers. In nonsmokers, age at menarche was associated with a reduced risk of CVD mortality that persisted after multivariate adjustment for confounders and adult BMI. The inverse associations were stronger for risk of death from CHD than from CERE. We did not observe an association between age at menarche and CVD mortality in smokers, which may be due to a true biologic interaction or other behavioral factors associated with smoking.

Our findings are in agreement with a Californian study of largely nonsmoking Seventh-day Adventist women (1,187 CVD deaths) that found a 6.0% and 8.6% reduced risk of CHD and stroke mortality, respectively, per category higher menarche age (9). They are also largely consistent with the EPIC-Norfolk study of Caucasian women (3,888 CVD events), which found that women with age at menarche 15–18 years compared with 8–11 years had reduced risk of incident CVD (16%) and CHD (17%) events, and all-cause (18%) mortality (10). Recently, a cohort of female textile workers in Shanghai, China found females with menarcheal age 13 years versus 15 years were at a 44% increased risk of ischemic heart disease (442 deaths), but not at an increased risk of stroke (11). The Nurses' Health Study (308 CHD events) found a nonsignificant inverse association between age at menarche at 13 years, compared with < 11 years, and risk of CHD (HR=0.60, 95%CI: 0.30–1.10)(22).

Our main findings, and those from studies described above, are inconsistent with a study of 37,965 post-menopausal Japanese women (1,010 CVD cases; 487 from stroke and 178 from CHD), which found no difference in risk of CVD, CHD, or stroke mortality in participants who reported menarche >16 years versus ≤13 years (12). However, consistent with our study, later age at menarche was associated with lower BMI and hypertension. Population differences and methodological approaches may explain the discrepant findings. First, in the Japanese study a large proportion of CVD death was due to hemorrhagic stroke, whereas in our study the majority was due to ischemic heart disease and stroke. Secondly, point estimates from their CHD analyses should be interpreted cautiously due to having only 18 deaths in the referent category (≤13 years). Finally, the Japanese study excluded pre-menopausal women and adjusted for hypertension and type 2 diabetes—factors that may be on the causal pathway between age at menarche and CVD mortality. When we further adjusted our models for self-reported history of diabetes and hypertension, associations regressed toward the null.

Findings from previous studies on age at menarche and CVD risk factors and events largely align with the CVD mortality studies. A cross-sectional study of 9,000 Chinese women aged 25–64 found that age at menarche was inversely associated with adult adiposity (BMI, waist circumference, and total and abdominal fatness), insulin resistance, and components of the metabolic syndrome (6). Several smaller studies of women from diverse populations have also reported an inverse association between age at menarche and CVD risk factors (2–5). Consistent with these studies, findings from our study and the EPIC-Norfolk study—the two largest studies on this topic to date—demonstrate that, in addition to being inversely associated with obesity, hypertension and type 2 diabetes, age at menarche was associated with CVD events and mortality after adjustment for adult adiposity measures.

In the current study, the reduced risk of CVD mortality associated with later menarche persisted after controlling for adult BMI, and was only moderately attenuated when adjusting for history of diabetes and hypertension at baseline. A higher childhood BMI may upregulate the growth axis (22), stimulating earlier age at menarche, and increasing the risk of hypertension, diabetes, and CVD, independent of adult BMI. The observed association might also be related to alternative pathways. We were unable to assess mediation by lipids and lipoproteins in our study. However, a recent study found that age at menarche was not associated with lipid or lipoprotein levels in late middle aged women after adjustment for adult BMI (23). Early menarche is associated with decreased sex-hormone binding globulin levels (24), which are inversely associated with risk of cardiometabolic disease in women (25–28). A recent study found that smoking modifies sex hormone levels in women (13). Thus, hormonal changes associated with age at menarche, and modified by smoking, may explain the inverse association between menarche age and CVD in nonsmokers but not in smokers. Future studies are needed to test this hypothesis.

Our study has a high level of statistical power and includes thorough adjustment approaches to address confounding and effect modification. A limitation of our study is the self-recall of age at menarche many years after the event; thus, misclassification was inevitable. However, adulthood retrospective reports of menarcheal age have been shown to be highly correlated ($r=0.79$) with original adolescent reports (29). We can also not rule out the potential for residual confounding by unmeasured socioeconomic or lifestyle factors related to age at menarche and CVD. Our study was also only able to adjust for self-reported measures anthropometry. However, self-report of height and weight has been shown to be highly valid across many populations as well as in Asian populations (30, 31). Other more specific measures of adiposity (eg, abdominal fat) may have mediated the age at menarche-CVD mortality association. Furthermore, we did not have anthropometric or physiologic data from childhood, which could shed light on etiology of the associations. It remains unclear whether

childhood adiposity is an early-life trigger of age at menarche, or menarche age is a proxy for the pace of sexual maturation, which itself leads to differences in adiposity, sex hormones, and metabolic factors in the pubertal period that track into adult life (3, 4, 6, 7).

In summary, the findings of an inverse association between age at menarche and CVD risk factors and CVD mortality are largely consistent, spare one null study in a Japanese cohort of women (12). Findings from our study and the EPIC-Norfolk suggest this association is independent of adult adiposity (10). Moreover, results from our study suggest a potential age at menarche-smoking interaction, with a linear graded inverse association in nonsmokers. Age at menarche could be a marker for childhood growth and development with repercussions on lifetime CVD risk. Life-course studies with anthropometric and physiologic measures are needed to fully explore potential causal mechanisms of the observed associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Siew-Hong Low of the National University of Singapore for supervising the fieldwork of the Singapore Chinese Health Study, and Kazuko Arakawa and Renwei Wang for the development and maintenance of the cohort study database. The Singapore Cancer Registry assisted with the identification of cancer outcomes via database linkages. Finally, we acknowledge the founding, long-standing Principal Investigator of the Singapore Chinese Health Study – Mimi C. Yu.

Funding

Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number T32HL007779 and the National Institutes of Health: R01 CA055069, R35 CA053890, R01 CA080205, R01 CA098497, R01 CA144034, R01 DK080720. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Abbreviations

CVD	cardiovascular disease
CHD	coronary disease
CERE	cerebrovascular disease
BMI	body mass index
FFQ	food-frequency questionnaire
ICD-9	international classification of disease codes version 9
HR	hazard ratio
PR	prevalence ratio
CI	confidence interval

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Table 1
Baseline Characteristics According to Age at Menarche Among Women in the Singapore Chinese Health Study

Characteristics	Age at menarche (year)					*P value
	12	13-14	15-16	17		
N (%)	4,551 (14.7)	12,015 (38.7)	10,640 (34.3)	3,852 (12.4)		
Age at enrollment **	52.8 (6.9)	55.2 (7.8)	57.5 (8.0)	59.7 (7.7)		<0.001
Birth year (mean) †	1939.2	1938.7	1938.6	1938.6		<0.001
BMI (kg/m ²) †	23.5	23.3	23.1	23.1		<0.001
Education (% secondary) †	39.2	22.1	14.9	11.6		<0.001
Smoking (% ever) †	8.9	8.8	8.4	9.0		0.59
Any physical activity (%) ††	26.4	22.8	21.8	21.1		<0.001
Diet score (% in highest 5 th quintile) ‡§	22.2	19.2	20.4	18.6		<0.001
Alcohol intake (% any) †	9.0	9.0	9.1	10.4		0.004
Premenopausal (%) †	28.8	28.4	27.8	28.2		0.30
Hormone therapy (% ever use) †	8.6	6.1	4.7	3.5		<0.001
Oral contraceptives (% ever use) †	27.6	26.9	25.9	25.1		0.01
Parity (% >2) †	52.8	63.4	69.1	71.0		<0.001

BMI = body mass index

* P-value for overall association

** Mean (standard deviation)

† Adjusted for age at enrollment

‡ Any physical activity = Report of any vigorous work or strenuous leisure physical activity

§ Diet score = Vegetable-fruit-soy dietary pattern

Adjusted Prevalence Ratios and 95% Confidence Intervals for Baseline Self-report CVD Risk Factors and CVD Events by Categories of Age at Menarche Among Women in the Singapore Chinese Health Study

Table 2

	Categories of age at menarche (year)					P trend*
	12	13 – 14	15 – 16	17		
N	4,551	12,015	10,640	3,852		
BMI>27.5 kg/m ² , cases	526	1,155	901	330		
PR (95% CI) [†]	1.30 (1.18, 1.43)	1.00	0.81 (0.75, 0.88)	0.82 (0.74, 0.92)		<0.001
Hypertension, cases	1,087	2,923	2,518	942		
PR (95% CI) [†]	1.06 (1.00, 1.12)	1.00	0.90 (0.86, 0.94)	0.87 (0.82, 0.92)		<0.001
Diabetes, cases	369	1,055	921	380		
PR (95% CI) [†]	1.18 (1.06, 1.31)	1.00	0.83 (0.77, 0.90)	0.83 (0.75, 0.92)		<0.001
Heart disease, cases	120	380	345	145		
PR (95% CI) [†]	1.12 (0.93, 1.35)	1.00	0.87 (0.75, 0.98)	0.91 (0.77, 1.08)		0.03
Stroke, cases	38	145	130	57		
PR (95% CI) [†]	0.98 (0.71, 1.37)	1.00	0.82 (0.66, 1.03)	0.78 (0.59, 1.05)		0.15

PR= prevalence ratio; CI = confidence interval; CVD = cardiovascular disease; BMI = body mass index

* P value for overall trend across age at menarche categories; age at menarche was modeled as a linear variable.

[†] Controlled for age at enrollment (continuous), year of interview (1993–95 vs. 1996–98), dialect (Hokkien vs. Cantonese), educational level achieved (no formal schooling, primary school, secondary school or above), smoking status (never, former, current), physical activity (2 hours/week moderate or any strenuous vs. lower levels of activity), alcohol use (none, monthly, weekly, daily), vegetable-fruit-soy dietary pattern (quintiles), total energy intake (kcal; continuous), oral contraceptive use (never vs. ever), parity (0, 1–2, 3–4, 5 live births), menopausal status/age (pre-menopausal, <50 years, 50 years), and hormone therapy use (estrogen or progesterone; never vs. ever).

[‡] Controlled for the above variables and baseline BMI (<18.5, 18.5–21.4 (referent), 21.5–24.4, 24.5–27.4, 27.5).

Table 3

a. Hazard Ratios of CVD Mortality by Age at Menarche Among Never Smoking Women in the Singapore Chinese Health Study

	Categories of age at menarche (year)					P trend [*]
	12	13 – 14	15 – 16	17		
N	4,551	12,015	10,640	3,852		
Person-years of follow-up	61048	164812	145350	52250		
Total cardiovascular disease mortality (ICD-9 390–459)						
CVD deaths	132	541	587	251		
Age CVD death, years [†]	68.9 (8.32)	71.4 (8.19)	72.8 (7.93)	73.9 (6.54)		
Reduced model HR (95% CI) [‡]	1.08 (0.89, 1.31)	1.00	0.88 (0.78, 0.99)	0.79 (0.68, 0.92)		<0.001
Full model HR (95% CI) [§]	1.06 (0.87, 1.29)	1.00	0.89 (0.79, 1.00)	0.80 (0.69, 0.93)		<0.001
Full model + Diabetes + Hypertension, HR (95% CI) [¶]	1.02 (0.84, 1.24)	1.00	0.95 (0.85, 1.07)	0.86 (0.74, 1.01)		0.04
Coronary heart disease mortality (ICD-9 410.0–414.9, 427.5)						
CHD deaths	75	309	290	130		
Age CHD death, years [†]	68.8 (8.37)	71.3 (8.17)	73.3 (7.58)	74.4 (6.18)		
Reduced model HR (95% CI) [‡]	1.07 (0.83, 1.38)	1.00	0.76 (0.65, 0.90)	0.72 (0.58, 0.88)		<0.001
Full model HR (95% CI) [§]	1.04 (0.80, 1.34)	1.00	0.76 (0.65, 0.90)	0.72 (0.58, 0.88)		<0.001
Full model + Diabetes + Hypertension, HR (95% CI) [¶]	1.01 (0.78, 1.30)	1.00	0.82 (0.70, 0.97)	0.79 (0.64, 0.97)		0.01
Cerebrovascular disease mortality (ICD-9 430–438)						
CERE deaths	40	149	197	79		
Age CERE death, years [†]	69.0 (7.59)	71.2 (8.22)	72.7 (7.99)	74.3 (6.45)		
Reduced model HR (95% CI) [‡]	1.23 (0.86, 1.75)	1.00	1.06 (0.85, 1.31)	0.88 (0.67, 1.17)		0.23
Full model HR (95% CI) [§]	1.22 (0.86, 1.74)	1.00	1.07 (0.86, 1.32)	0.89 (0.68, 1.18)		0.27
Full model + Diabetes + Hypertension, HR (95% CI) [¶]	1.20 (0.84, 1.70)	1.00	1.13 (0.91, 1.40)	0.95 (0.72, 1.26)		0.63

b. Hazard Ratios of CVD Mortality by Age at Menarche Among Ever Smoking Women in the Singapore Chinese Health Study

	Categories of age at menarche (year)					<i>P</i> trend [*]
	12	13 – 14	15 – 16	17	17	
<i>N</i>	314	1,060	1,095	495		
Person-years of follow-up	4,022	13,076	13,733	6,083		
Total cardiovascular disease mortality (ICD-9 390–459)						
CVD deaths	21	139	117	64		
Age CVD death, years [†]	72.8 (7.12)	72.6 (7.18)	74.9 (6.89)	74.1 (6.04)		
Reduced model HR (95% CI) [‡]	0.65 (0.41, 1.04)	1.00	0.68 (0.53, 0.87)	0.85 (0.63, 1.14)	0.44	
Full model HR (95% CI) [§]	0.68 (0.43, 1.09)	1.00	0.69 (0.54, 0.89)	0.87 (0.64, 1.17)	0.47	
Full model + Diabetes + Hypertension, HR (95% CI) [¶]	0.65 (0.41, 1.03)	1.00	0.71 (0.55, 0.91)	0.90 (0.67, 1.22)	0.67	
Coronary heart disease mortality (ICD-9 410.0–414.9, 427.5)						
CHD deaths	14	78	70	32		
Age CHD death, years [†]	73.2 (7.79)	72.1 (7.70)	73.7 (7.33)	75.0 (6.36)		
Reduced model HR (95% CI) [‡]	0.75 (0.42, 1.32)	1.00	0.74 (0.53, 1.02)	0.76 (0.50, 1.15)	0.28	
Full model HR (95% CI) [§]	0.76 (0.43, 1.36)	1.00	0.75 (0.54, 1.05)	0.76 (0.50, 1.16)	0.29	
Full model + Diabetes + Hypertension, HR (95% CI) [¶]	0.75 (0.42, 1.33)	1.00	0.77 (0.55, 1.08)	0.78 (0.51, 1.19)	0.39	
Cerebrovascular disease mortality (ICD-9 430–438)						
CERE deaths	5	36	29	22		
Age CERE death, years [†]	70.5 (4.16)	73.0 (6.98)	78.2 (5.66)	73.2 (5.19)		
Reduced model HR (95% CI) [‡]	0.64 (0.25, 1.63)	1.00	0.64 (0.39, 1.04)	1.13 (0.66, 1.92)	0.68	
Full model HR (95% CI) [§]	0.72 (0.28, 1.86)	1.00	0.64 (0.39, 1.06)	1.22 (0.71, 2.09)	0.63	
Full model + Diabetes + Hypertension, HR (95% CI) [¶]	0.68 (0.27, 1.75)	1.00	0.66 (0.40, 1.08)	1.26 (0.74, 2.17)	0.50	

HR = hazard ratio; CI = confidence interval; CVD = cardiovascular disease; CHD = coronary heart disease; CERE = cerebrovascular disease; ICD-9 = International Classification of Disease Codes Version 9

^{*} *P* value for overall trend across age at menarche categories; age at menarche was modeled as a linear variable.

[†] Mean (standard deviation)

[‡] Controlled for age at enrollment (continuous), year of interview (1993–95 vs. 1996–98), dialect (Hokkien vs. Cantonese), and educational level achieved (no formal schooling, primary school, secondary school or above).

[§]Controlled for variables in reduced model plus baseline physical activity (2 hours/week moderate or any strenuous vs. lower levels of activity), vegetable-fruit-soy dietary pattern (quintiles), total energy intake (kcal; continuous), alcohol use (none, monthly, weekly, daily), oral contraceptive use (never vs. ever), parity (0, 1–2, 3–4, 5 live births), menopausal status/age (pre-menopausal, <50 years, 50 years), hormone therapy use (estrogen or progesterone; never vs. ever), and baseline BMI (<18.5, 18.5–21.4 (referent), 21.5–24.4, 24.5–27.4, 27.5).

[¶]Controlled for variables in full model plus baseline self-reported history of physician-diagnosed diabetes and hypertension.

HR = hazard ratio; CI = confidence interval; CVD = cardiovascular disease; CHD = coronary heart disease; CERE = cerebrovascular disease; ICD-9 = *International Classification of Disease Codes Version 9*

^{*} *P*value for overall trend across age at menarche categories; age at menarche was modeled as a linear variable.

[‡]Mean (standard deviation)

[‡]Controlled for age at enrollment (continuous), year of interview (1993–95 vs. 1996–98), dialect (Hokkien vs. Cantonese), and educational level achieved (no formal schooling, primary school, secondary school or above).

[§]Controlled for variables in reduced model plus baseline physical activity (2 hours/week moderate or any strenuous vs. lower levels of activity), vegetable-fruit-soy dietary pattern (quintiles), total energy intake (kcal; continuous), alcohol use (none, monthly, weekly, daily), oral contraceptive use (never vs. ever), parity (0, 1–2, 3–4, 5 live births), menopausal status/age (pre-menopausal, <50 years, 50 years), hormone therapy use (estrogen or progesterone; never vs. ever), and baseline BMI (<18.5, 18.5–21.4 (referent), 21.5–24.4, 24.5–27.4, 27.5).

[¶]Controlled for variables in full model plus baseline self-reported history of physician-diagnosed diabetes and hypertension.