Original Paper

Association between Age at Menarche and Cardiovascular Disease Risk Factors in China: A Large Population-Based Investigation

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Key Words

Age at menarche · Cardiovascular disease · Risk factors · Large population

Abstract

Background: The association between age at menarche (AAM) and cardiovascular disease (CVD) has previously been investigated with controversial results. The relationship between the psychological characteristic of AAM and many cardiovascular risk factors remains unclear. **Purpose:** To assess the association between AAM and CVD risk factors in a large population. **Design and Setting:** 13,242 women aged 24–79 years were recruited from China mainland during 2009–2013 for a cross-sectional, population-based study to investigate the association between AAM and CVD risk factors. Information on AAM was obtained from self-report and information on CVD risk factors from physical examination. **Results:** In age-, body-mass-index- and height-adjusted analyses, AAM was positively associated with hypertension and 'college or above' educational level and incident CVD events. The adjusted odds ratios (ORs) and 95% confidence intervals for hypertension across AAM categories (≤ 12 , 13–14, 15–16, and ≥ 17 years) were 0.820 (0.70–0.96), 0.82 (0.70–0.96), 0.88 (0.79–0.99) and 1 (referent), respectively; adjusted ORs for high educational level ('college or above') were 0.29 (0.24–0.34), 0.60 (0.41–0.51), 0.69 (0.62–0.76), and 1 (referent), respectively; adjusted ORs for incident CVD events were 0.18 (0.08–0.41), 0.18 (0.08–0.41), 0.62 (0.41–0.93), 1 (referent), respectively. **Conclusions:** Earlier AAM were positively associated with incident CVD events, hypertension and 'college or above' educational level.

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Introduction

Age at menarche (AAM), the time of the first menstrual cycle, is an important developmental milestone in a female's life, from both social and medical perspectives. It signals the beginning of the ability to reproduce. The timing of menarche is determined by both genetic and environmental factors [1, 2]. Results from previous studies have shown that a female's AAM affects her health later in life and has been identified as a risk factor for several traits including breast cancer [3, 4], osteoporotic fracture [5], abnormal lung function [6] and depression [7, 8]. Moreover, recent researches mentioned that earlier menarche has also been associated with obesity [9], type 2 diabetes [10–12] as well as increased metabolic syndrome [13, 14], and all these confer an increased risk of cardiovascular disease (CVD). Though several studies have been conducted for Western and Asian women about the relationship between AAM and CVD [15–20], no consensus was achieved and the association of AAM with many cardiovascular (CV) risk factors remains unclear. These estimates should be considered with caution due to the fact that some studies are distinguishing between shared environment as well as a small sample size. If we are to figure out the association between the timing of sexual maturation and CVD risk factors, it could potentially be useful in developing effective prevention interventions for a female population with high CVD risk factors.

Accordingly, we conducted a large population study in China on this issue by pooling individual-level data from a total of 13,242 women. The aim of this study was to determine whether AAM is linked to CV risk factors such as physical activity, smoking habits, alcohol consumption and body mass index (BMI).

Materials and Methods

Subjects or Study Population

This study is a population-based health survey, retrospective study conducted in the cities of Beijing and Xiaogan (Hubei province) between 2009 and 2013. A total sample of 13,242 subjects was drawn from the target population consisting of residents aged 24–79 years from mainland China. The study design, detailed sampling method, investigation and data collection were done according to previous studies [17, 21]. The subjects were asked to answer a questionnaire or underwent a detailed medical interview, including questions regarding age, AAM, health and psychological status, lifestyle and physiological index. All clinical examinations were conducted in the Central Hospital of Xiaogan Health in the province of Hubei and the International Medical Center and Health Science Center of the Chinese PLA General Hospital in Beijing. All participants gave informed consent to take part, because data was analyzed anonymously, and no written consent was required. The study was approved by the Review Board/Ethics Committees of the Chinese PLA General Hospital.

We excluded those participants with incomplete or no information of AAM and/or CVD information. This brought the final analysis to 12,663 (95.6%) participants.

Assessment of AAM

AAM was defined as age at the first menstrual cycle and assessed in full years (as per the Gregorian calendar and related interpretation of age). Subjects' menarche age was obtained by asking participants in a personal survey. For analysis, AAM was categorized into four categories (≤ 12 , 13–14, 15–16, and ≥ 17 years) to reflect current AAM in China.

Assessment of CVD Risk Factors

We obtained the information about prevalent hypertension (HTN), diabetes mellitus (DM) and incident CVD events based on self-reported physician diagnosis of diabetes or self-reported medication use at baseline. In the present study, we have information on the subjects' incident coronary heart disease (CHD), heart failure and brain stroke events and set these together as incident CVD events. Subjects' data on smoking status (current smoker or non-smoker), alcohol consumption, physical activity level [level 1 (sedentary) to

level 4 (most active)] and highest educational qualifications (junior high school or below, senior high school, college or above) were extracted from standard questionnaires completed by participants in the study. Subjects' alcohol use was obtained by questions regarding the number of times alcohol was consumed in a week, the total number of alcoholic drinks each time, and the type of drink. One drink was defined as approximately equivalent to 50 ml of alcohol or 25 g of ethanol or 1 unit. We categorized the alcohol consumption as none, moderate use (1–3 units of alcohol per week) or greater (4 units or above of alcohol per week).

In addition, all participants underwent a standard clinical exam to measure their height, waist circumference (WC), weight, blood pressure and ST-T change. All measurement procedures are described in detail elsewhere [14, 19, 20]. BMI was calculated as weight in kilograms divided by height in meters squared. Based on World Health Organization (WHO) guidance, obesity was defined as a BMI of ≥ 30 . A fasting (at least 8 h) venous blood sample was also taken from all investigated participants to analyze the following indicators including hemoglobin (HGB), uric acid, fasting blood sugar (Glu), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein (LDL) and C-reaction protein. A 2-hour postprandial blood glucose (PG2h) was additionally measured exactly 2 h after eating a meal.

Psychological status, including job or life stress, job satisfaction, life satisfaction, distress and anxiety were measured in all study participants using a questionnaire. For each participant, we assessed the job or life stress with five levels: '0' for no stress, '1' for relatively small, '2' for general, '3' for large or big, and '4' for great, and then categorized it into three levels as no stress (0), medium (1–2), and great (3–4) for the sake of statistical analysis.

Statistical Analysis

The AAM was stratified (≤ 12 , 13–14, 15–16, and ≥ 17 years) for analysis of subjects' basic characteristics. Normally distributed variables are presented as the mean $\pm$ standard deviation (SD) and nonnormally distributed data as the median and interquartile range. Categorized variables are expressed as percentages. The p values are presented for the difference of these variables between the four categories.

The basic features of the anthropometric parameters were described by descriptive statistics in our study. Pearson correlation analysis was used to assess the correlation coefficient between the dependent variable, AAM and independent variables, such as BMI, WC and height. The correlation between AAM and CVD risk factors, such as BMI, WC and height, were analyzed with linear correlation. Multivariable logistic regression analysis model and Pearson test were performed for selecting main factors that influenced AAM. The group with AAM ≥ 17 years was set as the reference group in the categorized model.

The statistical significance level was set at $p < 0.05$. All analyses were performed using SPSS.

Results

Of the 13,242 women recruited, 579 (4.4%) women were excluded for the lack of AAM or CVD information and the remaining 12,663 subjects were included for analysis. The participants' age was between 24 and 79 years, with a mean age $\pm$ SD of 47.68 ± 8.9 years. The mean AAM was 14.7 ± 1.9 years, with a range of 8–22 years. The basic characteristics of these samples are provided in table 1 according to AAM.

In summary, women with older AAM (≥ 17 years group) had a lower current age, height, HDL, and a higher BMI, WC, TG, HGB, LDL, PG2h, systolic blood pressure, diastolic blood pressure, TC, and Glu. They were also more likely to be physically active and be a current smoker. The percentage of those with an education level of college or above, obesity (BMI ≥ 30)/central obesity (WC ≥ 80 cm), HTN, DM and CVD events increased across the increasing categories of AAM, as shown in table 1 ($p < 0.001$).

The association between AAM considering the four categories and single components of the CV risk factors is shown in table 2. After age, BMI and height adjustment, the adjusted odds ratio (ORs) and 95% confidence interval for HTN across menarche age categories (≤ 12 , 13–14, 15–16, and ≥ 17) were 0.82 (0.70–0.96), 0.82 (0.70–0.96), 0.88 (0.79–0.99) and 1 (referent), respectively; adjusted ORs for the high education level 'college or above' were 0.29 (0.24–0.34), 0.60 (0.41–0.51), 0.69 (0.62–0.76), and 1 (referent), respectively; adjusted ORs

Table 1. Person characteristics and CV risk factors by categories (approximate quintiles) of AAM

	Total number of patients	Categories of AAM										p trend	
		≤12 years (n = 1,425)		13–14 years (n = 4,972)		15–16 years (n = 4,003)		≥17 years (n = 2,263)					
		%	mean	SD	%	mean	SD	%	mean	SD			
Mean age, years	12,663		36.8	6.0		50.2	7.5		49.0	9.7	48.9	8.3	<0.001
BMI	12,653		22.9	3.6		23.26	3.3		23.7	3.3	24.2	3.2	<0.001
Waist circumference, cm	10,643		76.0	9.4		77.3	9.0		79.0	9.1	80.7	9.2	<0.001
Height, cm	12,659		161.5	5.2		161.4	5.2		161.3	5.3	161.0	5.3	<0.001
Systolic blood pressure, mm Hg	12,636		114.5	16.1		113.8	15.9		116.2	17.1	119.2	18.2	<0.001
Diastolic blood pressure, mm Hg	12,636		73.5	10.7		73.4	9.9		74.6	10.4	76.1	10.7	<0.001
TC, mmol/l	12,655		4.79	0.94		4.78	0.92		4.90	0.96	5.05	1.01	<0.001
HDL cholesterol, mmol/l	11,832		1.53	0.39		1.48	0.38		1.45	0.36	1.42	0.34	<0.001
LDL cholesterol, mmol/l	11,830		2.86	0.82		2.86	0.80		2.95	0.83	3.08	0.82	<0.001
TG, mmol/l	12,655		1.20	0.82		1.26	0.90		1.33	1.01	1.45	1.06	0.014
HGB, g/l	10,959		131.84	13.12		132.33	20.33		132.94	12.42	133.36	11.73	<0.001
Creatinine, μmol/l	10,714		58.63	9.60		58.44	15.96		57.34	9.92	57.22	9.58	<0.001
Fasting glucose, mg/dl	12,652		5.44	1.89		5.39	0.87		5.50	1.06	5.62	1.16	<0.001
PG2h, mmol/l	4,425		7.10	2.16		7.13	2.04		7.31	2.21	7.78	2.56	<0.001
College or above	10,542	79.3			68.1			53.8			40		<0.001
Alcohol consumption	12,663												
0 units/week (no)		80.8			78.1			79.4			79.1		0.003
1–3 units/week (middle)		12.1			14.7			13			14.6		0.003
≥4 units/week (high)		7.1			7.2			7.6			6.2		0.003
BMI ≥30	12,653	3.6			3.1			4.1			4.4		<0.001
WC ≥80 cm	10,643	33.3			37.8			47			55.5		<0.001
Current smoker	12,354	1.9			2.3			3.1			3.5		<0.001
HTN	12,654	8.5			8.9			12.1			15.6		<0.001
DM	12,637	3.1			2.7			3.8			5.3		<0.001
Low physical activity		59.4			47.7			44.2			40.5		<0.001
CVD events ¹		1.33			2.23			3.10			4.42		<0.001
CHD		0.63			1.65			2.05			3.45		<0.001
Heart failure		0.49			0.42			0.52			0.66		0.012
Brain stroke		0.42			0.30			0.65			0.62		0.015
Strain	10,800												
No strain		14.3			16.8			25.8			31.6		<0.001
Middle strain		52.9			55.2			53.5			49.3		<0.001
High strain		32.8			28			20.7			19		<0.001
p value: testing the difference between the 4 categories of AAM. ¹ Defined as CHD, heart failure and brain stroke.													

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Zheng et al.: Association between Age at Menarche and Cardiovascular Disease Risk Factors in China: A Large Population-Based Investigation

Table 2. Association of AAM with the CVD risk factors

Condition	Categories of AAM							
	≤12 years (n = 1,425)		13–14 years (n = 4,972)		15–16 years (n = 4,003)		≥17 years (n = 2,263)	
	crude OR (95% CI)	adjusted OR ¹ (95% CI)	crude OR (95% CI)	adjusted OR ¹ (95% CI)	crude OR (95% CI)	adjusted OR ¹ (95% CI)	crude OR (95% CI)	adjusted OR ¹ (95% CI)
High alcohol consumption (≥4 units/week)	0.98 (0.87–1.09)	0.98 (0.88–1.11)	1.06 (0.97–1.15)	1.06 (0.97–1.15)	1.03 (0.95–1.13)	1.04 (0.951–1.14)	1.00	1.00
Current smoker	1.16 (0.58–2.31)	1.15 (0.58–2.29)	1.10 (0.66–1.85)	1.15 (0.58–2.29)	1.19 (0.71–1.99)	1.18 (0.71–1.98)	1.00	1.00
HTN	0.82 (0.70–0.96)	0.820 (0.70–0.96)	0.81 (0.72–0.91)	0.82 (0.70–0.96)	0.88 (0.79–0.99)	0.88 (0.79–0.99)	1.00	1.00
DM	0.893 (0.687–1.161)	0.89 (0.69–1.17)	0.88 (0.73–1.06)	0.90 (0.69–1.17)	0.84 (0.69–1.02)	0.84 (0.70–1.02)	1.00	1.00
Low physical activity	1.61 (1.40–1.84)	1.61 (1.40–1.84)	1.18 (1.07–1.31)	1.18 (1.07–1.31)	1.09 (0.98–1.21)	1.09 (0.98–1.22)	1.00	1.00
Incident CVD	1.27 (1.18–1.37)	0.18 (0.078–0.408)	0.36 (0.23–0.56)	0.18 (0.08–0.41)	0.63 (0.41–0.95)	0.62 (0.41–0.93)	1.00	1.00
High strain	1.41 (1.28–1.55)	1.41 (1.28–1.55)	1.27 (1.18–1.37)	1.27 (1.18–1.37)	1.06 (0.98–1.14)	1.06 (0.98–1.14)	1.00	1.00
College or above	0.28 (0.24–0.34)	0.29 (0.24–0.34)	0.46 (0.41–0.51)	0.60 (0.41–0.51)	0.68 (0.61–0.76)	0.69 (0.62–0.76)	1.00	1.00
CI = Confidence interval. ¹ After being adjusted for age, BMI and height.								

for incident CVD events were 0.18 (0.08–0.41), 0.18 (0.08–0.41), 0.62 (0.41–0.93), and 1 (referent) respectively. The later AAM was significantly associated with a higher prevalence of HTN, a higher incidence of CVD and a lower prevalence of ‘college or above’ degree, but not with smoker status or others, and these variables were therefore not given.

Discussion

In this vast-range and large population-based retrospective study, we found that reported AAM was significantly and consistently associated with some CVD risk factors. Women with later AAM had a higher BMI, WC, TG, HGB, LDL, and PG2h, systolic blood pressure, diastolic blood pressure, TC, Glu and lower HDL levels during adulthood. Those who had later menarche (≥ 17 years) had a higher risk of obesity (BMI ≥ 30)/central obesity (WC ≥ 80 cm), HTN, DM and CVD events compared with other women. They are more likely to be physically active and be a current smoker, but the percentage with a ‘college or above’ degree of education is decreased. Although slightly attenuated, these associations between AAM and HTN, CVD incidence and ‘college or above’ education level persisted after adjustment for age, BMI and height.

Comparison with Other Studies

AAM serves as a significant event in a female’s life as well as an important indicator of sexual maturity. A number of factors such as one’s physical condition as well as genetic and living environment factors contribute to the timing of menarche [1, 2]. Recent studies also demonstrate that the timing of the first menstrual period has important implications for the health of pre- and postmenopausal women, such as breast cancer (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2888798/>), osteoporosis and endometrial cancer [3–6, 10, 13]. However, the studies implied that the association between AAM and CVD risk are sparse and the conclusions are contradictory.

Among these sparse studies, several groups claimed that AAM was inversely associated with CVD events and risk factors. In an EPIC-Norfolk study of 15,807 Caucasian women (3,888 CVD events), it was found that women with early menarche (≤ 12 years) had higher risks of incident CVD [1.17 (1.07–1.27)], incident CHD [1.23 (1.06–1.43)], HTN [1.13 (1.02–1.24)], and CVD mortality [1.28 (1.02–1.62)], and the association was only partly mediated by increased adiposity [16]. This study is consistent with the Fels Longitudinal Study of 391 Caucasian females as they found that girls reporting menarche at an earlier age are more likely to exhibit adverse changes of disease risk factors during adolescence, such as insulin, blood pressure and lipids [19]. Recently, a large cohort study of Chinese women in Singapore, who originated from the contiguous provinces of Fujian and Guangdong in the southern part of China, found that there was a significant interaction between AAM and smoking ($p < 0.05$). This provides evidence for a potential AAM-smoking interaction in relation to CVD risk [20]. Although this study is inconsistent with a study of 37,965 postmenopausal Japanese women which found no difference in risk of CVD, CHD, or stroke mortality in participants who reported menarche before age 16 versus 13 years or younger, the authors attributed the inconsistent findings to the population differences and methodological approaches [22]. A study of 6,242 women aged 21–92 years also found that later menarche (> 18 years) was significantly associated with lower CVD risk (OR = 0.71, 95% confidence interval, 0.57–0.89; $p = 0.002$) [15].

There are also some rare studies in which women who lived in a local area of China were recruited. In a retrospective historical cohort study of 7,349 women from the Guangzhou Biobank Cohort Study (enrolled in 2003–2004), Heys et al. [23] concluded that early AAM

(12.5 years) had a threshold effect on the metabolic syndrome, central obesity, and elevated fasting blood glucose. In another study, a previous cross-sectional study of 9,000 Chinese women aged 25–64 years (enrolled in 2004–2005) found that AAM was inversely associated with body fatness (BMI, WC and abdominal and total fat mass), insulin resistance (homeostasis model assessment), and total number of metabolic syndrome components [18]. Early AAM increased the risk of CVD events, CVD mortality, and overall mortality in women, which has been proven in other studies as well [16, 24, 25].

However, there are still some papers that have rather weak conclusions about the correlation between AAM and CVD [26–28]. In a previous review of the literature on reproductive risk factors and CVD events in postmenopausal women, the authors concluded that AAM has no association or statistically significant inverse association with CVD risk [29]. One prospective study of US female participants, aged 30–55 years (308 cases of CHD) found a nonsignificant association [age-adjusted hazard ratio of 1.3 (0.8–2.1) for menarche before 11 years compared with menarche at age 13 years] [26]. In another hospital-based case-control study of 202 women with acute myocardial infarction and 374 control subjects, no consistent association was observed between AAM and myocardial infarction risk [28].

In the current study of a large population-based cohort, we found that later AAM is consistently associated with increased risks of CVD events and some CVD risk factors such as HTN. Even if most of the CVD risk factors, such as obesity, smoking, DM, low physical activity, blood pressure and LDL increase with the time of AAM, they interact very weakly. Progressive improvement in education of the population can contribute to the control of some CVD risk factors such as the contemporary epidemic of HTN and smoking, as well as a higher prevalence of CVD [30, 31]. It is consistent with the results of our study that the increase in the incident CVD events, the odds of HTN or educational qualifications of ‘college or above’ are associated with later menarche, and such cases persisted even after adjusting for age, BMI and height.

Strengths and Limitations

The strength of our study includes the large sample size, drawn from the general population, which resulted in its representativeness. The large-scale regional feature and the wide age range (24–79 years) serve as great advantages of our study. Because China has maintained a rapidly growing economy for years, which resulted in the great change of the citizens’ lifestyles as well as nutritional status, this could potentially affect the timing of menarche. The study also covers a wide range of risk factors and a measure of overall CV risk factors rather than self-reported data, which could reduce biases.

However, several limitations in the present study should also be mentioned. Due to the design of this study of a retrospective analysis, we used cross-sectional data and the subjects’ recalled AAM from a large sample of women who participated. There might have been a misclassification of AAM. However, menarche is a key milestone in a girl’s physiological development, which makes women more likely to remember it even in later adulthood. It has been proven that recall of AAM is reliable over a long period of time [32, 33]. What is more, subjects were also unaware of this hypothesis and random misclassification make it more conservative. There are some variables that have possible misclassifications and they need to be considered. Some of the covariables like psychological condition, smoking habits, alcohol consumption and physical activity were measured by self-reports. Furthermore, we did not have any information on measures of BMI, weight or WC during childhood as well as adolescence, as it has been proven that the BMI in the twenties is strongly associated with the BMI in the youth and in the teenage years [34]. With this, it could help to shed light on the etiology of the associations we focused on.

The geographical difference could also be an important factor which potentially affects these associations. Different groups have previously investigated this issue and demonstrated that the incidence and the prevalence of important CVD risk factors varied greatly from geographical region. In addition, the AAM had also been found to be different in regions with different economic development levels in previous studies [35–37]. However, we did not collect detailed geographical information of participants in this study and thus, we could not provide experimental evidence of whether there was a geographical difference in these relationships. This may be a limitation of our study and deserves further investigation in future work.

In addition, since the timing of menarche could be partly determined by environmental factors, the difference in socioeconomic condition and family income also resulted in the variation of girls' AAM, which could thus affect the association with CVD [38, 39]. Family income across early life had a significant impact on nutritional and psychosocial status, and a high family income with better socioeconomic conditions and welfare could result in a decrease in AAM [36, 39–42]. Besides that, a low family income has also proven to be related with increased CVD risk factors, CVD events and mortality [38, 43]. Although the family income across early life was not included in our study, based on these studies above, we suggested that there may be an association between family income and AAM and CVD risks with a complicated pattern.

Conclusion and Implication

The present study is based on a large number of participants to provide sufficient power for effects, as well as to confirm the absence of an association. In conclusion, it is shown in our study that a later AAM plays a role in the development of some CVD risk factors, such as HTN or 'college or above' education level, subsequent to the development of CVD in women. However, the association is only partially mediated by height. Although we cannot modify AAM, early identification of female menarche history may help to identify women with increased risk of CVD (age ≥ 17 years in our study) and provide help to increase the effectiveness of CVD prevention interventions.

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Statement of Ethics

The study was approved by the Review Board/Ethics Committees of the Chinese PLA General Hospital. All participants gave informed consent to take part, because data was analyzed anonymously, and no written consent was required.

Disclosure Statement

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this study and thus all authors declare that they have no conflicts of interest.

References

- 1 Jahanfar S, Lye MS, Krishnarajah IS: Genetic and environmental effects on age at menarche, and its relationship with reproductive health in twins. *Indian J Hum Genet* 2013;19:245–250.
- 2 Rees M: The age of menarche. *ORGYN* 1995;4:2–4.
- 3 Apter D, Vihko R: Early menarche, a risk factor for breast cancer, indicates early onset of ovulatory cycles. *J Clin Endocrinol Metab* 1983;57:82–86.
- 4 Lujan Irastorza JE, Garcia Rodriguez F, Figueroa Preciado G, Hernandez Marin I, Ayala AR: Early menarche as a risk factor of breast cancer. *Ginecol Obstet Mex* 2006;74:568–572.
- 5 Naves M, Diaz-Lopez JB, Gomez C, Rodriguez-Rebollar A, Cannata-Andia JB: Determinants of incidence of osteoporotic fractures in the female Spanish population older than 50. *Osteoporos Int* 2005;16:2013–2017.
- 6 Macsali F, Real FG, Plana E, Sunyer J, Anto J, et al: Early age at menarche, lung function, and adult asthma. *Am J Respir Crit Care Med* 2011;183:8–14.
- 7 Deecher D, Andree TH, Sloan D, Schechter LE: From menarche to menopause: exploring the underlying biology of depression in women experiencing hormonal changes. *Psychoneuroendocrinology* 2008;33:3–17.
- 8 Patton GC, Hibbert ME, Carlin J, Shao Q, Rosier M, et al: Menarche and the onset of depression and anxiety in Victoria, Australia. *J Epidemiol Community Health* 1996;50:661–666.
- 9 Bralic I, Tahirovic H, Matanic D, Vrdoljak O, Stojanovic-Spehar S, et al: Association of early menarche age and overweight/obesity. *J Pediatr Endocrinol Metab* 2012;25:57–62.
- 10 He C, Zhang C, Hunter DJ, Hankinson SE, Buck Louis GM, et al: Age at menarche and risk of type 2 diabetes: results from 2 large prospective cohort studies. *Am J Epidemiol* 2010;171:334–344.
- 11 Stockl D, Doring A, Peters A, Thorand B, Heier M, et al: Age at menarche is associated with prediabetes and diabetes in women (aged 32–81 years) from the general population: the KORA F4 Study. *Diabetologia* 2012;55:681–688.
- 12 Conway BN, Shu XO, Zhang X, Xiang YB, Cai H, et al: Age at menarche, the leg length to sitting height ratio, and risk of diabetes in middle-aged and elderly Chinese men and women. *PLoS One* 2012;7:e30625.
- 13 Glueck CJ, Morrison JA, Wang P, Woo JG: Early and late menarche are associated with oligomenorrhea and predict metabolic syndrome 26 years later. *Metabolism* 2013;62:1597–1606.
- 14 Stockl D, Meisinger C, Peters A, Thorand B, Huth C, et al: Age at menarche and its association with the metabolic syndrome and its components: results from the KORA F4 study. *PLoS One* 2011;6:e26076.
- 15 Qiu C, Chen H, Wen J, Zhu P, Lin F, et al: Associations between age at menarche and menopause with cardiovascular disease, diabetes, and osteoporosis in Chinese women. *J Clin Endocrinol Metab* 2013;98:1612–1621.
- 16 Lakshman R, Forouhi NG, Sharp SJ, Luben R, Bingham SA, et al: Early age at menarche associated with cardiovascular disease and mortality. *J Clin Endocrinol Metab* 2009;94:4953–4960.
- 17 Kivimaki M, Lawlor DA, Smith GD, Elovainio M, Jokela M, et al: Association of age at menarche with cardiovascular risk factors, vascular structure, and function in adulthood: the Cardiovascular Risk in Young Finns study. *Am J Clin Nutr* 2008;87:1876–1882.
- 18 Feng Y, Hong X, Wilker E, Li Z, Zhang W, et al: Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases. *Atherosclerosis* 2008;196:590–597.
- 19 Remsberg KE, Demerath EW, Schubert CM, Chumlea WC, Sun SS, et al: Early menarche and the development of cardiovascular disease risk factors in adolescent girls: the Fels Longitudinal Study. *J Clin Endocrinol Metab* 2005;90:2718–2724.
- 20 Mueller NT, Odegaard AO, Gross MD, Koh WP, Yuan JM, et al: Age at menarche and cardiovascular disease mortality in Singaporean Chinese women: the Singapore Chinese Health Study. *Ann Epidemiol* 2012;22:717–722.
- 21 Canoy D, Boekholdt SM, Wareham N, Luben R, Welch A, et al: Body fat distribution and risk of coronary heart disease in men and women in the European Prospective Investigation Into Cancer and Nutrition in Norfolk cohort: a population-based prospective study. *Circulation* 2007;116:2933–2943.
- 22 Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, et al: Relationships of age at menarche and menopause, and reproductive year with mortality from cardiovascular disease in Japanese postmenopausal women: the JACC study. *J Epidemiol* 2006;16:177–184.
- 23 Heys M, Schooling CM, Jiang C, Cowling BJ, Lao X, et al: Age of menarche and the metabolic syndrome in China. *Epidemiology* 2007;18:740–746.
- 24 Jacobsen BK, Oda K, Knutsen SF, Fraser GE: Age at menarche, total mortality and mortality from ischaemic heart disease and stroke: the Adventist Health Study, 1976–1988. *Int J Epidemiol* 2009;38:245–252.
- 25 Jacobsen BK, Heuch I, Kvale G: Association of low age at menarche with increased all-cause mortality: a 37-year follow-up of 61,319 Norwegian women. *Am J Epidemiol* 2007;166:1431–1437.
- 26 Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, et al: A prospective study of age at menarche, parity, age at first birth, and coronary heart disease in women. *Am J Epidemiol* 1987;126:861–870.
- 27 Bertuccio P, Tavani A, Gallus S, Negri E, La Vecchia C: Menstrual and reproductive factors and risk of non-fatal acute myocardial infarction in Italy. *Eur J Obstet Gynecol Reprod Biol* 2007;134:67–72.
- 28 La Vecchia C, Decarli A, Franceschi S, Gentile A, Negri E, et al: Menstrual and reproductive factors and the risk of myocardial infarction in women under fifty-five years of age. *Am J Obstet Gynecol* 1987;157:1108–1112.
- 29 de Kleijn MJ, van der Schouw YT, van der Graaf Y: Reproductive history and cardiovascular disease risk in postmenopausal women: a review of the literature. *Maturitas* 1999;33:7–36.

- 30 Gupta R, Gupta VP, Ahluwalia NS: Educational status, coronary heart disease, and coronary risk factor prevalence in a rural population of India. *BMJ* 1994;309:1332–1336.
- 31 Liu K, Cedres LB, Stamler J, Dyer A, Stamler R, et al: Relationship of education to major risk factors and death from coronary heart disease, cardiovascular diseases and all causes. Findings of three Chicago epidemiologic studies. *Circulation* 1982;66:1308–1314.
- 32 Must A, Phillips SM, Naumova EN, Blum M, Harris S, et al: Recall of early menstrual history and menarcheal body size: after 30 years, how well do women remember? *Am J Epidemiol* 2002;155:672–679.
- 33 Bosetti C, Tavani A, Negri E, Trichopoulos D, La Vecchia C: Reliability of data on medical conditions, menstrual and reproductive history provided by hospital controls. *J Clin Epidemiol* 2001;54:902–906.
- 34 Mattsson N, Ronnema T, Juonala M, Viikari JS, Raitakari OT: Childhood predictors of the metabolic syndrome in adulthood. The Cardiovascular Risk in Young Finns Study. *Ann Med* 2008;40:542–552.
- 35 Wong ND: Epidemiological studies of CHD and the evolution of preventive cardiology. *Nat Rev Cardiol* 2014;11:276–289.
- 36 Herman-Giddens ME: The decline in the age of menarche in the United States: should we be concerned? *J Adolesc Health* 2007;40:201–203.
- 37 Lawlor DA, Bedford C, Taylor M, Ebrahim S: Geographical variation in cardiovascular disease, risk factors, and their control in older women: British Women's Heart and Health Study. *J Epidemiol Community Health* 2003;57:134–140.
- 38 Lemstra M, Rogers M, Moraros J: Income and heart disease: neglected risk factor. *Can Fam Physician* 2015;61:698–704.
- 39 Yermachenko A, Dvornyk V: Nongenetic determinants of age at menarche: a systematic review. *Biomed Res Int* 2014;2014:371583.
- 40 Donoso MA, Munoz-Calvo MT, Barrios V, Garrido G, Hawkins F, et al: Increased circulating adiponectin levels and decreased leptin/soluble leptin receptor ratio throughout puberty in female ballet dancers: association with body composition and the delay in puberty. *Eur J Endocrinol* 2010;162:905–911.
- 41 Sun Y, Tao FB, Su PY, Mai JC, Shi HJ, et al: National estimates of the pubertal milestones among urban and rural Chinese girls. *J Adolesc Health* 2012;51:279–284.
- 42 Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, et al: The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. *Endocr Rev* 2003;24:668–693.
- 43 Kretsoulas C, Anand SS: The impact of social determinants on cardiovascular disease. *Can J Cardiol* 2010;26:8c–13c.