Published in final edited form as:

Atherosclerosis. 2008 February ; 196(2): 590–597.

Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases

Yan Feng¹, Xiumei Hong^{2,3,4}, Elissa Wilker¹, Zhiping Li³, Wenbin Zhang³, Delai Jin³, Xue Liu³, Tonghua Zang³, Xiping Xu⁴, and Xin Xu¹

¹Program for Population Genetics, Harvard School of Public Health, Boston, MA 02115

²School of Life Science, University of Science and Technology of China, Hefei, Anhui, China

³Anhui Institute of Biomedicine, Anhui Medical University, Hefei, Anhui, China

⁴Center for Population Genetics, School of Public Health, University of Illinois, Chicago, IL

Abstract

Background—Early menarche is associated with increased adult body fatness, however this association has been studied primarily in young women. The impact of changes in some metabolic risk factors of cardiovascular disease (CVD) after menopause remains controversial and ageing is an important confounder.

Objectives—To investigate the effect of age at menarche, reproductive years, and years post-menopause on body composition and metabolic risk factors for CVD independent of the normal ageing process in a large sample size of Chinese women.

Design—9097 women aged 25 to 64 were recruited from Anhui, China in 2004–2005. Anthropometric measurement, body composition, blood pressure, plasma lipids, fasting glucose and insulin, as well as a questionnaire-based interview on menstruation and lifestyle information were obtained from each participant.

Results—After adjusting for age and other covariates, age at menarche was inversely associated with body fatness, HOMA-IR, triacylglycerol and the total number of metabolic syndrome components, and was positively associated with HDL-C ($p < 0.05$). The number of reproductive years was associated with increased body fatness, decreased total cholesterol and HDL-C ($p < 0.05$). Post-menopausal women had significantly lower BMI but higher abdominal fat percentage, increased plasma levels of triacylglycerol, total cholesterol, HDL-C, and LDL-C, and lower systolic blood pressure than pre-menopausal women ($p < 0.05$).

Conclusion—Age at menarche, reproductive years, and menopause status were significantly associated with body composition, insulin sensitivity and blood lipid levels.

Keywords

age at menarche; menopause; reproductive years; metabolic syndrome; Chinese women

Address for correspondence and reprints: Xin Xu, MD, PhD, Program for Population Genetics, Harvard School of Public Health, 665 Huntington Ave., FXB-101, Boston, MA, 02115, USA, Tel: 617-432-4572, Fax: 617-432-2956, Email: xin_xu@harvard.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Metabolic syndrome (MetS) is the clustering of metabolic risk factors for cardiovascular diseases (CVD) including obesity, insulin resistance, dyslipidemia, hypertension and hyperglycemia [1,2]. Understanding the relationship between reproductive history and metabolic risk factors may lead to better prevention and management of CVD in women. Menarche and menopause are two landmarks in a woman's reproductive life and early menarche has been demonstrated to be associated with increased adult body mass index (BMI) in many longitudinal studies [3–8] and cross-sectional studies [9,10]. Early menarche has also been associated with many cardiovascular disease risk factors and metabolic syndrome [11–14]. However, because most of these studies were conducted in populations of adolescent girls or young adult women, the impact of early menarche on CVD and its risk factors in older women, remains unknown. A recent meta-analysis from eighteen studies showed that the pooled relative risk estimate for postmenopausal versus premenopausal status and cardiovascular disease was 1.36 (96%CI, 1.15–1.60), however, the association disappeared after controlling for age and smoking [15]. The relationship between menopause and specific components of MetS has been widely studied in many populations, but inconsistent results have been reported with respect to triacylglycerol (TG) and high density lipoprotein cholesterol (HDL-C), blood pressure, insulin resistance and blood glucose [16].

Using menarche and menopause as markers, a woman's lifespan can be divided into three reproductive stages. Women in different stages are exposed to different hormonal environments, which may assert different effects on metabolic risk factors. As a result, the length of each stage can be regarded as a measure of exposure to the corresponding hormonal conditions, however the normal process of ageing confounds the assessment of effects of the lengths of these stages on CVD and its metabolic risk factors. In the present study, we examined the age-independent effects of age at menarche, reproductive years, and years post-menopause on metabolic risk factors for CVD in over 9000 Chinese women.

Subjects and Methods

Subjects

We conducted a family-based cross-sectional survey on MetS in two counties (Dongzi and Wangjiang) of Anhui Province, China, during 2004 and 2005. Dongzi and Wangjiang, separated by the Yangzi River, are two agricultural counties in southern Anhui with populations of 540,000 and 600,000, respectively. Subjects were recruited as part of this genetic epidemiological study of MetS. Families were eligible to participate if there were a minimum of three siblings aged 25–64 years old, of which two were 40–64 years old. Parents and siblings whose ages were not within 25–64 years were not enrolled. Also excluded were patients with type 1 diabetes, renal failure, chronic diseases such as tuberculosis, malignancy, rickets or other metabolic bone diseases, and thyrotoxicosis, individuals with chronic glucocorticoid use, as well as pregnant women. A total of 9097 women and 9536 men from 5695 families were enrolled in the study. Informed consents were obtained from all participants. This study was approved by both the Human Subject Committees at the Harvard School of Public Health and at the Anhui Medical University.

Data collection

Anthropometry measurement and physical examination—Height was measured without shoes to the nearest 0.1 cm on a portable stadiometer and weight was measured in light indoor clothing without shoes to the nearest 0.1 kg. Waist circumference (WC) was measured as the minimum circumference between the inferior margin of the ribcage and the crest of the ilium [17] and hip circumference was measured at the level of maximum extension of the

buttocks. Body mass index (BMI) was calculated as weight/height² (kg/m²). Blood pressure was measured on the right arm of participants in a relaxed, sitting position, independently by two research staff members with two reads taken by each at least 30 min apart. Participants were advised to avoid cigarette smoking, alcohol, caffeinated beverages and exercise for at least 30 min before their blood pressure measurement. The median of four readings of blood pressure was used in the analysis.

Laboratory Assays—Participants were required to fast at least 10 hours before the blood samples were taken. Serum and plasma were separated from blood cell in the field within 30 min after the blood was drawn and kept refrigerated. Serum glucose was measured within 2 hours by modified hexokinase enzymatic method (Hitachi 7020 Automatic Analyzer, Japan). The serum TC, TG and HDL-C were measured the same day using commercial available reagents (Hitachi 7020 Automatic Analyzer, Japan). Level of LDL-C was calculated using the Friedewald equation in participants with ≤ 4.5 mmol/l triacylglycerols: $LDL-C = TC - HDL-C - TG/2.2$ [18]. Standard quality control procedures were performed each day with standard samples that came with the reagents (CV<8%). Plasma insulin was measured by electrochemiluminescence (ECL) method on an Elecsys 2010 system (Roche, Switzerland). Duplicate analyses were also conducted daily using samples collected from study participants (CV<10% (mean= 3%). The insulin resistance index of homeostatic model assessment (HOMA-IR) was calculated from fasting glucose and insulin level using the HOMA2 calculator (www.dtu.ox.ac.uk/homa). The laboratory where the above assays were conducted participated in “Quality Accreditation of Clinical Laboratory”, the quality control program from China National Centre for Clinical Laboratory [19], and passed the quality control test every year.

Measurement of fat mass and lean mass—Whole-body and abdominal fat as well as lean mass were measured by dual-energy X-ray absorptiometry (GE-Lunar, USA). The central abdominal region was defined by cursor manipulation outlining the region that extends between the top of the second and the bottom of the fourth lumbar vertebrae horizontally and to the inner areas of the ribcage laterally to exclude some abdominal subcutaneous fat, a method which has been validated and used in previous studies [20,21]. In subsequent analyses, fat percentage in whole body or abdominal region was defined as fat mass/(fat mass + lean mass) in the corresponding region.

Questionnaire-based interview—A questionnaire-based interview was used to collect information on the participants’ occupations, physical activity, smoking and alcohol consumption history, dietary habits, disease history including hypertension and diabetes, and the women’s menstruation and reproductive history, including age at menarche, date of last menstrual period, and regularity of the menstrual cycle. Age at menarche ≥ 20 years was treated as error and set to missing (n=91). Early menarche (EM), intermediate menarche (IM) and late menarche (LM) were defined as age at menarche below 25th percentile, between 25th and 75th percentile and above 75th percentile of the total population, respectively.

Definition of menopausal status and length of reproductive stages

In the interview, each female subject was asked whether menstruation had stopped. If it had, the subject was asked to report how many months ago menstruation had stopped and whether it had stopped naturally. If menstruation had not stopped the subject was asked to report the regularity of menstrual periods. Based on this information, pre-menopause was defined as having regular menstrual period every 21–40 days without significant changes in the past year. Post-menopause was defined as menstruation stopped for at least 12 months and no history of hysterectomy or oophorectomy, or current pregnancy or lactation. A total of 4409 and 2250 women were classified as pre- and post-menopausal, respectively. The menopausal status of the remaining 2438 women could not be determined. Based on examination of the age

distributions in pre- and post- menopausal women, an age range of 40–55 was selected to examine the menopause effect, due to overlap of this age range in these two groups. We further excluded 16 women whose menopause was reported before 35 years of age. We eventually used 2391 pre- and 1429 post- menopausal women in the multiple linear regression and smooth curve of MetS- related phenotypes across age in the analyses of menopause's effects.

The length of pre-menarche stage was established as age at menarche; the length of reproductive years were calculated from age at menarche to age at interview and ages at menopause for pre- and post-menopausal women, respectively. For pre-menopausal women, the post-menopausal years were set to 0.

Definition of metabolic syndrome

Metabolic syndrome was defined using the new International Diabetes Federation definition [22]. A subject had MetS if the first condition and two or more of the condition 2–5 are met:

1. WC ≥ 90 cm in men or ≥ 80 cm in women;
2. TG > 1.7 mmol/L or under special treatment for TG abnormality;
3. HDL-C < 1.04 mmol/L in men or < 1.29 mmol/L in women or under special treatment for HDL-C abnormality;
4. Systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg or under treatment of previously diagnosed hypertension;
5. Fasting blood glucose ≥ 5.6 mmol/L or previously diagnosed type 2 diabetes.

Statistical methods

The characteristics of the total population and the 2391 pre- and 1429 post-menopausal women aged 40 to 55 years were expressed as mean values with standard deviations (SD) for continuous variables. We first looked at the smoothing curves of MetS-related traits across age in pre- and post- menopausal women, and EM/IM/LM groups which were generated using a locally weighted linear regression method implemented in the `supsmu` function in R (<http://www.r-project.org>). The effects of menopause status on MetS-related phenotypes were examined in these selected women using multiple linear regressions with adjustment for age, age squared, physical activity level and age at menarche. Logistic regressions were used for binomial outcomes including affection status of MetS and its individual components. Age at menarche, reproductive years, and years post-menopause are highly correlated with age. To examine their effects on MetS-related phenotypes independent from the normal ageing process, we first adjusted each MetS-related phenotype by age using the loess regression model and then used the residuals in a regression analysis with these three variables as independent variables. Generalized Estimation Equations (GEEs) with independent working correlation matrices were used to adjust for trait correlation among siblings in the regression. Triacylglycerol, fasting insulin and HOMA-IR were log-transformed for better normality in regression analyses. All p values were two-tailed, with statistical significance defined as $p < 0.05$.

Results

Characteristic of the study population

A total of 9097 women were included in the current study. The characteristics of the study population are presented in Table 1. In general, our study population is lean, with a mean BMI of 22.2 kg/m^2 . The percentage overweight (BMI $24\text{--}28 \text{ kg/m}^2$) and obese (BMI $\geq 28 \text{ kg/m}^2$) were 20.8% and 3.0%, respectively. Most subjects reported farming as their occupation (91%).

Although few (1%) had regular intentional exercise, most subjects led a physically active life, with 89% reporting moderate to heavy daily physical activity. Cigarette smoking and alcohol consumption were very rare (3.3% and 1.9% respectively) in these Chinese women.

Menopause status and metabolic phenotypes

The age at menopause in our total population ranged from 27 to 60 years old (Figure 1A), with a median of 47 years. The median current age in all pre- and post-menopausal women was 40 and 53 years, respectively. In order to examine the effect of menopause status on MetS, we selected participants within the 40–55 age range, for which there was overlap in pre- and post-menopausal women. The phenotypes of the selected 2391 pre- and 1429 post-menopausal women are presented in Table 1. The t-test shows that the post-menopausal women appeared leaner but more centrally obese than pre-menopausal women, with lower BMI and total fat mass, but higher abdominal fat mass ($p<0.05$). Meanwhile, the fasting glucose, blood lipids (triacylglycerol, total cholesterol, HDL-C, LDL-C) and blood pressure were significantly higher in post-menopausal women ($p<0.05$) (Table 1). Because most of the above phenotypes were age-related and the mean age of pre-menopausal women was 7 years younger than that of post-menopausal women, age is an important confounder in the association between menopause and MetS-related phenotypes. We first looked at the trends of these metabolic phenotypes by age. Smoothing curves of BMI, abdominal fat percentage, triacylglycerol, total cholesterol, HDL-C, and LDL-C across age in pre- and post-menopausal women are presented in Figure 2. Since the age effect was similar in most of the phenotypes between pre- and post-menopausal women, we used multiple linear regression to test the association. After adjustment for age, age squared, physical activity level, and age at menarche in regression analyses, post-menopausal women still had significantly lower BMI but higher abdominal fat percentage, increased plasma levels of triacylglycerol, total cholesterol, HDL-C, and LDL-C, and lower systolic blood pressure than premenopausal women ($p<0.05$) (Table 1). We also examined the effect of menopausal status on each component of the MetS using logistic regression. Menopause was a significant risk factor for hypertriglyceremia (OR=1.35, 95%CI: 1.05–1.74, $p=0.02$), but a protective factor for elevated blood pressure (OR=0.75, 95%CI: 0.60–0.94, $p=0.01$), and not associated with high WC (OR=0.85, 95%CI: 0.67–1.08, $p=0.19$) or decreased HDL-C level (OR=0.84, 95%CI: 0.67–1.04, $p=0.11$), after adjustment for age, age squared, physical activity level and age at menarche. Overall, menopause was not significantly associated with metabolic syndrome (OR=0.77, 95%CI: 0.58–1.03, $p=0.08$).

The association of metabolic phenotypes with age at menarche, reproductive years and years post menopause

The distribution of age at menarche in our study population is shown in Figure 1B, with a mean of 14.9 years. The age ranges for EM, IM and LM were 8–13, 14–16, and 17–19 years, respectively, according to their definitions. Age at menarche was positively associated with current age ($\beta=0.08$, $p<0.001$), indicating that younger women had earlier menarche. The mean age at menarche was 13 in women currently in their 20s, while it was 16 in women in their 50s. The smoothing curves of some MetS-related phenotypes across age in women with EM, IM and LM are shown in Figure 3. The association of MetS-related phenotypes with age at menarche, reproductive years and years post-menopause are shown in Table 2. After excluding the ageing effect, the body composition assessed by BMI, waist circumference, and total and abdominal fat was inversely associated with age at menarche (pre-menarche years), but positively correlated with reproductive years ($p<0.001$). Years post-menopause was only significantly associated with abdominal fat percentage ($p=0.01$). Age at menarche was also inversely associated with HOMA-IR ($p<0.01$). Relationships with lipid profile were more complicated. Age at menarche was associated with increased HDL-C and decrease TG ($p<0.01$); the number of reproductive years was associated with decreased HDL-C and TC ($p<0.05$); Years post-menopause was associated with increased TG, TC, and LDL-C ($p<0.05$).

The associations between age at menarche and HOMA-IR, triacylglycerol and HDL were substantially attenuated after adjustment for BMI, while the effect of years post-menopause on lipid increased slightly (Table 2). The years post-menopause were also associated with blood pressure ($p<0.05$), but the significance disappeared after adjustment for BMI (Table 2). Compared to women with intermediate age at menarche (IM), women with early menarche (EM) were more significantly at risk for MetS (OR=1.32, 95%CI: 1.14–1.53, $P<0.001$) after adjustment for age and physical activity. Fasting glucose level was not associated with age at menarche, reproductive years, or years post-menopause.

Discussion

This study demonstrates that early menarche, longer reproductive years, and menopause were significantly associated with increased body fatness, which was assessed by BMI, waist circumference, total body fat (percentage) and abdominal fat (percentage), and some vascular-unfavorable lipid profile (increased serum triacylglycerol and total cholesterol, and decreased HDL-C) in adult women independent of the normal ageing process.

Natural menopause is associated with an increased central adiposity [23–25] and it contributes to the worsening of lipid profile in post-menopausal women [16]. In our analysis on menopausal status, post-menopausal women had significantly lower BMI, higher abdominal fat percentage, higher TC, LDL-C, HDL-C and TG than pre-menopausal women. However, when we analyzed the lengths of three reproductive stages simultaneously we did not find any significant association of years after menopausal with BMI and HDL-C. One explanation is that menopausal status is inversely correlated with reproductive years; i.e. for women of the same age, post-menopausal women tend to have a shorter reproductive period than pre-menopausal women. Hence the association of post-menopausal status with decreased BMI and increased HDL-C may be an indirect effect mediated by association of reproductive years with increased BMI and decreased HDL-C. Similar to many studies which shown that early menarche was associated with increased body fatness in adolescent girls and young adult women [3–8,13], we observed an inverse correlation between age at menarche and body fat across all age groups of adult women in our study, especially in women of middle age. The mechanism underlying the association is still unclear. It has been suggested that childhood BMI drives the age at onset of sexual maturation and hence the age at menarche[4,26,27]. Both the Bogalusa heart Study [27] and the 1958 British Born Study [4] found that the association between age at menarche and adult BMI was substantially attenuated by childhood BMI. There are emerging data suggesting that the rate of weight increase in the childhood in facts determines the age at puberty through complex mechanisms involving leptin [26]. Excessive caloric intake and reduced physical activity in the early life may be a cause of early menarche [28]. Therefore, early menarche may not be itself a determinant of an unfavourable cardiovascular profile, but may simply reflect a negative metabolic imprinting during the pre-puberal life. It has been shown that ischemic heart disease risks decreased with increasing age at menarche in elderly women [14] and girls with early menarche have more deleterious changes in insulin, glucose, blood pressure and lipid through childhood, adolescence and young adulthood [11,13]. Increased body fat, especially abdominal fat, partially explained the increased insulin resistance and dyslipidemia in women with early menarche age. While most of the previous studies were conducted in adolescent girls or young women and with relative small sample size [11,13], our study is the first report with a large sample size to show the inverse association of age at menarche and metabolic CVD risk factors in women of middle age, who are at a greater risk of developing CVD. Similar to other reports [29], we observed a decline in age at menarche in the younger generation. This may related to the improving socioeconomic factors, such as increased nutrient and caloric intake as well as improvements in overall health conditions in the past decades in China. However, the potential risk of early menarche on some chronic diseases which are associated with obesity and dyslipidemia, such as cardiovascular diseases,

requires further investigation. After adjustment for age at menarche and years after menopause, we found that number of reproductive years is associated with increased both total and abdominal body fat percentage and decreased HDL-C, which are unfavorable to CVD. The reproductive years can be regarded as a measurement of cumulative exposure to sex hormones. In our data, we also found significant higher body fat in pre-menopausal than post-menopausal women and men than women (data not showed here). All the above evidences indicate that female hormones may increase body fat accumulation.

Age is an important metabolic risk factor and is positively correlated with lengths of the three reproductive stages. To assess the effects of the lengths of the three reproductive stages on metabolic risk factor independent of the normal ageing process, we first removed the effect of age prior to the analyses. This may result in underestimated effect sizes of the lengths of stages because reproductive stages are part of the ageing process.

The major strengths of our study are fairly large sample size and relatively homogeneous lifestyle in the study population. Most subjects were farmers with similar physical activity levels. Female cigarette smokers and alcohol users are very rare. However, our study has a few limitations. First, this is a cross sectional study, therefore the effect of childhood BMI on association between age at menarche and adult body composition cannot be studied. Secondly, ages at menarche and menopause were self-reported and subject to recall bias. Though we did not measure estrogen level to confirm menopause status, it has been shown that the recalled and the true age at menarche are highly correlated [30] and self-reported ages at menarche and menopause are most commonly used in epidemiologic studies. In addition, though our population is quite different from Western populations in terms of nutrition and lifestyle, which may pose some limits to generalizability, most of our findings were consistent with studies in other populations.

In this study we found significant association of age at menarche, reproductive years, menopausal status, and years post-menopause with body composition and metabolic risk factors for CVD in a large sample size of Chinese women. In general, earlier onset of menarche and longer reproductive years were associated vascular-unfavorable changes in the metabolic risk factors. It is also interesting to note post-menopausal women had lower BMI but higher abdominal fat percentage, increased plasma levels of triacylglycerol, total cholesterol, HDL-C, and LDL-C, and lower systolic blood pressure than pre-menopausal women after adjusting for age and physical activity in our study population.

Acknowledgement

We would like to thank the local Bureaus of Health of Dongzhi and Wangjiang in Anhui province of China for their support. This study was supported by NIH grants R01 HL073882 and R01 AR45651. Elissa Wilker was supported by a training grant T32 ES 07069.

Funding source: NIH grants R01 HL073882, R01 AR45651 and T32 ES 07069

References

1. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539–553. [PubMed: 9686693]
2. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–2497. [PubMed: 11368702]
3. van Lenthe FJ, Kemper CG, van Mechelen W. Rapid maturation in adolescence results in greater obesity in adulthood: the Amsterdam Growth and Health Study. *Am J Clin Nutr* 1996;64:18–24. [PubMed: 8669409]

4. Power C, Lake JK, Cole TJ. Body mass index and height from childhood to adulthood in the 1958 British born cohort. *Am J Clin Nutr* 1997;66:1094–1101. [PubMed: 9356525]
5. Pierce MB, Leon DA. Age at menarche and adult BMI in the Aberdeen children of the 1950s cohort study. *Am J Clin Nutr* 2005;82:733–739. [PubMed: 16210700]
6. Okasha M, McCarron P, McEwen J, Smith GD. Age at menarche: secular trends and association with adult anthropometric measures. *Ann Hum Biol* 2001;28:68–78. [PubMed: 11201332]
7. Laitinen J, Power C, Jarvelin MR. Family social class, maternal body mass index, childhood body mass index, and age at menarche as predictors of adult obesity. *Am J Clin Nutr* 2001;74:287–294. [PubMed: 11522550]
8. Garn SM, LaVelle M, Rosenberg KR, Hawthorne VM. Maturation timing as a factor in female fatness and obesity. *Am J Clin Nutr* 1986;43:879–883. [PubMed: 3717062]
9. Wattigney WA, Srinivasan SR, Chen W, Greenlund KJ, Berenson GS. Secular trend of earlier onset of menarche with increasing obesity in black and white girls: the Bogalusa Heart Study. *Ethn Dis* 1999;9:181–189. [PubMed: 10421080]
10. Mandel D, Zimlichman E, Mimouni FB, Grotto I, Kreiss Y. Age at menarche and body mass index: a population study. *J Pediatr Endocrinol Metab* 2004;17:1507–1510. [PubMed: 15570987]
11. Remsberg KE, Demerath EW, Schubert CM, Chumlea WC, Sun SS, Siervogel RM. 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. [PubMed: 15728207]
12. Ibanez L, Potau N, Chacon P, Pascual C, Carrascosa A. Hyperinsulinaemia, dyslipaemia and cardiovascular risk in girls with a history of premature pubarche. *Diabetologia* 1998;41:1057–1063. [PubMed: 9754824]
13. Frontini MG, Srinivasan SR, Berenson GS. Longitudinal changes in risk variables underlying metabolic Syndrome X from childhood to young adulthood in female subjects with a history of early menarche: the Bogalusa Heart Study. *Int J Pbes Relat Metab Disord* 2003;27:1398–1404.
14. Cooper GS, Ephross SA, Weinberg CR, Baird DD, Whelan EA, Sandler DP. Menstrual and reproductive risk factors for ischemic heart disease. *Epidemiology* 1999;10:255–259. [PubMed: 10230834]
15. Atsma F, Bartelink ML, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause* 2006;13:265–279. [PubMed: 16645540]
16. Carr MC. The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metab* 2003;88:2404–2411. [PubMed: 12788835]
17. Lee J, Ma S, Heng D, Tan CE, Chew SK, Hughes K, Tai ES. Should Central Obesity Be an Optional or Essential Component of the Metabolic Syndrome? Ischemic heart disease risk in the Singapore Cardiovascular Cohort Study. *Diabetes Care* 2007;30:343–347. [PubMed: 17259505]
18. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502. [PubMed: 4337382]
19. Shen Z, Yang Z. The problems and strategy relevant to the quality management of clinical laboratories. *Clin Chem Lab Med* 2001;39:1216–1218. [PubMed: 11798079]
20. Samaras K, Kelly PJ, Chiano MN, Spector TD, Campbell LV. Genetic and environmental influences on total-body and central abdominal fat: the effect of physical activity in female twins. *Ann Intern Med* 1999;130:873–882. [PubMed: 10375335]
21. Carey DG, Jenkins AB, Campbell LV, Freund J, Chisholm DJ. Abdominal fat and insulin resistance in normal and overweight women: Direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. *Diabetes* 1996;45:633–638. [PubMed: 8621015]
22. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. *Lancet* 2005;366:1059–1062. [PubMed: 16182882]
23. Poehlman ET, Toth MJ, Gardner AW. Changes in energy balance and body composition at menopause: a controlled longitudinal study. *Ann Intern Med* 1995;123:673–675. [PubMed: 7574222]
24. Bjorkelund C, Lissner L, Andersson S, Lapidus L, Bengtsson C. Reproductive history in relation to relative weight and fat distribution. *Int J Obes Relat Metab Disord* 1996;20:213–219. [PubMed: 8653141]

25. Toth MJ, Tchernof A, Sites CK, Poehlman ET. Effect of menopausal status on body composition and abdominal fat distribution. *Int J Obes Relat Metab Disord* 2000;24:226–231. [PubMed: 10702775]
26. Dunger DB, Ahmed ML, Ong KK. Effects of obesity on growth and puberty. *Best Pract Res Clin Endocrinol Metab* 2005;19:375–390. [PubMed: 16150381]
27. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. The relation of menarcheal age to obesity in childhood and adulthood: the Bogalusa heart study. *BMC Pediatr* 2003;3:3. [PubMed: 12723990]
28. Moisan J, Meyer F, Gingras S. A nested case-control study of the correlates of early menarche. *Am J Epidemiol* 1990;132:953–961. [PubMed: 2239910]
29. Demerath EW, Towne B, Chumlea WC, Sun SS, Czerwinski SA, Remsberg KE, Siervogel RM. Recent decline in age at menarche: the Fels Longitudinal Study. *Am J Hum Biol* 2004;16:453–457. [PubMed: 15214063]
30. Must A, Phillips SM, Naumova EN, Blum M, Harris S, Dawson-Hughes B, Rand WM. Recall of early menstrual history and menarcheal body size: after 30 years, how well do women remember? *Am J Epidemiol* 2002;155:672–679. [PubMed: 11914195]

Figure 1. The distribution of ages at menopause (A) and at menarche (B) in the study population

Figure 2. The smoothing curves of some metabolic phenotypes across age in pre-(n=2391, solid line) and post- (n=1429, dash line) menopausal women aged 40 to 55 years
 BMI: body mass index; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol

Figure 3. The smoothing curves of some metabolic phenotypes across age in women with early (EM, solid line), intermediate (IM, dash line) and late menarche (LM, dot line) in the total study population (n=9097)

BMI: body mass index; HOMA-IR: insulin resistance index of homeostatic model assessment; HDL-C: high density lipoprotein cholesterol

Characteristics of study population and Comparison between pre- and post- menopausal women aged between 40 and 55 years old (mean±SD)

Table 1

	Total (N=9097)	Pre- (N=2391)	Post- (N=1429)	Multiple regression of menopause status [†]	
				β (Se)	p
Age (yrs)	44.8±7.4 [*]	43.7±3.0	51.0±2.6 [*]	--	--
Age at menarche (yrs) ^{††}	15±2	15±2	15±2	NS	NS
Age at menopause (yrs)	46.6±4.4	--	46.3±3.7	--	--
Reproductive years (yrs)	27.5±5.4	28.9±3.4	30.8±4.0 [*]	--	--
Weight (kg)	52.3±7.5	53.3±7.4	51.5±7.4 [*]	-1.68 (0.33)	<0.001
Height (cm)	153.5±5.1	153.7±5.0	153.1±5.2 [*]	NS	NS
Waist circumference (cm)	73.8±8.2	74.4±8.1	74.5±8.3	NS	NS
BMI (kg/m ²)	22.2±2.8	22.5±2.8	22.0±2.8 [*]	-0.65 (0.15)	<0.001
Waist hip ratio	0.82±0.06	0.82±0.06	0.83±0.06 [*]	NS	NS
Total fat mass (kg)	15.10±5.37	15.51±5.36	14.97±5.37 [*]	NS	NS
Abdominal fat mass (kg)	1.09±0.54	1.11±0.54	1.15±0.55 [*]	NS	NS
Total fat %	28.56±6.79	28.85±6.69	28.70±6.93 [*]	NS	NS
Abdominal fat %	28.35±9.45	28.36±9.35	29.63±9.67 [*]	1.22 (0.50)	0.015
Fasting glucose (mmol/l)	5.55±0.93	5.52±0.83	5.69±1.05 [*]	NS	NS
Fasting insulin (IU/ml) [#]	4.61±1.81	4.71±1.79	4.35±1.79 [*]	NS	NS
HOMA-IR [#]	0.62±1.81	0.63±1.79	0.59±1.79 [*]	NS	NS
Triacylglycerol (mmol/l) [#]	1.20±1.55	1.17±1.55	1.34±1.58 [*]	0.09 (0.02)	<0.001
Total cholesterol (mmol/l)	4.42±0.85	4.34±0.79	4.74±0.91 [*]	0.32 (0.05)	<0.001
HDL-C (mmol/l)	1.41±0.37	1.39±0.36	1.48±0.39 [*]	0.06 (0.02)	0.002
LDL-C (mmol/l)	2.41±0.68	2.36±0.65	2.60±0.74 [*]	0.19 (0.04)	<0.001
SBP (mmHg)	119±19	117±17	123±21 [*]	-3.60 (0.98)	<0.001
DBP (mmHg)	75±11	75±10	77±12	NS	NS

* p<0.05 in unpaired t tests comparing pre- and post- menopausal women.

[†] using pre-menopausal women as reference group and adjusting for age, age², physical activity level and age at menarche (except for ††)

[#] log-transformed before statistical analysis and geometric mean and anti-log SD are presented.

Abbreviation: BMI: body mass index; HOMA-IR: insulin resistance index of homeostatic model assessment; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure

Table 2
The GEE regression of menstrual characteristics on age-adjusted metabolic phenotypes* in the total population (N=9097)

outcomes	Age at menarche (yr)			Reproductive years			Years post-menopause		
	β	Se	p	β	Se	p	β	Se	p
Model 1: outcome = age at menarche + reproductive years + years post-menopause									
BMI (kg/m ²)	-0.127	0.020	<0.001	0.033	0.007	<0.001	-0.015	0.009	0.09
Waist circumference (cm)	-0.355	0.057	<0.001	0.082	0.019	<0.001	-0.013	0.026	NS
Total fat mass	-0.318	0.037	<0.001	0.059	0.013	<0.001	0.002	0.017	NS
Abdominal fat mass	-0.036	0.004	<0.001	0.008	0.001	<0.001	0.002	0.002	NS
Total fat percentage	-0.501	0.047	<0.001	0.075	0.017	<0.001	0.036	0.023	NS
Abdominal fat percentage	-0.715	0.066	<0.001	0.089	0.023	<0.001	0.080	0.032	0.01
Fasting glucose (mmol/l)	-0.007	0.006	NS	0.002	0.002	NS	0.001	0.003	NS
HOMA-IR [#]	-0.023	0.004	<0.001	0.004	0.001	0.005	0.002	0.002	NS
Triacylglycerol (mmol/l) [#]	-0.013	0.003	<0.001	0.000	0.001	NS	0.004	0.001	0.006
Total cholesterol (mmol/l)	-0.006	0.006	NS	-0.004	0.002	0.04	0.007	0.003	0.007
HDL-C (mmol/l)	0.007	0.003	0.006	-0.002	0.001	0.004	0.000	0.001	NS
LDL-C (mmol/l)	-0.006	0.005	NS	-0.001	0.002	NS	0.004	0.002	0.04
SBP (mmHg)	0.220	0.120	NS	0.029	0.042	NS	-0.130	0.060	0.03
DBP (mmHg)	0.026	0.075	NS	0.041	0.025	NS	-0.067	0.033	0.04
Total number of MetS components	-0.033	0.008	<0.001	0.007	0.003	0.007	0.002	0.004	NS
Model 2: outcome = age at menarche + reproductive years + years post-menopause + BMI									
HOMA-IR [#]	-1.38	0.004	<0.001	NS	NS	NS	NS	NS	NS
Triacylglycerol (mmol/l) [#]	-0.008	0.003	0.01	NS	NS	NS	0.006	0.001	<0.001
Total cholesterol (mmol/l)	NS	NS	NS	-0.006	0.002	0.001	0.009	0.003	<0.001
HDL-C (mmol/l)	0.005	0.003	0.05	-0.001	0.001	0.09	NS	NS	NS
LDL-C (mmol/l)	NS	NS	NS	-0.004	0.002	0.02	0.006	0.002	0.004
SBP (mmHg)	0.375	0.117	0.001	NS	NS	NS	-0.073	0.059	0.21
DBP (mmHg)	NS	NS	NS	NS	NS	NS	-0.026	0.031	0.41

* phenotypes were adjusted for age in loess regression model and the residual were used in the GEE regression.

[#] log-transformed before statistical analysis

Abbreviation: BMI: body mass index; HOMA-IR: insulin resistance index of homeostatic model assessment; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure