Effect of the age at menarche and menopause status interaction on type 2 diabetes: the Henan Rural Cohort Study

Lulu Zhang[1], Yuqian Li[2], Xiaokang Dong [1], Wen Zhou[1], Chongjian Wang [1], Zhenxing Mao[1], Xiu Yang[1], Mengying Fan[1], Shengna Han[3]*, Linlin Li[1]*

[1] *Department of Epidemiology and Health Statistics, College of Public Health, Zhengzhou University, 100 Kexue Avenue, Zhengzhou, Henan 450001, China*

[2]*Department of Clinical Pharmacology, School of Pharmaceutical Science, Zhengzhou University, 100 Kexue Avenue, Zhengzhou, Henan 450001, China*

[3]*Department of Pharmacology, School of Basic Medical Sciences, Zhengzhou University, 100 Kexue Avenue, Zhengzhou, Henan 450001, China*

**Correspondence author:*

Department of Epidemiology and Health Statistics, College of Public Health, Zhengzhou University, 100 Kexue Avenue, Zhengzhou, Henan 450001, China

Tel.: +86-13607688936; Fax: +0371-67781868

E-mail address: hanshengna@126.com (S. Han), lilinlin@zzu.edu.cn (L. Li).

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Abstract

Purpose: The aims of this study were to evaluate the effect of age at menarche (AM) on type 2 diabetes mellitus (T2DM) and to assess whether the fasting plasma glucose (FPG) and homeostasis model assessment (HOMA) index responses to AM and menopause status interact in Chinese rural adults.

Methods: A cross-sectional, population-based study including 23138 participants was performed. Logistic regression and multivariable linear regression were performed to investigate the relationship between AM and glucose status. Generalized linear model was utilized to calculate the interaction term of AM and menopause status on FPG and the HOMA index. Interaction plot was used to interpret the significant interaction effect.

Results: Women in the later menarche age group (≥ 18 years) had a 17.7% lower risk of T2DM (95% CI: 0.712, 0.951, *P* =0.008), after adjusting for multiple variables.

Further adjustment for BMI completely attenuated this association (OR=0.884, 95% CI: 0.764, 1.024, *P* =0.099). A significant interaction effect of AM and menopause status on T2DM (*P* =0.004) was observed. The adverse effects of menopausal status on FPG and HOMA-2 of insulin resistance decreased with increasing menarche age, and the age ranges were limited to <18 and 9-19 years, respectively.

Conclusions: Later menarche was associated with a lower risk of T2DM, and the association appears to be mediated by BMI. More importantly, the adverse effect of menopause status on T2DM was decreased along with increasing menarche age.

Keywords: Interaction effect, age at menarche, menopause status, type 2 diabetes mellitus

Abbreviations

AM age at menarche

BMI body mass index

FPG Fasting plasma glucose

HOMA2-IR (HOMA)-2 of insulin resistance

HOMA2-ß (HOMA)-2 of ß-cell function

MSs menopause status

OGTT oral glucose tolerance test

TG triglyceride

T2DM type 2 diabetes mellitus

WC waist circumference

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent risk factors for mortality and cardiovascular diseases (CVD). It was reported that approximately 5 million deaths from T2DM were record in 2015 (1). The International Diabetes Federation (IDF) in 2017 showed that the number of people with diabetes in the 18-99 age group worldwide was 451 million, an increase of 8.7% from 415 million in 2015. It is expected that by 2045 the number will increase to 693 million. In 2010, the prevalence of diabetes had reached 11.6% in the Chinese adult population (2). Therefore, it is urgently to identify potential risk factors for prevention of T2DM.

Menarche and menopause, representing the beginning and end of the reproductive life of a woman, and its temporal development may have important health implications in later life. Many epidemiologic studies of western countries have examined the association between age at menarche (AM) and T2DM, but the findings have been inconsistent, with some showing that early menarche was associated with a higher risk of T2DM (3-5), while others reported no such association existed (6). In addition to menarche, early menopause may predispose women to osteoporosis, hypertension, and total mortality (6-8). Data from Italy reported a higher risk of diabetes among postmenopausal women than premenopausal women (9). Furthermore, a growing number of studies have suggested significant interactive effects between AM and race, hypertension, waist circumference (WC), triglyceride (TG) and menopause status on T2DM development (4,10). However, only a few studies have examined the interaction association of AM and menopause status on T2DM, and no modification effect was observed (3).

Hence, the main aims of this study were to evaluate the effect of AM on T2DM and to assess whether the fasting plasma glucose (FPG) and homeostasis model assessment (HOMA) index responses to AM and menopause status interact in Chinese rural adults.

Materials and methods

Study participants

The study participants were derived from the Henan Rural Cohort Study, which included 39259 participants aged between 18 and 79 years from five rural areas in Henan province of China during July 2015 and September 2017. Briefly, a multistage and stratified random cluster sampling design method was adopted to obtain the target population. Detailed information about data collection has been reported previously (11,12). Of these participants, only women were included in this analysis (n=23769). We excluded participants if they had a history of type 1 diabetes (n=2) or cancer (n=252), those who were without the information on T2DM (n=35), AM (n=217) or menopause status (n=17) on a standard questionnaire. Additionally, exclusion was those with AM earlier than 8 years or later than 22 years (n=108), probably an abnormal physiological age (13). Ultimately, 23138 participants remained for the current analyses. The survey was approved by the Zhengzhou University Life Science Ethics Committee, and was in accordance with the guidelines of the Helsinki Declaration. Written informed consent was signed by all the participants.

Data collection and laboratory measurement

A structured questionnaire was administered by well-trained interviewers to collect the general sociodemographic data (age, gender, education level and socioeconomic status, etc.), lifestyles characteristics (alcohol drinking, smoking status, physical activity, etc.), reproductive factors (AM, menopause status, age at menopause, parity, prior or current use of oral contraceptive pills, etc.), and family and individual history of disease. Education level was grouped into elementary school or below, junior high school and high school or above. Based on the International Physical Activity Questionnaire (IPAQ) (14), physical activity was divided into low, moderate and high levels. Alcohol drinking was considered as drinking alcohol at least 12 times per year. Smoking was defined as at least one cigarette per day for six consecutive months. Socioeconomic status was evaluated based on average monthly individual income (<500, 500~, >1000 renminbi (RMB)).

Height and weight were measured twice following a standardized protocol with the readings taken to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Overweight and obesity were defined as 24 kg/m^2 $\leq$ BMI < 28 kg/m^2 and BMI $\geq$ 28 kg/m^2, respectively. Parity was defined as the total number of live births and categorized as no children, 1 child and $\geq$ 2 children. The HOMA-2 of insulin resistance (HOMA2-IR) and HOMA-2 of ß-cell function (HOMA2- ß) were calculated using the updated computer-based HOMA index of insulin resistance (HOMA2-IR) and computer-based HOMA2- ß % (https://www.dtu.ox.ac.uk/homacalculator/) (15,16).

Venous blood samples were drawn in the absence of anticoagulant therapy after overnight fasting (at least 8 hours), and the serum were stored in a -80°C freezer before the analysis. FPG was measured using enzymatic methods by ROCHE Cobas C501 automatic biochemical analyzer.

AM and menopause status

AM and menopause status were obtained by self-reported (17). Participants were asked with the questions: "At what age did your first menstruation begin?" And "Have you had your menopause?" And "How old were you when you were menopausal?" Women were considered as menopausal if they had stopped menstruating for more than 1 year. Based on quintiles (6), the timing of menarche was classified as ≤14, 15, 16, 17 and ≥18 years, with the 16 years of age as the reference group. Menopause status was divided into premenopausal and postmenopausal status, with the premenopausal status as the reference group.

Ascertainment of cases

The diagnostic criteria for T2DM was as recommended by the American Diabetes Association (ADA) (2009) (18). Participants were defined as having T2DM if their FPG ≥ 7.0 mmol/l or if they had a self-reported previous diagnosis of diabetes by a physician, excluding gestational diabetes mellitus, type 1 diabetes, and diabetes due to other causes.

Statistical analysis

Participants' characteristics were shown as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. Differences between the T2DM group and the non-T2DM group were assessed using t tests for continuous variables and chi-square test for categorical variables.

Multivariable linear regression was applied to investigate AM and its associations with FPG, HOMA2-IR, and HOMA2-ß. To evaluate the association of T2DM across categories of age at menarche, we used binary logistic regression to estimate odds ratios (ORs) and 95% confidence interval (CI) for T2DM. Trend tests were also performed by entering the continuous variables into the logistic regression models to study the association across the increasing quintiles. Four models were performed to progressively reduce confounding associations. Model 1 was adjusted for age, and further adjusted for education level, physical activity, smoking status, alcohol drinking, average monthly individual income and family history of diabetes (model 2). Model 3 was additionally adjusted for parity and prior or current use of oral contraceptive pills. Because adult BMI may represent a mediation factor rather than a confounder associated with menarche age and T2DM, we adjusted adult BMI in a separate model (model 4) (5,19).

To examine potential effect modifiers, subgroup analyses were conducted, along with the adjusted the variables in model 3. We performed the analyses based on BMI (obesity/overweight, normal/underweight), menopause status (premenopausal, postmenopausal), smoking status (non-smokers, smokers) or physical activity (low, moderate, and high) by introducing a cross-product term with menarche age. The effects of AM, menopause status, and their interaction were tested using a generalized linear model. First, we estimated the effects of AM and menopause status on FPG and HOMA index, respectively. Secondly, the effects of AM and menopause status were tested together in one single model. Finally, models including the interaction term were tested. All models adjust for the confounding factors in model 3.

All data analyses were performed with the SPSS 25.0 statistical software packages and R software version 3.3.1. The significance level was set at a two-tailed probability (*P*) value < 0.05. When a trend of interaction effect was observed, the regression estimates of menopause status were plotted with their 95% CI as a function of menarche age in the interaction plot. The R-package Interplot was used to depicting interaction plots.

Results

Basic characteristics of the participants

Of the 23138 participants, the mean age was 54.9 years. There were 8010 premenopausal women (34.6%) and 15128 postmenopausal women (65.4%) in this study. Compared to non-T2DM women, those who had T2DM were, on average, older, less educated, with lower income and physical activity, higher BMI and more likely to have family history of diabetes (Table 1). Current smokers were not found to be related to T2DM (P >0.05). Women in later menarche age ware older, had a lower BMI and FPG than those in the reference group (data not shown).

Association of AM with FPG, HOMA2-IR and HOMA2-ß

Table 2 showed the associations of menarche age with FPG, HOMA2-IR and HOMA2-ß. After adjusting multiple variables in model 3, each 1-year increase in menarche was associated with a 0.023 mmol/l lower FPG (95% CI: -0.032, -0.013, P < 0.001), 1.0% lower HOMA2-IR (95% CI: -0.015, -0.005, P < 0.001) but no significant association with HOMA2-ß. Furthermore, the later onset of menarche (≥18) was associated with a 0.107 mmol/L (95% CI: -0.171, -0.042) lower FPG and 3.6% lower HOMA2-IR (95% CI: -0.070, -0.002) versus the reference group (16 years). After adjusting for age in model 1, later menarche was associated with a 2.189 higher HOMA2-ß (95% CI: 0.186, 4.193, P =0.032), however, the association was not significant when we further adjusted other confounders (P >0.05).

AM and T2DM

Logistic regression results for the association of AM with T2DM are displayed in Figure 1. After adjusting multiple variables in model 3, each one-year higher menarche age was associated with 5.5% reduction in T2DM presence (95% CI: 0.924, 0.966, $P<0.001$). Furthermore, women who experienced menarche in later age ≥ 18 years had a 17.7% lower risk for T2DM (95% CI: 0.712, 0.951, $P=0.008$). However, the identified association was no longer significant after further adjusting for BMI (OR=0.884, 95% CI: 0.764, 1.024, $P=0.099$).

Interaction effect of AM, menopause status and T2DM

Table 3 showed the association between AM and T2DM was similar across all participant subgroups with no significant interactions between BMI, smoking status and physical activity, however, this changed when the menopause status was included. There was a significant interaction effect between menarche age, menopause status and T2DM ($P_{interaction}=0.004$). Generalized linear model was performed using analysis with and without the interaction term of AM and menopause status (Table 4). The effects of menopause status on the FPG and HOMA index were plotted as a function of menarche age. Figure 2 visualizes how increasing menarche age modify the effect of menopause status on FPG and HOMA2-IR. The gray part of the plot represents the 95% CI of the estimated effect of menopause status on FPG and HOMA index at different menarche age. There were statistically significant effects of AM and menopause status on FPG in analyses no matter whether entering the model alone or together. This changed when the interaction term was introduced. There was no significant association between menarche age and FPG, however, the AM-menopause interaction was statistically significant for FPG ($P_{interaction}$ =0.002). According to the model, for every 1 year increase in menarche age the adverse health effect of menopause status on FPG is reduced by 3.4%. Moreover, the trends toward significance means that the significance of the main menopause status effect should be interpreted for specific menarche age. Based on our results, the harmful effect of menopause status on FPG was decreased along with the increase of menarche age, with the effective range of menarche age was less than 18 years. At later menarche (≥ 18 years), the effect of menopause status on FPG may not be statistically significant as before (Figure 2 (A)). There were significant effects of AM and menopause status on HOMA2-IR in models excluding the interaction term. The association was modified when the interaction term was included. Although the *P* value of AM and menopause status on HOMA2-IR was not statistically significant ($P_{interaction}$ >0.05), an interaction was also observed between 9-19 years old (Figure 2

(B)). In this range, the unfavorable effect of menopause status on HOMA2-IR was weaken along with the menarche age delay. Neither the models nor the interaction plot could detect an interaction effect of AM and menopause status on HOMA2-ß ($P_{interaction}$ >0.05, plot not shown).

Discussion

In this large population-based study, we evaluated the associations between menarche age, and the interaction effect of AM and menopause status on T2DM. To our knowledge, this is the first study to examine the interact effect of menarche age and menopause status on FPG and HOMA index among rural Chinese women. As menarche age increased women had lower values of FPG and HOMA2-IR. Later menarche (≥18 years) was negatively and significantly associated with T2DM after adjusting for multiple variables. After further adjustment for BMI, the association was attenuated, suggesting that BMI may mediate the association. We found a significant interaction between menarche age and menopause status on T2DM. More importantly, the adverse health effect of menopause status on FPG and HOMA2-IR was decreased along with the increase of menarche age, with the ranges of menarche age was restricted to <18 years and 9-19 years, respectively.

Our findings were consistent with the previous studies that had reported that later menarche was associated with lower glucose, obesity, diabetes and CVD risk (6,13,20,21). Later menarche was negatively associated with T2DM after adjustment the confounders in model 3, however, the association was no longer significant with further control for BMI. Our results strengthen the hypothesis that the association may be largely mediated by BMI (3,5). Unlike other studies (22,23), we did not find that early menarche was associated with an increased risk of T2DM. The reasons for the inconsistent results were unknown and possibly a result of difference in participants' characteristics, sample size, race and menarche age grouping. Evidence from a few studies in Asia, particularly conducted on Chinese women, where most of them had experienced their first menstrual period during their later teenager years (mean age at menarche over 16 years) suggested that the association may differ from that in western populations, for reasons that are not properly understood (6,24).

Of note, in our study there was a statistically significant interaction between menarche age and menopause status, which has not been found in other studies (3,25). Our data indicated that per 1-year increase in menarche age, the adverse health effect of menopause status on FPG was decreased by 3.4%. However, the harmful effect decreased with increasing menarche age, with a limited menarche range of less than 18 years old. At later menarche (≥ 18 years), the decreased effect of menopause status on FPG may not be as obvious as before. Furthermore, even though no statistically significant association was observed, the interaction of the two traits on HOMA2-IR was presented between 9-19 years. The unfavorable effect of menopause status was weakened with the delay of menarche. In contrast to our study, no such association was found in other studies (26,27), perhaps because these other studies were restricted to the premenopausal/postmenopausal women. However, consistent with these studies (3,5), we found that there was no statistically significant interaction between BMI, smoking status, or physical activity and menarche age. The ARIC study, a prospective cohort of 15792 participants in the USA aged 45-65 from four communities, found a significant interaction between early menarche age and race for prevent diabetes (4). In our study participants were selected from rural areas of China, and the lack of racial differences may be the cause of the inconsistent results.

Although the mechanisms underlying the interaction of menarche age and menopause status are unknown, they may be related to hormones and obesity later in life. Early menarche is associated with higher cumulative exposure to estradiol and progesterone. Progesterone suppresses the expression of insulin-secreting cell proliferation (28), insulin release and glucose transport 4 (29,30), leading to increased insulin resistance (31) and elevated fasting blood glucose, eventually developing into diabetes. Previous studies also showed that estradiol is associated with insulin resistance (32) and an increased risk of T2DM (33,34). In the current study, menarche age was negatively associated with FPG and HOMA2-IR, while BMI mediate the association. Furthermore, women with early menarche was also related to higher BMI and early menopause, as well as lower sex hormone-binding globulin (SHBG), which were established risks for T2DM (35,36). A Mendelian Randomization Study reported a significant positive association between higher BMI and risk of T2DM (37). In addition, evidence from a follow-up study indicated that women with later menarche age were more likely to have lower BMI and to be less obese (38). With increasing menarche age women are more likely to have a lower FPG, BMI and a later menopause age, which may decrease the unfavorable effect of menopause status on T2DM. Further research is required to explore the related mechanisms of the menarche age-menopause status interaction on T2DM.

The strengths of the present study included the first time to depicted the dynamic trends of the interact association between menarche age and menopause status on T2DM. Although previous studies have explored the effect, no significant association was found. A second strength is that the study had a large sample sizes of 23138 participants, from premenopausal women to postmenopausal women, covering a wide age span. In addition, the study design encompassed a comprehensive evaluation of known and underlying confounding factors, and even adjusting for the potential mediating effect of BMI, we consider the results reliable. However, several limitations for this study should be considered. First, the cross-sectional study is limited in its ability to infer whether a causal association exist. Second, participants did not undergo an oral glucose tolerance test (OGTT), which may underestimate the prevalence of

T2DM. Due to its convenience, acceptability and cost-effectiveness, however, FPG was more commonly used than OGTT in large-scale epidemiological researches. Third, because menarche age and menopause status were retrospectively assessed by recall, misclassification is likely in some instances. However, it has been demonstrated that menarche age and menopause status were well-recalled into adulthood, with the information exhibiting a high correlation with prospectively assessed childhood data (39). Furthermore, any misclassification would be expected to be no difference with the status of T2DM.

Conclusions

In this study, later menarche was associated with a lower risk of T2DM, and the association appears to be mediated by BMI. There was a significant interaction of menarche age and menopause status on T2DM. With the increase of menarche age, the adverse health effect of menopause status on T2DM was decreased in Chinese rural adults. Further studies are needed to confirm the finding and explore the mechanisms of the interaction effect.

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L.L.L and S.N.H. conceived and designed the study. L.L.Z., Y.Q.L., X.K.D., W.Z., C.J.W, Z.X.M, X.Y. and M.Y.F. accomplished data collection and provided critical revision of the manuscript. L.L.Z, X.K.D. and W.Z conducted the analyses. L.L.Z. drafted the manuscript. All authors have read and approved the final manuscript. We thank all subjects who participated in this study. We are also grateful for the research team who contributed to the laboratory measurement and data collection. Thanks to anonymous reviewers for their valuable comments and suggestions, which have helped us to improve the present paper.

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Figure legends

Figure 1. OR and 95% CI for T2DM by category of age at menarche. Results presented are ORs for T2DM in each menarche age group compared with the reference category (16 years). Model 1 was adjusted for age, and further adjusted for education level, physical activity, smoking status, alcohol drinking, average monthly individual income and family history of diabetes (model 2). Model 3 was additionally adjusted for parity and prior or current use of oral contraceptive pills. Model 4 adjusted for the covariates in model 3 and also BMI.

Figure 2 (A-B). Regression estimates of menopause status on FPG (A) and HOMA2-IR (B) as a function of age at menarche. The gray part of the plot represents the 95% CI of the estimated effect of menopause status on FPG and HOMA index at different menarche age. Adjusted for age, education level, smoking status, alcohol drinking, average monthly individual income, physical activity, family history of diabetes, parity, and prior or current use of oral contraceptive pill.

Table legends

Table 1. Basic characteristics of the participants according to T2DM status

Table 2. The association between age at menarche with FPG, HOMA2-IR, and HOMA2-ß

Table 3. Subgroup analyses of the association between age at menarche and T2DM according to potential risk factors.

Table 4. Estimated effects of AM (years), Menopause status and their interaction on FPG, HOMA2-IR, and HOMA2-ß.

Figure 1

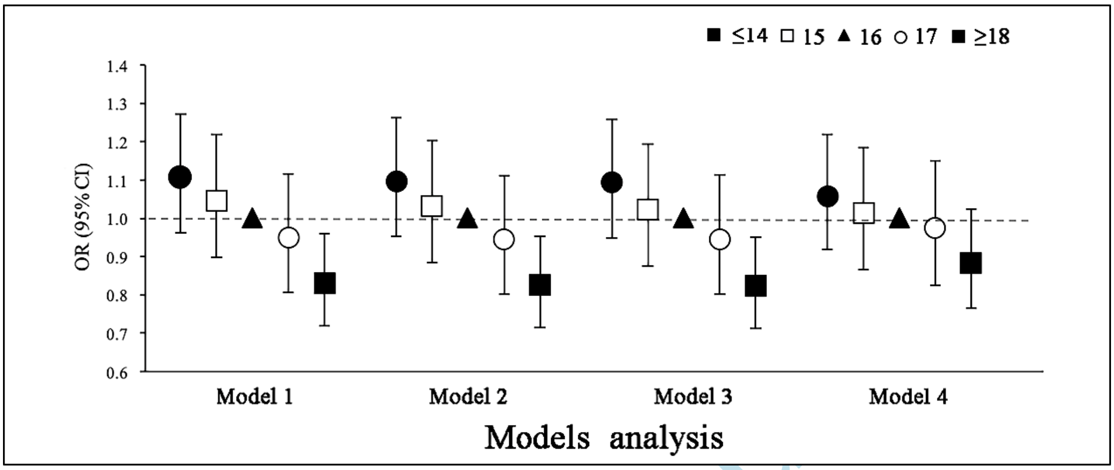
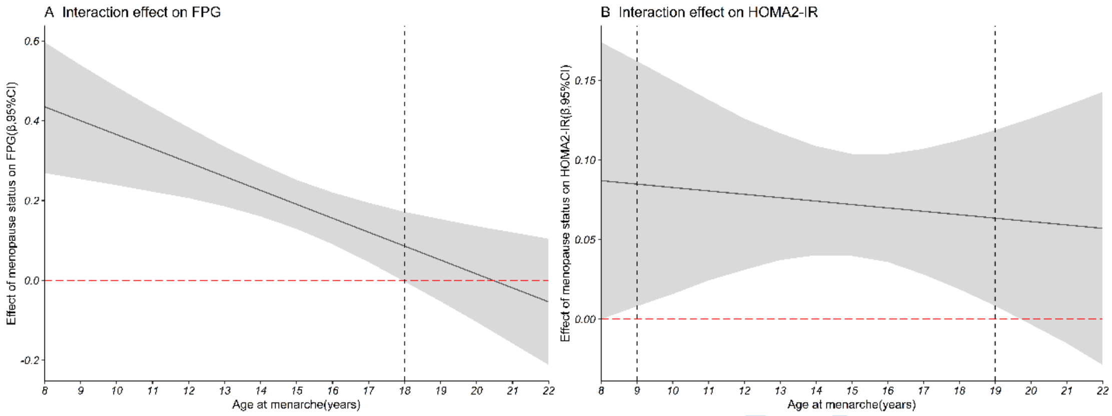

■ ≤14 □ 15 ▲ 16 ○ 17 ■ ≥18
OR (95% CI)
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
Model 1
Model 2
Model 3
Model 4
Models analysis

Figure 2



A Interaction effect on FPG
Effect of menopause status on FPG(β,95%CI)
0.6
0.4
0.2
0.0
-0.2
8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Age at menarche(years)
B Interaction effect on HOMA2-IR
Effect of menopause status on HOMA2-IR(β,95%CI)
0.15
0.10
0.05
0.00
8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Age at menarche(years)

Table 1 Basic characteristics of the participants according to T2DM status

Characteristics	Non-T2DM (n=20904)	T2DM (n=2234)	*P*
Age(years), mean ±SD	54.3±12.1	60.9±8.9	<0.001
BMI(kg/m^2), mean ±SD	24.9±3.6	26.3±3.8	<0.001
Education level, n (%)			<0.001
Elementary school or below	10493(50.2)	1525(68.3)	
Junior high school	7719(36.9)	569(25.5)	
High school or above	2692(12.9)	140(6.3)	
Average monthly individual income, n (%)			<0.001
<500 RMB	7247(34.7)	905(40.5)	
500~ RMB	7073(33.8)	721(32.3)	
>1000 RMB	6584(31.5)	608(27.2)	
Physical activity, n (%)			<0.001
Low	6125(29.3)	819(36.7)	
Moderate	9346(44.7)	906(40.6)	
High	5433(26.0)	509(22.8)	
Current regular smokers, n (%)	51(0.2)	8(0.4)	0.309
Current regular drinking, n (%)	566(2.7)	32(1.4)	<0.001
Family history of diabetes, n (%)	841(4.0)	214(9.6)	<0.001
Age at menarche(years), n (%)			<0.001
≤14	7068(33.8)	621(27.8)	
15	3657(17.5)	381(17.1)	
16	3436(16.4)	371(16.6)	
17	2503(12.0)	305(13.7)	
≥18	4240(20.3)	556(24.9)	
Menopause status, n (%)			<0.001
Premenopausal	7694(36.8)	316(14.1)	
Postmenopausal	13210(63.2)	1918(85.9)	
Use of oral contraceptive pills, n (%)	567(2.7)	26(1.2)	<0.001
Parity, n (%)			<0.001
0	192(0.9)	12(0.5)	

1-2	13179(63.2)	1095(49.0)
≥3	7498(35.9)	1127(50.4)

Abbreviations: BMI, body mass index.

Table III Subgroup analyses of the association between age at menarche and T2DM according to potential risk factors.

Subgroup	Total/cases	Adjusted *OR* (95% *CI*) [a]	$P_{\text{for interaction}}$
BMI			0.603
Obesity/overweight	13745/1610	0.961(0.936-0.987)	
Normal/underweight	9326/615	0.949(0.911-0.989)	
Menopause status			0.004
Premenopausal	8010/316	0.977(0.915-1.043)	
Postmenopausal	15128/1918	0.943(0.921-0.966)	
Smoking status			0.280
Non-smokers	23079/2226	0.946(0.925-0.967)	
Smokers	59/8	0.966(0.602-1.550)	
Physical activity			0.552
Low	6944/819	0.955(0.920-0.991)	
Moderate	10252/906	0.931(0.899-0.964)	
High	5942/509	0.957(0.915-1.002)	

a: Model adjusted for age, smoking status, alcohol consumption, average monthly individual income, education level, physical activity, family history of diabetes, parity, use of oral contraceptive pills.

Table IV Estimated effects of AM (years), Menopause status and their interaction on FPG, HOMA2-IR, and HOMA2-ß

	AM (years)		MS_S	
outcome	ß (95%CI)	*P*	ß (95%CI)	*P*
FPG				
AM	-0.023 (-0.032, -0.013)	<0.001		
MS_S			0.183(0.122, 0.245)	<0.001
AM+ MS_S	-0.023(-0.033, -0.013)	<0.001	0.185(0.123, 0.246)	<0.001
AM+MS_S + AM-MS_S	0.002(-0.018, 0.022)	0.802	0.696(0.367, 1.025)	<0.001
HOMA2-IR				
AM	-0.010(-0.015, -0.005)	<0.001		
MS_S			0.066(0.033, 0.098)	<0.001
AM+ MS_S	-0.010(-0.015, -0.005)	<0.001	0.066(0.034, 0.099)	<0.001
AM+MS_S + AM-MS_S	-0.008(-0.018, 0.002)	0.107	0.104(-0.068, 0.276)	0.240
HOMA2-ß				
AM	0.112(-0.193, 0.418)	0.471		
MS_S			-1.200(-3.107, 0.708)	0.218
AM+ MS_S	0.115(-0.191, 0.420)	0.463	-1.208(-3.115, 0.700)	0.215
AM+MS_S + AM-MS_S	-0.220(-0.802, 0.362)	0.460	-7.961(-18.171, 2.249)	0.126

Estimates were obtained using generalized linear model.

All models adjusted for age, education level, physical activity, smoking status, alcohol drinking, average monthly individual income and family history of diabetes, parity and prior or current use of oral contraceptive pills.

Table 2 The association between age at menarche with FPG, HOMA2-IR, and HOMA2-ß

	Model 1	Model 2	Model 3
Outcome	*ß* (95% *CI*)	*ß* (95% *CI*)	*ß* (95% *CI*)
FPG			
≤14	0.017(-0.042, 0.076)	0.011(-0.048, 0.069)	0.010(-0.049, 0.068)
15	0.014(-0.052, 0.080)	0.010(-0.056, 0.076)	0.008(-0.058, 0.073)
16	Reference	Reference	Reference
17	-0.027(-0.099, 0.046)	-0.030(-0.102, 0.042)	-0.030(-0.102, 0.043)
≥18	-0.101(-0.165, -0.036) *	-0.104(-0.168, -0.040) *	-0.107(-0.171, -0.042) *
Continuous	-0.023(-0.033, -0.013) *	-0.022(-0.032, -0.013) *	-0.023((-0.032, -0.013) *
HOMA2-IR			
≤14	0.013(-0.018, 0.044)	0.014(-0.016, 0.045)	0.013(-0.018, 0.044)
15	-0.003(-0.038, 0.031)	-0.004(-0.039, 0.030)	-0.004(-0.039, 0.030)
16	Reference	Reference	Reference
17	-0.015(-0.053, 0.023)	-0.018(-0.057, 0.020)	-0.018(-0.056, 0.020)
≥18	-0.028(-0.062, 0.006)	-0.035(-0.068,0.001)	-0.036(-0.070, -0.002) *
Continuous	-0.009(-0.014, -0.004) *	-0.010(-0.015, -0.005) *	-0.010(-0.015, -0.005) *
HOMA2-ß			
≤14	0.432(-1.390, 2.255)	0.749(-1.069, 2.567)	0.709(-1.111, 2.529)
15	-0.474(-2.517, 1.569)	-0.396(-2.433, 1.641)	-0.380(-2.419, 1.658)
16	Reference	Reference	Reference
17	0.885(-1.367, 3.138)	0.734(-1.512, 2.980)	0.731(-1.517, 2.978)
≥18	2.189(0.186, 4.193) *	1.805(-0.195, 3.805)	1.764(-0.238, 3.766)
Continuous	0.227(-0.078, 0.532)	0.112(-0.193, 0.417)	0.112(-0.193, 0.418)

*: P <0.05.

FPG, fasting plasma glucose; HOMA2-IR, Homeostasis model assessment (HOMA)-2 insulin resistance; HOMA2-ß, Homeostasis model assessment (HOMA)-2 of ß-cell function.

Model 1: adjusted for age;

Model 2: model 1+ smoking, alcohol drinking, average monthly individual income, education level, physical activity, family history of diabetes;

Model 3: model 2+ parity, use of oral contraceptive pills.