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Duration of Reproductive Period and Metabolic Syndrome and its Components: Findings from the Henan Rural Cohort Study in Menopausal Women

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Abstract

Purpose

The main purpose of this study was to examine the association between the duration of the reproductive period and metabolic syndrome (MetS) as well as its individual components within a rural population.

Methods

In all, 14596 menopausal women were enrolled from the Henan Rural Cohort study. Logistic regression and linear regression were used to evaluate the association between the duration of reproductive period and MetS and its components. Furthermore, the mediation and interaction effects were assessed by the utilization of mediation analyses and generalized linear model techniques.

Results

Each year of increased reproductive period correlated with an increased risk of MetS ($P < 0.05$). This association changed slightly after adjusting for body mass index (BMI) and remained statistically significant A positive association between the duration of reproductive period and central obesity, abnormal FPG, abnormal BP, abnormal TG, and abnormal HDL-C were revealed (all $P < 0.05$). The relationship with abnormal and abnormal TG were attenuated after adjusting for BMI and remained statistically significant except for central obesity, abnormal BP and abnormal HDL-C. In addition, BMI mediated the relationship between the duration of reproductive period and MetS and its components.

Conclusions

The longer duration of reproductive period might raise a woman's risk of MetS and its components. More importantly,

the association was largely mediated by BMI.

Trial Registration
The Henan Rural Cohort Study has been registered at the Chinese Clinical Trial Register (Registration number: ChiCTR-OOC-15006699). Date of registration: 2015-07-06. http://www.chictr.org.cn/showproj.aspx?proj=11375.

Keywords: Duration of Reproductive Period, Metabolic Syndrome, Body Mass Index, Mediation Effect, Menopausal Women

List of Abbreviations

- MetS: Metabolic syndrome.
- CVD: Cardiovascular disease.
- AAM: Age at menarche.
- BMI: Body mass index.
- IPAQ: International Physical Activity Questionnaire.
- WC: Waist circumference.
- BP: Blood pressure.
- FPG: Fasting plasma glucose.
- TG: Triglycerides.
- TC: Total cholesterol.
- HDL-C: High-density lipoprotein cholesterol.
- IDF: The International Diabetes Federation.

Introduction

Metabolic syndrome (MetS) is a group of metabolic disorders, including insulin resistance, hyperglycemia, central obesity, hypertension, and dyslipidemia, which may increase the risk of cancer, diabetes, polycystic ovary syndrome, cardiovascular disease (CVD), and kidney diseases [1-10]. Between 10 and 50 percent of people globally are affected by MetS, and its incidence has been on the rise both domestically and internationally in recent years, 64 million people are suffering from MetS in China, with a significantly higher incidence in women than in men (32.3 vs. 30.0%) [11-14].

After adjusting for confounding factors common to both males and females, including age, geographic location, race, lifestyle habits, and genetic predispositions, it becomes apparent that the gender disparity in MetS is influenced by specific reproductive characteristics in women. Several studies have highlighted the correlation between MetS and reproductive variables, such as parity, age at first pregnancy, age at menarche [9,15,16]. The onset of menarche and menopause represent critical life milestones for women [17]. Prolonged exposure to hormonal fluctuations throughout the reproductive period may contribute to an increased risk of CVD, and breast cancer [18,19].

Several studies have identified early menarche and menopause as distinct risk factors for MetS [20-23]. However, limited research has specifically explored the relationship between MetS and the duration of the reproductive period. This gap in the literature motivated our investigation into the association between the duration of the reproductive period and MetS, along with its components, in menopausal women from rural areas characterized by diverse lifestyles. Furthermore, epidemiological evidence indicates that the risk of MetS increases with body mass index (BMI), with higher rates of MetS observed in obese women [24,25]. The present study expands on this by assessing the potential contribution of BMI to the risk of MetS.

Methods

Study Design and Participants

This study conducted a cross-sectional analysis using baseline data from the Henan Rural Cohort, established in five rural areas of Henan Province, China, between July 2015 and September 2017. The cohort survey achieved a response rate of 93.7%, with permanent residents aged 18 to 79 years being surveyed. Detailed information regarding the study design, sampling methods, and data collection procedures has been published elsewhere [26]. The analysis focused on postmenopausal women, with a total of 15,482 participants initially included. Participants were excluded based on the following criteria: (1) Those with age at menarche (AAM) < 8 or > 22 years (n = 166), and those with age at menopause < 40 or > 60 years (n =1), which may indicate an abnormal physiological age [27,28]. (2) Those without the information that we need to analyze (n = 172). After exclusions, 14,596 participants remained in the final sample. The study protocol was approved by the Zhengzhou University Life Science Ethics Committee, and informed consent was obtained from all participants.

Covariates Variables

This study encompasses three key components: a questionnaire, a physical examination, and laboratory tests. The educational level category was divided into three groups: primary school or lower, junior high school, and high school or higher. Per capita monthly income was classified into three categories: <500 RMB, 500–999 RMB, and ≥1000 RMB. Participants who consumed alcohol at least 12 times per year were considered current drinkers. Current smokers were

defined as individuals who smoked at least one cigarette per day for a minimum of six months [29]. Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ), which classifies activity levels into low, moderate, and high [30]. Adequate fruit and vegetable intake were defined as consumption exceeding 500 g per day, while a high-fat diet was characterized by daily consumption of 75 g or more of meat from livestock and poultry [31].

A consistent and standardized protocol was followed by qualified and experienced examiners to collect all anthropometric measurements. Participants were measured while standing with their feet together, their upper back in contact with a wall, arms at their sides, and shoes removed. Weight was recorded with participants wearing only a lightweight gown and underwear. Waist circumference (WC) was measured at a point 1.0 cm above the navel, with participants in light clothing. Blood pressure (BP) was measured using an electronic sphygmomanometer (Omron HEM-7071A, Japan), with three readings taken while the subject was seated after 5 minutes of rest to ensure accuracy. Prior to BP measurement, participants were instructed to refrain from smoking, consuming alcohol, drinking caffeinated beverages, and exercising for at least 30 minutes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. After an overnight fast of at least 8 hours, venous blood samples were collected to measure fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) levels using a Cobas c501 analyzer (Roche, Switzerland).

Definition of MetS

The definition of MetS provided by the International Diabetes Federation (IDF) was utilized in this study [32]. Participants were classified as having MetS if they exhibited central obesity, defined by a WC of ≥ 90 cm for men or ≥ 80 cm for women, along with two or more of the following risk factors: (1) Abnormal TG: TG levels ≥ 1.7 mmol/L; (2) Abnormal HDL-C: HDL-C levels < 1.04 mmol/L for men and < 1.3 mmol/L for women; (3) Abnormal FPG: FPG levels ≥ 5.6 mmol/L or the use of anti-diabetic medication; (4) Abnormal BP: BP ≥ 130/85 mmHg or the use of antihypertensive medication.

Group of Reproductive Ages

The duration of the reproductive period is defined as the number of years between menarche and menopause [33]. In this study, postmenopausal women were categorized into three groups based on tertiles of key characteristics relevant to the analysis, these included: duration of the reproductive period (18-31 years, 32-35 years, and 36-49 years), age at menarche (8-15 years, 16-17 years, and 18-22 years), and age at menopause (40-48 years, 49-51 years, and 52-60 years) [23].

Statistical Analysis

The study results for continuous variables are presented as means ± standard deviations, while categorical variables are expressed as frequencies and percentages for each subgroup. To assess demographic and reproductive age differences between groups, Student's t-test and the Chi-square test were employed. Adjusting for BMI in the models was essential, as BMI may act as an intermediary factor in the relationship between the duration of the reproductive period and MetS. Two models were constructed: Model 1, which was adjusted for age, education level, per capita monthly income, physical activity, adequate vegetable and fruit intake, high-fat diet, and parity; and Model 2, which included the adjustments from Model 1, in addition to BMI. To further examine whether BMI mediated the relationship between MetS and the duration of the reproductive period and its components, a mediation analysis was conducted. A generalized linear model was utilized to assess the interactions between high-risk factors and the duration of the reproductive period. Statistical analyses were performed using SPSS software version 26.0 and R version 4.0.0. A P-value of < 0.05 (two-tailed) was considered statistically significant.

Results

Basic Characteristics of the Study Population

Variables	**Duration of reproductive period (years)**			P_{trend} [a]
	18~31	32~35	36~49	
N (%)	4933(33.80)	5338(36.60)	4325(29.60)	
Age (year)	62.63±8.12	61.15±7.63	60.85±6.71	<0.001
Educational level				<0.001
Elementary school or below	3523(37.50)	3388(36.06)	2484(26.44)	
Middle school	1144(28.37)	1517(37.61)	1372(34.02)	
High school or above	266(22.77)	433(37.07)	469(40.16)	
Per capital monthly income (RMB)				<0.001
~499	2171(36.73)	2062(34.88)	1678(28.39)	
500~999	1507(32.19)	1772(37.85)	1403(29.97)	
1000~	1255(31.35)	1504(37.57)	1244(31.08)	

Physical activity				<0.001
Low	1599(35.84)	1633(36.60)	1230(27.56)	
Moderate	2014(32.12)	2316(36.93)	1941(30.95)	
High	1320(34.17)	1389(35.96)	1154(29.87)	
Current smokers	18(39.13)	17(36.96)	11(23.91)	0.114
Current drinking	100(33.78)	98(33.11)	98(33.11)	0.612
Vegetable and fruit [b]	1827(32.22)	2097(36.98)	1747(30.80)	0.005
High-fat diet (yes)	536(31.20)	618(35.97)	564(32.83)	0.005
BMI (kg/m2)	24.72±3.67	25.12±3.54	25.50±3.54	<0.001
Age at menarche (years)	17.16±2.13	16.17±1.88	14.91±1.88	<0.001
Age at menopause (years)	45.50±3.00	49.72±2.00	52.92±2.49	<0.001
Contraceptive pills (yes)	76(31.54)	98(40.66)	67(27.80)	0.413
Parity	2.55±0.50	2.47±0.51	2.47±0.51	<0.001
WC (cm)	83.52±10.38	84.24±10.01	85.19±9.98	<0.001
SBP (mmHg)	130.72±20.90	131.10±20.78	131.36±20.30	0.330
DBP (mmHg)	77.52±11.46	78.51±11.38	78.91±11.17	<0.001
FPG (mmol/L)	5.69±1.60	5.70±1.61	5.75±1.63	0.216
TC (mmol/L)	4.99±0.99	5.05±1.02	5.03±0.98	0.006
TG (mmol/L)	1.75±1.11	1.79±1.11	1.84±1.25	0.002
HDL-C (mmol/L)	1.38±0.34	1.38±0.34	1.35±0.33	<0.001
LDL-C (mmol/L)	3.03±0.83	3.07±0.85	3.05±0.83	0.068
History of lactation (yes)	4826(33.73)	5237(36.60)	4246(29.67)	0.440

Table 1: Demographic Characteristics of Participants Stratified by Duration of Reproductive Period

Chi-square test or ANOVA test; [b], Adequate vegetable and fruit intake(yes). RMB, Renminbi; BMI, Body mass index; weight (kg)/height (m)^2; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; TC, total cholesterol, MetS, metabolic syndrome. Values are means and standard deviation (mean ± SD) for continuous variables, and numbers and percentages (n (%)) for categorical variables.

The demographic characteristics of the participants are presented in Table 1. Among the 14,596 women included in the study, the average age at menopause was 49.24 ± 3.89 years, with a mean age of 61.56 ± 7.58 years and an average reproductive period of 33.11 ± 4.34 years. The average age at menarche was 16.13 ± 2.16 years. Of the participants, 42.79% were found to have MetS. Statistically significant differences were observed between the three reproductive period groups in terms of age, educational level, per capita monthly income, physical activity, vegetable and fruit intake, high-fat diet, BMI, age at menarche, age at menopause, parity, WC, DBP, total TC, TG, and HDL (all $P < 0.05$, with P for trend < 0.05). Women with a longer reproductive period were generally younger, had fewer children, higher education levels, lower vegetable and fruit intake, a higher fat diet, lower HDL-C levels, and later age at menarche. Additionally, they tended to have higher BMI, WC, TG, TC, DBP, and age at menopause (all $P < 0.05$).

Association Between Duration of Reproductive Period with Metabolic Syndrome and Its Components

	Duration of reproductive period [a]	**Duration of reproductive period** [b]		
		18~31	**32~35**	**36~49**
Central obesity				
Model 1	1.033(1.025, 1.041) *	Ref.	1.169(1.077, 1.270) *	1.386(1.268, 1.515) *
Model 2	0.995(0.983,1.007)	Ref.	0.958(0.849, 1.080)	0.943(0.829, 1.073)
Abnormal FPG				
Model 1	1.016(1.008, 1.025) *	Ref.	1.042(0.960, 1.131)	1.134(1.040, 1.236) *
Model 2	1.009(1.000, 1.017) *	Ref.	1.001(0.920, 1.089)	1.046(0.957, 1.142)
Abnormal BP				
Model 1	1.019(1.011, 1.027) *	Ref.	1.136(1.049, 1.231) *	1.206(1.109, 1.312) *
Model 2	1.008(0.999, 1.016)	Ref.	1.080(0.994, 1.173)	1.083(0.992, 1.181)
Abnormal TG				

Model 1	1.022(1.014, 1.030) *	Ref.	1.094(1.011, 1.184) *	1.246(1.146, 1.355) *
Model 2	1.013(1.005, 1.021) *	Ref.	1.048(0.967, 1.137)	1.140(1.047, 1.243) *
Abnormal HDL-C				
Model 1	1.013(1.006, 1.021) *	Ref.	0.993(0.917, 1.074)	1.162(1.069, 1.262) *
Model 2	1.004(0.996, 1.012)	Ref.	0.944(0.871, 1.024)	1.055(0.968, 1.149)
MetS				
Model 1	1.031(1.023, 1.039) *	Ref.	1.139(1.051, 1.233) *	1.375(1.264, 1.495) *
Model 2	1.012(1.003, 1.021) *	Ref.	1.032(0.941, 1.131)	1.144(1.039, 1.260) *

Table 2: Ors (95% cis) for Metabolic Syndrome and its Components According to the Duration of Reproductive Period in Rural Chinese Women

Data are odds ratios (95% confidence intervals). [a], continuous variable; [b], classified variable; *, $P < 0.05$.

FPG, fasting plasma glucose; BP, blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein; MetS, metabolic syndrome.

Model 1: adjusted for age, educational level, per capita monthly income, physical activity, adequate vegetable and fruit intake, high-fat diet, and parity;

Model 2: adjusted as in model 1 plus BMI.

Linear and logistic regression analyses were conducted to evaluate the relationship between reproductive period duration and MetS, along with its components, as presented in Table 2. Each additional year of reproductive duration was associated with an increased risk of MetS (OR = 1.031; 95% CI = 1.023-1.039; P < 0.05) in Model 1. This association was slightly attenuated after adjusting for BMI (Model 2), but remained statistically significant (OR = 1.012; 95% CI = 1.003-1.021). Among the individual components of MetS, a positive correlation was observed between reproductive period duration and central obesity (OR = 1.033; 95% CI = 1.025-1.041), abnormal FPG (OR = 1.016; 95% CI = 1.008-1.025), abnormal BP (OR = 1.019; 95% CI = 1.011-1.027), abnormal TG (OR = 1.022; 95% CI = 1.014-1.030), and low HDL-C (OR = 1.013; 95% CI = 1.006-1.021). The associations with abnormal FPG (OR = 1.009; 95% CI = 1.000-1.017) and abnormal TG (OR = 1.013; 95% CI = 1.005-1.021) were slightly weakened after BMI adjustment (Model 2), yet remained statistically significant, except for central obesity, abnormal BP, and low HDL-C. Reproductive period duration was positively associated with the risk of MetS, with ORs (95% CI) of 1.000, 1.139 (1.051-1.233), and 1.375 (1.264-1.495) for women with reproductive durations of 18-31 (reference), 32-35, and 36-49 years, respectively, in Model 1 (P < 0.05). After adjusting for BMI (Model 2), this relationship was attenuated. Compared to the reference group, the ORs for central obesity, abnormal FPG, abnormal BP, abnormal TG, and abnormal HDL-C were 1.386 (95% CI = 1.268-1.515), 1.134 (95% CI = 1.040-1.236), 1.206 (95% CI = 1.109-1.312), 1.246 (95% CI = 1.146-1.355), and 1.162 (95% CI = 1.069-1.262) in women with a reproductive period of 36-49 years in Model 1. After BMI adjustment (Model 2), the association with abnormal TG remained statistically significant, with an OR of 1.140 (95% CI = 1.047-1.243).

The relationship between MetS and its components with age at menarche and menopause is presented in Table S1. In Model 1, age at menarche was inversely associated with MetS, central obesity, abnormal FPG, abnormal BP, abnormal TG, and abnormal HDL-C (P for trend < 0.05). After further adjustment for BMI in Model 2, the only significant association observed was with abnormal FPG (P for trend = 0.017). Regarding age at menopause, a later age was associated with an increased risk of MetS and its components, including central obesity, abnormal BP, and abnormal TG, in Model 1 (P for trend < 0.05). No significant association was found between age at menopause and abnormal FPG or abnormal HDL-C (P for trend = 0.627 and 0.188, respectively).

Mediating Role of Body Mass Index

Figure 1 illustrates a model depicting the relationship between the duration of the reproductive period and MetS, mediated by BMI. After adjusting for confounding variables, including age, educational level, per capita monthly income, physical activity, adequate intake of vegetables and fruits, high-fat diet, and parity, the total effect of the reproductive period duration on MetS remained significant in the mediation analysis (OR, 1.031; 95% CI, 1.023-1.039; P < 0.001). BMI exerted a notable indirect influence (OR, 1.028; 95% CI, 1.023-1.394; P < 0.001), as well as a significant direct effect (OR, 1.012; 95% CI, 1.003-1.021; P = 0.007) in mediating the relationship between MetS and the duration of the reproductive period. Sensitivity analyses presented in Table S2, which excluded individuals reporting menopause due to disease (n = 760), yielded similar results, reinforcing the association between reproductive period duration and MetS risk. These findings suggest that BMI partially mediates the relationship between reproductive period duration and the risk of MetS.

Table S3 presents the mediation analysis results of BMI in the relationship between reproductive period duration and MetS components. The adjusted direct associations were as follows: 1.009 (95% CI: 1.001-1.017) for abnormal FPG, 1.008 (95% CI: 1.000-1.016) for abnormal BP, 1.004 (95% CI: 1.004-1.012) for abnormal HDL-C, 1.013 (95% CI: 1.005-1.021) for abnormal TG, and 1.005 (95% CI: 1.017-1.007) for central obesity. The adjusted indirect associations

were 1.009 (95% CI: 1.007-1.010) for abnormal FPG, 1.012 (95% CI: 1.010-1.014) for abnormal BP, 1.011 (95% CI: 1.009-1.013) for abnormal HDL-C, 1.010 (95% CI: 1.008-1.012) for abnormal TG, and 1.071 (95% CI: 1.058-1.085) for central obesity. Thus, BMI fully mediates the relationship between reproductive period duration and abnormal BP, abnormal HDL-C, and central obesity. Furthermore, BMI mediates 52.15% of the estimated association between reproductive period duration and abnormal FPG, and 46.47% of the estimated association between reproductive period duration and abnormal TG.

Subgroup Analyses

We further performed stratified analyses to investigate potential modifications, as shown in Figure 2 and Table S4. Upon stratification by high-fat diet, we observed a significant association between the duration of the reproductive period and MetS in individuals not on a high-fat diet. A statistically significant interaction was detected only between the duration of the reproductive period and high-fat diet (P interaction = 0.010). Additionally, no significant differences were found with respect to age, educational level, per capita monthly income, physical activity, adequate vegetable and fruit intake, parity, age at menarche, or age at menopause (all P interaction > 0.05).

Discussion

This study represents the first attempt to evaluate the associations between the reproductive period and MetS and its components in a rural, cross-sectional setting. Overall, the findings suggest that a longer reproductive period is linked to metabolically unfavorable changes after menopause, independent of aging. In this large, population-based cohort study, after adjusting for relevant covariates, we observed that women with a longer reproductive period were at a higher risk for MetS, as well as several of its components, including central obesity, abnormal BP, elevated FPG, low HDL-C, and high TG, among Chinese postmenopausal women in rural areas.

The present study is consistent with previous results [23,34]. Similar finding was reported in another research, which revealed that postmenopausal women from Southeast China who had a longer reproductive period were more likely to have MetS, and this study observed that women with more than 20 years since menopause were more likely to experience MetS and elevated BP when compared with those with less than 10 years since menopause [34]. The relatively small sample size of postmenopausal parous women might be a factor that should be taken into account for the negative results. Our findings were in line with Cao et al [23]. who discovered that a higher risk of MetS was substantially correlated with a longer duration of reproductive period and earlier age at menarche. Cao et al [23]. also found that the highest tertile of years of menstruation was significantly related to elevated WC and elevated TG. Similarly, a study found that early menarche, longer reproductive years, and menopause were significantly associated with increased body fatness among 9097 women aged 25 to 64 in Anhui, China, which may indicate that women's hormones may increase body fat accumulation, and this current study make a further finding that the associations between duration of reproductive period and abnormal BP, abnormal FPG, abnormal HDL-C [16].

The results of the National Health and Nutrition Examination Survey are inconsistent with the observation that a longer duration of reproductive years was associated with a lower risk of cardiovascular and cerebrovascular diseases, and this association was mainly observed in the older women who had a reproductive duration ranging from 36 to 40 years [35]. A conflicting finding from the Women's Health Initiative found that women with short reproductive-period durations (<30 years) had an increased risk of type 2 diabetes [36]. Korean research found that having a prolonged reproductive period was linked to a greater frequency of MetS when age was taken into account, but longer reproductive years were linked with a decreased frequency of MetS controlling for other variables (aspartate aminotransferase, alanine aminotransferase, and white and red blood cell counts) [28]. The inconsistent finding may be due to the differences in study design, geographic location, number of participants and adjustment for confounders. In consideration of the contrary results observed by the aforementioned studies, the effect of the duration of reproductive years on MetS and its components needs to be further explored in studies with a larger sample size.

After further adjustment for BMI, the strength of the association between the duration of reproductive period and MetS and its components were attenuated, which suggested that BMI may mediate the observed association between the duration of reproductive period and MetS and its components. Our findings are consistent with many previous results [37-42]. Prior research has investigated that the longer reproductive period may contribute to high BMI, which may have an impact on metabolic disorders [42]. Research from the China Kadoorie Biobank indicated a high correlation between obesity and the age of menopause and the duration of the reproductive period, and increased adiposity may lead to local insulin resistance and subsequently contribute to systemic insulin resistance [37]. Recently, a study found that BMI partially mediated the relationship between age at menarche and T2DM [38]. The Henan Rural Cohort Study found that the relationship between menarche age and hypertension was mediated by BMI, and BMI was speculated to influence on hypertension through complex interactions between oxidative stress, inflammation, hyperleptinemia, insulin resistance, the renin angiotensin–aldosterone system, and the renal sympathetic nervous system [39,40]. Obesity may raise serum TG levels as one of the acquired causes of hypertriglyceridemia, and it is often associated with an elevation in serum cholesterol [41].

Although the exact mechanisms underlying the association between the duration of the reproductive period and the risk of MetS remain inconclusive, several potential hypotheses have been proposed. First, a longer reproductive period

may reflect a greater cumulative exposure to female hormones, which could contribute to the accumulation of body fat [37-42]. Second, studies have reported that postmenopausal women with longer reproductive periods tend to have higher fat intake and lower levels of physical activity, factors that could lead to weight gain and increased BMI. Specifically, exposure to a high-fat diet has been shown to significantly affect the expansion of visceral adipose tissue, which has been linked to a reduced risk of metabolic dysfunction [43]. Third, the interaction between the duration of the reproductive period and high-fat diet may provide further insight into the observed association. For individuals with longer reproductive periods, lower health literacy and unhealthy lifestyle choices may exacerbate negative effects on metabolic parameters. Additionally, girls with earlier menarche often experience more significant negative changes in insulin levels, blood pressure, and cholesterol, which are associated with the age of menarche and the development of MetS [44]. A potential explanation for this is that childhood obesity, which often leads to hyperinsulinemia, may accelerate sexual maturity and contribute to prolonged elevated blood glucose levels, thus serving as a risk factor for MetS [16]. Furthermore, hormonal shifts occurring during menopause offer another plausible mechanism for the relationship between menopausal age and MetS [45].

Strengths and Limitations

Using data from a large rural cross-sectional study in China, this research aimed to estimate and model the relationship between the duration of the reproductive period and the occurrence of MetS and its components in postmenopausal women, while controlling for socio-demographic factors, anthropometric measures, and reproductive characteristics. A key strength of this study lies in its large sample size and its concurrent assessment of three reproductive factors—duration of the reproductive period, age at menarche, and age at menopause—along with MetS. However, several limitations should be noted. First, as a cross-sectional study, it cannot establish causality between the duration of the reproductive period and MetS in postmenopausal women, necessitating further exploration in well-designed prospective studies. Second, the age at menarche was self-reported, which may introduce recall bias [46]. Nonetheless, previous studies have demonstrated the validity and reliability of self-reported age at menarche and menopause. Third, the duration of the reproductive period was not consistent across all study groups; women with shorter reproductive years were followed for a longer period than those with a longer reproductive duration. This introduces the potential for risk window bias, as the group with a shorter reproductive duration had a longer observation window compared to those with longer reproductive periods.

Conclusion

In conclusion, the present study offers compelling evidence that MetS is more prevalent and associated with an extended reproductive period in postmenopausal women residing in rural China. Furthermore, this association appears to be partially mediated by BMI. To validate these findings and further explore the underlying mechanisms of the interaction effect, additional research is urgently needed.

Ethics Approval

Ethics approval was obtained from the "Zhengzhou University Life Science Ethics Committee", and written informed consent was obtained for all participants. Ethic approval code: [2015] MEC (S128).

Consent for Publication

Consent to Publish declaration. I confirm that the work described in this manuscript has not been published before (except in the form of an abstract or as part of a published lecture, review, or thesis). The author(s) have approved the manuscript and agree with its submission to your esteemed journal. I also agree to the transfer of copyright of this work to the journal.

Availability of Data and Material

The data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

Conflict of Interest

All authors have read and approved this version of the article, and declared that they have no competing or financial interests to disclosure.

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Author Contributions

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Age at menarche (years)					Age at menopause(years)			
	8~15	16~17	18~22	P trend	40~48	49~51	52~60	P trend
Central obesity								
Model 1	Ref.	0.829(0.762, 0.902) *	0.678(0.620, 0.742) *	< 0.001	Ref.	1.061(0.977, 1.151)	1.252(1.148, 1.366) *	< 0.001
Model 2	Ref.	1.046(0.926, 1.182)	1.076(0.945, 1.226)	0.263	Ref.	0.923(0.819, 1.040)	1.015(0.895, 1.150)	0.940
Abnormal FPG								
Model 1	Ref.	0.916(0.845, 0.994) *	0.801(0.733, 0.875) *	< 0.001	Ref.	1.024(0.944, 1.111)	1.020(0.937, 1.109)	0.627
Model 2	Ref.	0.965(0.888, 1.049)	0.894(0.816, 0.978) *	0.017	Ref.	1.000(0.921, 1.086)	0.974(0.894, 1.062)	0.568
Abnormal BP								
Model 1	Ref.	0.987(0.912, 1.069)	0.867(0.796, 0.945) *	0.002	Ref.	1.110(1.026, 1.202) *	1.139(1.049, 1.236) *	0.001
Model 2	Ref.	1.067(0.983, 1.159)	1.012(0.926, 1.107)	0.668	Ref.	1.081(0.996, 1.173)	1.075(0.988, 1.170)	0.076
Abnormal TG								
Model 1	Ref.	0.906(0.837, 0.980) *	0.851(0.782, 0.927) *	< 0.001	Ref.	1.104(1.021, 1.194) *	1.175(1.083, 1.274) *	< 0.001
Model 2	Ref.	0.962(0.888, 1.043)	0.969(0.887, 1.057)	0.434	Ref.	1.080(0.997, 1.170)	1.121(1.031, 1.219) *	0.006
Abnormal HDL-C								
Model 1	Ref.	0.899(0.831, 0.972) *	0.863(0.793, 0.940) *	< 0.001	Ref.	0.986(0.912, 1.066)	1.060(0.978, 1.150)	0.188
Model 2	Ref.	0.957(0.883, 1.038)	0.988(0.905, 1.079)	0.709	Ref.	0.958 (0.884, 1.038)	1.004(0.923, 1.091)	0.985
MetS								
Model 1	Ref.	0.909(0.840, 0.983) *	0.757(0.695, 0.825) *	< 0.001	Ref.	1.101(1.016, 1.191) *	1.244(1.146, 1.349) *	< 0.001
Model 2	Ref.	1.058(0.966, 1.159)	1.020(0.924, 1.126)	0.600	Ref.	1.049(0.958, 1.149)	1.141(1.039, 1.252)	0.006

Data are odds ratios (95% confidence intervals). *, $P < 0.05$.FPG, fasting plasma glucose; BP, blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein; MetS, metabolic syndrome.

Supplementary Table 1: Ors (95% cis) for Metabolic Syndrome and its Components According to Age at Menarche and Age at Menopause in Rural Chinese Women

Model 1: adjusted for age, educational level, per capital monthly income, physical activity, adequate vegetable and fruit intake, high fat diet, and parity; Model 2: adjusted as in model 1 plus BMI.

	Duration of reproductive period [a]	Duration of reproductive period [b]		
		18~31	32~35	36~49
Central obesity				
Model 1	1.270(1.187, 1.360) *	Ref.	1.318(1.221, 1.422) *	1.386(1.116 1.678) *
Model 2	0.938(0.849,1.037□	Ref.	0.966(0.864, 1.080)	0.770(0.567, 1.045)
Abnormal FPG				
Model 1	1.092(1.022, 1.168) *	Ref.	1.068(0.990, 1.152)	1.301(1.073, 1.577) *
Model 2	1.026(1.000, 1.099) *	Ref.	0.999(0.924, 1.080)	1.166(0.958, 1.419)
Abnormal BP				
Model 1	1.206(1.130, 1.287) *	Ref.	1.197(1.111, 1.289) *	1.497(1.236, 1.812) *

Model 2	1.148(1.041, 1.192) *	Ref.	1.099(1.017, 1.187) *	1.306(1.072, 1.592) *
Abnormal TG				
Model 1	1.134(1.063, 1.210) *	Ref.	1.167(1.084, 1.256) *	1.151(0.951, 1.393)
Model 2	1.058(0.990, 1.131)	Ref.	1.318(1.221, 1.422) *	1.368(1.116, 1.678) *
Abnormal HDL-C				
Model 1	1.056(1.006, 1.066) *	Ref.	1.073(0.997, 1.155)	1.045(0.864, 1.264)
Model 2	0.976(0.913, 1.044)	Ref.	0.998(0.916, 1.066)	0.908(0.747, 1.106)
MetS				
Model 1	1.031(1.023, 1.039) *	Ref.	1.279(1.188, 1.378) *	1.389(1.148, 1.679) *
Model 2	1.071(1.263, 1.155) *	Ref.	1.098(1.008, 1.197) *	1.040(0.835, 1.296)
N = 13836. Data are odds ratios (95% confidence intervals). *, $P < 0.05$.				

Supplementary Table 2: Sensitivities Analyses of the Association Between the Duration of Reproductive Period and Metabolic Syndrome and its Components Further Excluding Those Who Reported with Menopausal for Disease Reasons (n = 760)

FPG, fasting plasma glucose; BP, blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein; MetS, metabolic syndrome.

Model 1: adjusted for age, educational level, per capital monthly income, physical activity, adequate vegetable and fruit intake, high fat diet, and parity; Model 2: adjusted as in model 1 plus BMI.

Mediation analysis	**Total effect**	**Direct effect path c′**	**Path a**	**Path b**	**Indirect effect path ab**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Abnormal FPG	1.016(1.008,1.025)	1.009(1.001,1.017)	1.080(1.065,1.094)	1.118(1.107,1.129)	1.009(1.007,1.010)
Abnormal BP	1.019(1.011,1.027)	1.008(-1.000,1.016)	1.0780(1.065,1.094)	1.168(1.156,1.1800)	1.012(1.010,1.014)
Abnormal HDL-C	1.014(1.006,1.021)	1.004(-1.004,1.012)	1.080(1.065,1.094)	1.146(1.134,1.157)	1.011(1.009,1.013)
Abnormal TG	1.022(1.014,1.030)	1.013(1.005,1.021)	1.080(1.0653,1.0943)	1.138(1.127,1.012)	1.010(1.008,1.0120)
Central obesity	1.033(1.025,1.042)	1.005(-1.017,1.007)	1.080(1.065,1.094)	2.444(2.370,2.520)	1.071(1.058,1.085)

Supplementary Table 3: Mediation Analysis of The Relationship Between Duration of Reproductive Years and Components of Metabolic Syndrome by Body Mass Index

Adjusted for age, education level, per capital monthly income, physical activity, adequate vegetables and fruits intake, high fat diet and parity. Path c′ indicates the path from duration of reproductive years to components of MetS (Outcome) when controlled for BMI (Mediator).

Path a indicates the path from duration of reproductive years to BMI (Mediator), Path b indicates the path from BMI (mediator) to components of MetS (Outcome). Path ab coefficients represent 5000 bootstrapped samples and bias-corrected 95% CIs.

Variables	**OR (95% CI)**	**P Interaction**
Age		0.470
< 65	1.034(1.023, 1.044) *	
≥ 65	1.027(1.015, 1.040) *	
Educational level		0.297
≤ Primary school	1.028(1.018, 1.037) *	
> Primary school	1.038(1.023, 1.052) *	
Income (RMB) [a]		0.359

≤ 1000	1.035(1.026, 1.044) *	
1001~	1.021(1.006, 1.037) *	
Vegetables/fruits [b]		0.761
No	1.033(1.023, 1.043) *	
Yes	1.029(1.016, 1.042) *	
High fat diet		0.011
No	1.035(1.026, 1.043) *	
Yes	1.005(0.982, 1.028)	
Physical activity		0.968
Low	1.033(1.019, 1.047) *	
Moderate	1.031(1.018, 1.043) *	
High	1.033(1.017, 1.148) *	
Age at menarche		0.370
≤15	1.021(1.008, 1.035) *	
≥16	1.031(1.020, 1.042) *	
Age at menopause		0.718
≤50	1.030(1.018, 1.043) *	
≥51	1.050(1.029, 1.072) *	
Parity		0.188
≤ 2	1.026(1.014, 1.038) *	
≥ 3	1.033(1.023, 1.044) *	

[a], per capital monthly income (RMB); [b], Adequate vegetables and fruits intake (yes). *, $P < 0.05$.

Supplementary Table 4: Associations Between Duration of Reproductive Years and Metabolic Syndrome Stratified by Potential Modifiers

Note: Results were adjusted for age, education level, per capital monthly income, physical activity, adequate vegetables and fruits intake, high fat diet and parity (unless stratified by the respective factor).

Figure Legends

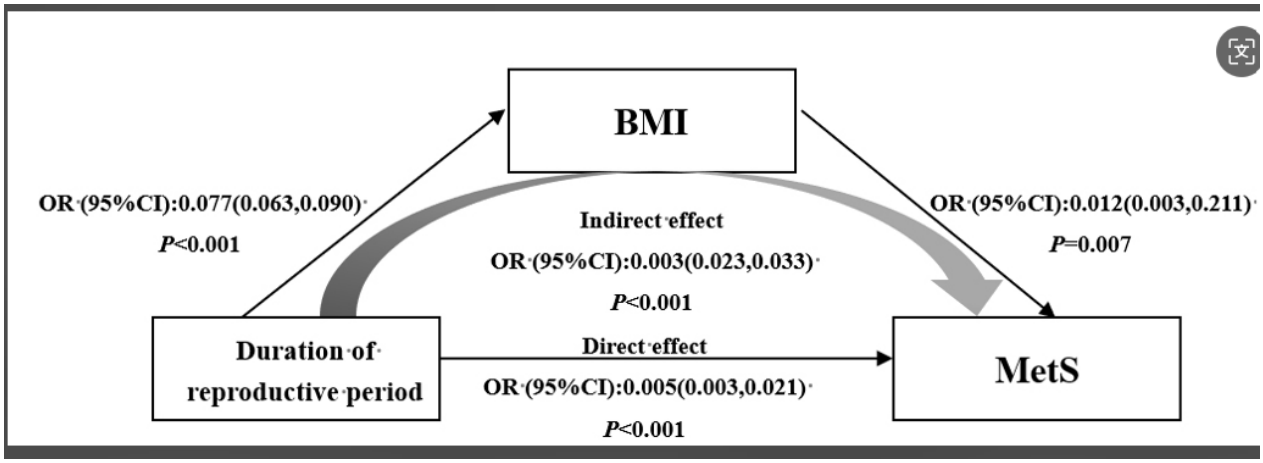

Figure 1: Mediation effect to body mass index on the relationship between duration of reproductive period and metabolic syndrome. Adjusted for age, educational level, per capita monthly income, physical activity, adequate vegetable and fruit intake, high-fat diet, and parity.

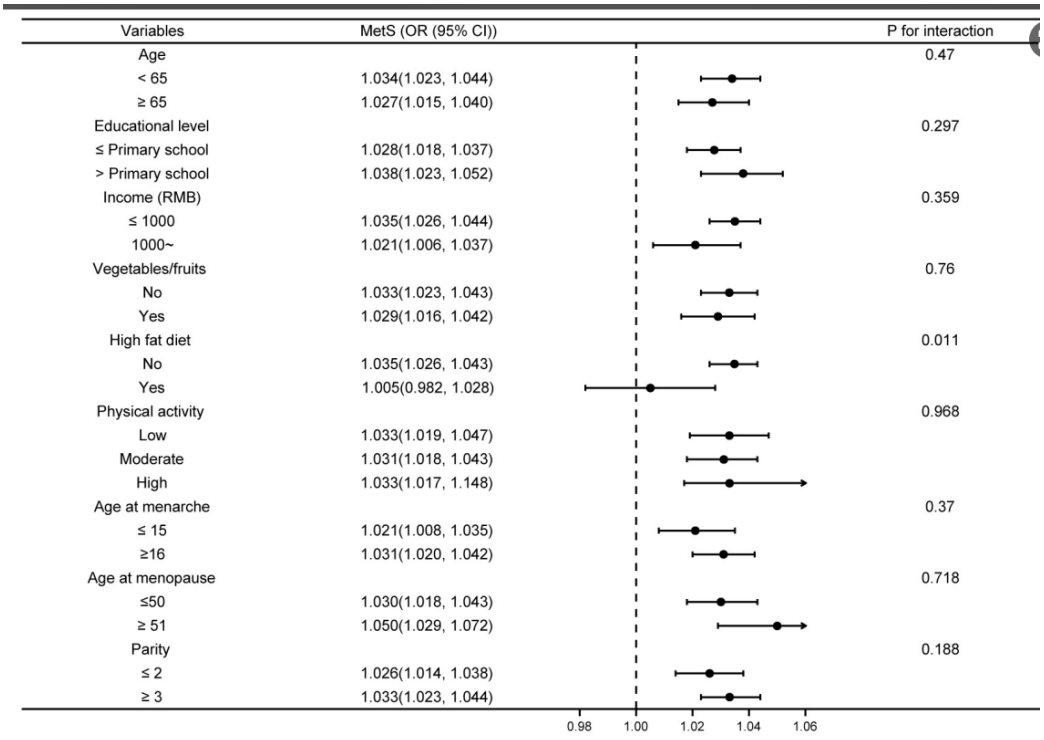

Figure 2: Odds ratio of metabolic syndrome (and 95% confidence interval) associated with duration of reproductive period according to potential modifiers. Adjusted for age, education level, per capita monthly income, physical activity, adequate vegetables and fruits intake, high-fat diet and parity (unless stratified by the respective factor).