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ORIGINAL STUDY

Mediatory role of abdominal obesity in the association of early menopause with diabetes among middle-aged and older Chinese women

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Abstract

Objective: The aim of this study was to assess the association of early menopause with diabetes and the mediating effect of abdominal obesity.

Methods: This cross-sectional study was conducted among 5,693 participants. The data from the second follow-up (2015) of the China Health and Retirement Longitudinal Study were used. Participants self-reported their age at menopause and were divided into three age groups (<45, 45-54, and >54 years) according to the 10th, 10th to 90th, and 90th percentiles, with a menopausal age of 45 to 54 years serving as reference. The total effect was decomposed into direct and indirect (mediating) effects using logistic regression based on the Karlson-Holm-Breen method.

Results: Compared to the menopausal age of 45 to 54 years, early menopause (<45 years) was associated with diabetes (odds ratio = 2.19, 95% CI: 1.29-3.69) among Chinese women. The mediating effect of early menopause (<45 years) on diabetes was 4.98% ($P = 0.321$) for abdominal obesity.

Conclusions: Early menopause may be associated with diabetes among Chinese women. Moreover, the mediating effect of abdominal obesity makes up a small percentage and has no statistical significance. Further studies are needed to examine other mechanisms behind the association of early menopause with diabetes.

Key Words: Abdominal obesity – Chinese women – Diabetes – Menopause.

Diabetes has become a global health challenge in the 21st century.[1] It is estimated that in 2017 about 451 million adults were suffering from diabetes globally. These figures are expected to reach 693 million by 2045,[2] and the prevalence of diabetes in China has increased significantly over the last few decades. The prevalence of diabetes among Chinese adults increased rapidly from 0.9% in 1980 to 10.9% in 2013.[3,4] Within the Chinese population, women younger than 60 years have a lower prevalence of diabetes than men, whereas women 60 years older have a higher prevalence.[5] Given the higher risk of diabetes in older women, exploring unique factors affecting women within these age groups is necessary.

Menopause is a crucial transition in a woman's reproductive life as it marks the end of fertility.[6] Menopause is a universal physiologic process in women, but the age at which one attains menopause varies widely. Some scholars believe that diabetes may be associated with menopausal age and recently explored this issue[7,8]; however, whether menopausal age affects the risk of diabetes remains to be elucidated. Two cross-sectional studies from China and Mexico reported that early menopause was associated with diabetes.[9,10] Moreover, two prospective cohort studies conducted in Europe found that early menopause was an independent marker for diabetes risk among postmenopausal women.[11,12] Two cross-sectional studies from Latin American and Japan, as well as one prospective cohort study from Europe, all, however, failed to find the relationship between menopausal age and diabetes.[13-15]

In addition, researchers who identified early menopause as a risk factor for diabetes have not elucidated its mechanism. Obesity may partly explain the association of early menopause with diabetes.[10] Some studies reported that estrogen levels in postmenopausal women decreased, and the absence of estrogen may be a key obesity-triggering factor.[16] Moreover, human studies have shown that women receiving hormone therapy had lower central body fat distributions.[17] Women with early menopause may have had more prolonged exposure to hormonal changes and a higher risk of abdominal obesity. Abdominal obesity can also highly predict the incidence of diabetes.[18] Thus, we wonder that whether, and to

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what extent, abdominal obesity plays a mediatory role in the association of age at menopause with diabetes. To our knowledge, data are seldom available regarding this topic.

Therefore, the aim of this study was to assess the association of early menopause with diabetes and the mediating effect of abdominal obesity in this association.

METHODS

Study population

This study used data from the second follow-up of the China Health and Longitudinal Retirement Survey (CHARLS) performed in 2015. The rationale and methodology of CHARLS has been previously reported in detail.[19] A total of 21,069 participants were recruited, including 10,025 men and 11,044 women who answered questionnaires and underwent medical examinations. Of these 11,044 women, 5,351 were excluded because their information on menopausal status and age at menopause was unavailable, their menopausal age was not within the 40 to 64 age range, they were premenopausal, or they had been diagnosed with diabetes before attaining menopause. Ultimately, 5,693 participants were included in this study. In this study, we excluded women who were younger than 41 years old (439 persons) or older than 64 years old (32 persons). The cut-off age of 40 years was chosen to exclude ''premature'' or atypical menopause, which is usually defined as the cessation of menses before the age of 40.[20] The cut-off age of 65 was adopted to exclude women who reported continued vaginal bleeding after the age of 65 years as the bleeding was more likely to be caused by pathological processes than by menstruation.[21] Thus, we chose women between the ages of 40 and 64, which included participants more likely to have typical menopause. In order to determine whether this study was representative, we compared the demographic characteristics of the included and the excluded populations. No statistical differences in population characteristics, such as age and education were observed between the two groups of people. The ethics review committee of Peking University reviewed and approved the CHARLS. All participants filled in the informed consent form.

Diagnosis of diabetes

In the present study, according to the Chinese Diabetes Association criteria, participants would be defined as having diabetes if they meet one of the following criteria: (1) glycated hemoglobin 48 mmol/mol or higher (6.5%); (2) fasting plasma glucose 126 mg/dL or higher (7.0 mmol/L); (3) self-reported doctor's diagnosis of diabetes; and (4) taking treatment (including Chinese traditional medicine, Western modern medicine, and insulin injections) to control diabetes.[22]

Age at menopause

Women were determined to be in menopause if they had ceased menstruation for at least 1 year, and menopausal age was defined as the self-reported age of the last month of menstruation. Women were asked, ''Have you started menopause?'' The options included ''Yes'' and ''No.'' If the answer was ''Yes,'' they were then further asked ''When did you begin the menopause?'' The age at menopause was divided into three categories (<45, 45-54, >54 y) according to the 10th, 10th to 90th, and 90th percentiles, with a menopausal age of 45 to 54 years used as reference.

Assessment of covariates

Age, nationality (Han nationality and minority nationality), marital status (married, single, and divorced/windowed), educational level (primary school education or below and high school education or above), smoking status (current smokers and current nonsmokers), alcohol intake (current drinkers and current nondrinkers), sleep duration, disability, parity, age at menarche, and depressive symptom risks were obtained by self-reporting via questionnaires. Sleep time was the sum of the individual's nap duration and overnight sleeping duration. Disability included physical disabilities, brain injury/mental retardation, hearing problems, visual problems, and speech impediments. The depressive symptom score was measured by the 10-item Center for Epidemiological Studies-Depression Scale in the CHARLS survey. Depressive symptom risk, a dichotomous variable indicating whether participants had depressive symptoms, was identified with 10 points serving as a cut-off point score using 10-item Center for Epidemiological Studies-Depression Scale; respondents who scored more than 10 points were considered to have depressive symptom risks.

The height, weight, waist circumference, and blood pressure of the participants were obtained through a physical examination. Body mass index is equal to the weight (kg) divided by the height squared (m^2). Abdominal obesity was defined as a waist circumference of 85 cm or higher. Fasting glucose levels, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and total cholesterol were measured by laboratory examinations.

Statistical analysis

For continuous variables, if the Bartlett test for equal variances among different groups was not statistically significant, a one-way analysis of variance was used to test the differences of means, otherwise, the Kruskal-Wallis equality-of-populations rank test was used. Pearson χ^2 test was conducted to compare the distribution of categorical variables in different groups. The mediation analysis was performed using logistic regression based on the Karlson-Holm-Breen method.[23] As shown in Figure 1, the total effect is the effect of menopausal age on diabetes. The direct effect is the effect of menopausal age on diabetes when controlling for abdominal obesity. The intermediate (indirect) effect is the effect of menopausal age on diabetes through abdominal obesity. The proportion of mediating effects among the total effect (magnitude of the mediating effect) is calculated by dividing the indirect effect by the total effect. The covariates in this study included age, nationality, marital status, educational level, smoking status, alcohol intake, sleep duration, disability, parity, age at menarche, depressive symptom risk, blood pressure, body mass index, abdominal obesity (yes/ no),

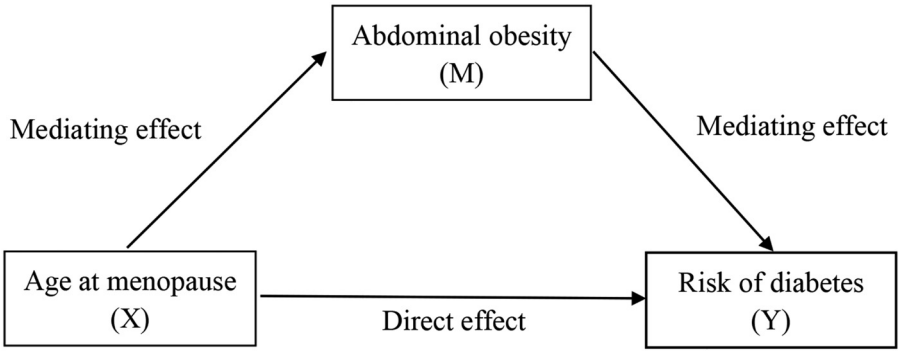

FIG. 1. Framework of mediation analysis.

triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and total cholesterol as previously mentioned. All statistical analyses were carried out using STATA version 16.0 (Stata Corporation, College Station, TX). Statistical significance was defined as a two-tailed *P* value less than 0.05.

RESULTS

Participant characteristics

Participant characteristics stratified by age at menopause are summarized in Table 1. Of the 5,693 participating women, 955 (17.38%) had diabetes. The mean ± standard deviation of age at menopause was 49.6 ± 3.6 years among these participants. Women with late menopause tended to be older, have lower marriage rates, higher parity, and diagnosed disabilities. Women with early menopause were, however, more likely to be of Han nationality and have lower educational backgrounds.

The association of menopausal age with diabetes

The association of menopausal age with diabetes is shown in Table 2. Compared to women who attained menopause at 45 to 54 years, those having early menopause (<45 years) had a higher rate of diabetes after adjusting for potential risk factors (odds ratio [OR] = 2.19, 95% CI: 1.29-3.69). No significant relationships between later menopause (>54 y) and diabetes were, however, found (OR = 1.17, 95% CI: 0.65-2.10) compared to those with menopause at 45 to 54 years after adjusting for potential risk factors.

Mediation analysis

Table 2 displays the results of the mediation analysis after adjusting for all potential covariates. In terms of abdominal obesity, the partial mediating effect on the association of early menopause (<45 y) with diabetes was observed. The mediating effect (indirect effect) was 4.98% ($P = 0.325$) out of the total effect of early menopause (<45 y) on diabetes.

DISCUSSION

Because diabetes is a prevalent chronic disease affecting middle-aged and older women and is associated with disability, microvascular complications, excess atherosclerotic diseases, and mortality,[24] investigating the prevention and treatment of

TABLE 1. *Baseline characteristics of participants according to age at menopause*

	Total ($N = 5,693$)	<45 y ($n = 382$)	45-54 y ($n = 4,809$)	>54 y ($n = 502$)	*P*
Age (y)	62.80 ± 8.89	62.38 ± 10.50	62.42 ± 8.79	66.38 ± 7.73	<0.001
Han nationality (%)	86.21	90.31	86.03	83.86	0.020
Married (%)	80.73	77.23	81.62	74.9	<0.001
Primary school education or below (%)	78.75	83.25	77.98	82.67	0.004
Current smokers (%)	5.78	8.38	5.57	5.78	0.078
Current drinkers (%)	13.61	10.47	13.89	13.35	0.169
Sleep duration (h)	6.67 ± 2.23	6.76 ± 2.37	6.68 ± 2.26	6.58 ± 2.38	0.530
Disability (%)	34.39	38.48	33.5	39.84	0.004
Number of children	2.23 ± 1.75	2.34 ± 1.81	2.20 ± 1.72	2.43 ± 1.89	0.013
Age at menarche	16.00 ± 2.00	16.00 ± 3.00	16.00 ± 2.00	16.00 ± 2.00	0.172
Body mass index (kg/m^2)	24.25 ± 4.06	24.52 ± 4.20	24.24 ± 4.10	24.16 ± 3.61	0.437
Abdominal obesity (%, WC ≥85 cm)	57.42	59.42	56.91	60.76	0.273
Systolic blood pressure (mm Hg)	129.15 ± 20.65	128.69 ± 20.10	128.92 ± 20.44	131.43 ± 21.38	0.042
Diastolic blood pressure (mm Hg)	74.39 ± 11.40	74.25 ± 12.14	74.39 ± 11.32	74.51 ± 11.68	0.954
Triglycerides (mg/dL)	195.42 ± 38.00	194.46 ± 34.16	195.18 ± 38.14	198.30 ± 39.31	0.179
LDL cholesterol (mg/dL)	111.77 ± 21.85	112.05 ± 31.30	111.50 ± 31.85	114.08 ± 32.25	0.205
HDL cholesterol (mg/dL)	51.97 ± 11.57	51.16 ± 10.60	52.05 ± 11.68	51.75 ± 11.21	0.319
Total cholesterol (mg/dL)	150.39 ± 94.84	148.62 ± 86.91	150.60 ± 96.05	149.80 ± 89.24	0.916
Diabetes (%)	17.38	21.51	17.05	17.35	0.093
Depressive symptom risk (%)	42.03	42.15	42.00	42.23	0.994

Data are means ± standard deviation for continuous; variables or *n* (%) for categorical variables.
LDL/HDL, low-density/high-density lipoprotein; WC, waist circumference.

TABLE 2. *The adjusted results of mediation of abdominal obesity on the association of menopausal age with diabetes, with a menopausal age of 45 to 54 years serving as reference*

Age at menopause	Effect	OR (95% CI)	β	SE (β)	*z*	*P*	Mediation (%)
	Total effect	2.19 (1.29-3.69)	0.783	0.267	2.93	0.003	
<45 y	Direct effect	2.10 (1.25-3.55)	0.744	0.266	2.79	0.005	4.98
	Indirect effect	1.04 (0.96-1.12)	0.039	0.040	0.98	0.325	
	Total effect	1.17 (0.65-2.10)	0.156	0.300	0.52	0.603	
>54 y	Direct effect	1.16 (0.65-1.09)	0.150	0.300	0.50	0.615	3.21
	Indirect effect	1.01 (0.93-1.09)	0.005	0.039	0.14	0.890	

Total effect is the effect of age at menopause on diabetes without considering abdominal obesity; direct effect is the effect of age at menopause on diabetes when controlling for abdominal obesity; indirect effect is the effect of age at menopause on diabetes through abdominal obesity. Mediation (%) is calculated by indirect effect/total effect × 100.
OR, odds ratio; SE, standard error.

diabetes is imperative. Although previous studies indicated that early menopause was a risk factor of diabetes and this association tended to be partially mediated by abdominal obesity,[10] whether and to what extent abdominal obesity plays a mediatory role in the association of early menopause with diabetes remain unclear. Thus, it is necessary to qualitatively and quantitatively assess the mediatory role of abdominal obesity among the effect of early menopause on diabetes.

Our findings showed that early menopause (<45 y) had a significant positive effect on diabetes (OR = 2.19, 95% CI: 1.29-3.69). In line with our results, two other prospective studies conducted in European populations also reported a positive association of early menopause (<40 y) with diabetes.[11,25] The cut-off points of menopausal age in those two studies, however, differed from the present study. In addition, only three cross-sectional studies have been conducted to date among the Chinese population concerning the relationship between menopausal age and diabetes. The Dongfeng-Tongji cohort study conducted in the Hubei province used a similar category of menopausal age and found that early menopause (<45 y) may be independently associated with an increased prevalence of diabetes, which is consistent with our results.[10] A study from Fujian province, however, reported that menopausal age was not associated with diabetes.[26] Moreover, studies carried out in Zhejiang province suggested that later menopause (≥53 y) was associated with an increased prevalence of diabetes.[27] Compared to the above three studies, our research used national data which was more representative of the population. The reasons for the inconsistent results were unknown and were possibly due to differences in sample size, participant characteristics, study design, and menopausal age grouping. Therefore, additional studies are necessary to clarify the role of menopausal age in the development of diabetes.

Up to the present, the mechanisms linking early menopause with diabetes remain unclear. Various studies found that abdominal obesity may play a mediatory role in the association of early menopause with diabetes.[10] The energy intake of postmenopausal women did not change; however, the decrease of estrogen receptor-α activation in ventromedial hypothalamic neurons was not conducive to sympathetic nervous system activation of brown adipose tissue to thermogenesis, inhibiting energy consumption and further leading to an increase in body fat. In addition, the activity of estrogen receptor α 17β-estradiol in the ventromedial nucleus of the hypothalamus decreased, which weakened the ability of the sympathetic nervous system to regulate the distribution of adipose tissue and was conducive to the accumulation of abdominal fat. The increase in abdominal fat may decrease insulin sensitivity and further cause diabetes.[7] Our mediation analysis, however, found that the indirect (mediating) effect of abdominal obesity was only 4.98% of the total effect of early menopause on diabetes and had no statistical significance.

In contrast, early menopause possessed a direct effect (95.02%) on diabetes, which may be rationally explained. Early menopause may affect diabetes in multiple ways. Animal experiments suggested that estrogen reduced the risk of diabetes by protecting against insulin resistance.[28] Both the Women's Health Initiative and the Heart and Estrogen/Progestin Replacement Study trial (estrogen therapy in women who have heart disease) demonstrated a 35% decrease in the onset of diabetes among women randomized to estrogen therapy.[29] The direct effects of estrogen on the pancreas as well as the indirect effects on corticosteroids and glucagon sensitivity are all considered to contribute to glucose metabolism.[30] Moreover, studies have shown that the disruption of the hypothalamic pituitary ovarian axis leads to the increase in pituitary follicle stimulating hormone and gonadotropin release, which may explain the association of early menopause with diabetes.[31,32] Due to the lack of data on hormone levels in this study, we were unable to investigate the mediating effects of estrogen, follicle-stimulating hormone, and gonadotropin.

DNA damage repair may be related to the age of menopause as well as to diabetes. A similar meta-analysis study on genome wide association found 17 loci for menopausal age, which was previously linked to DNA damage repair and replication, conferring important roles in determining longevity.[31] Genetic variation may cause a soma with lower efficiency in DNA maintenance and repair to age faster than those with a higher efficiency of DNA maintenance and repair. Hence, early menopause may be considered as a sign of aging body tissues, which may be used to predict future health conditions such as diabetes and hypertension.[33] Therefore, further investigations should explore genetic factors related to menopausal age and whether certain genetic characteristics explain the relationship between menopause and diabetes.

One obvious strength of our research is that it uses data from a large sample, which makes this study more representative. Potential limitations in this study, however, must also be considered. First, because this was a cross-sectional study, we could not evaluate causal associations. Second, our study relied on self-reported menopausal ages, which may induce recall bias. The indices of validity and reproducibility as well as observer variation for assessments are also absent. Nevertheless, menopausal age by recall highly aligns with that of other studies,[10,34] implying that recall bias may have little effect on this study's results. Third, because the CHARLS's investigators did not inquire about the causes of menopause, we were unable to confirm whether participants naturally attained menopause or acquired menopause as a result of surgery. Therefore, the results of this study should be carefully applied. Fourth, the number of pregnancies is a very important confounding factor in this study; however, there are no data on the number of pregnancies in this database. This study only uses the number of children to replace the number of pregnancies. The number of children is, however, not exactly equal to the number of pregnancies. Finally, despite adjusting for a comprehensive set of potential confounders, we were still unable to exclude residual confounding factors such as estrogen therapy, use of contraceptives, and physical activity.

CONCLUSIONS

In summary, this large national cross-sectional study provided evidence that early menopause may be associated with diabetes. Moreover, the mediating effect of abdominal obesity makes up a small proportion of the total effect of early menopause on diabetes and has no statistical significance. Accordingly, further studies should examine other mechanisms behind this association.

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