Menopause and the risk of metabolic syndrome among middle-aged Chinese women

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Abstract

Objective: This study explored the relationship between menopause and metabolic syndrome (MetS), stroke, hyperlipidemia, diabetes and hypertension. 

Study design: This cross-sectional study surveyed 440 women in Yuci, China in 2012.

Main outcome measures: MetS, diabetes, hypertension, hyperlipidemia, stroke, and behavioral and demographic variables.

Results: The prevalence of MetS in this study was 40.28% to 49.66% (p=0.065) among pre- and post-menopausal women, respectively, after adjusting for age.

Conclusions: The prevalence of diabetes, stroke, hypertension, and hyperlipidemia was higher among post- than pre-menopausal women. Health screenings for women in China should consider the increased risk for metabolic disorders during the postmenopausal stage of life.

Keywords: Post-reproductive health; public health; chronic disease; menopause

Introduction

Lifestyle characteristics, such as diet and levels of physical activity, are changing rapidly in China [1], thus significantly altering the metabolic profile of the population [2]. Changes in lifestyle characteristics contribute to increased rates of disease, such as diabetes and cardiovascular disease (CVD) [3, 4].

Metabolic syndrome (MetS) refers to a group of inter-related risk factors, which include abdominal obesity, dyslipidemia, insulin resistance, impaired glucose regulation, and hypertension (HTN). MetS affects 20%–30% of the population in developed countries, [5] and is associated with a significant risk of CVD and type 2 diabetes, especially in men >45 years of age and women >55 years of age [6]. With development of an industrialized and urbanized society, chronic diseases now account for 80% of all deaths in China [7], having increased significantly in recent years [4].

The rate of chronic diseases, including CVD, among men exceeds that of women in mid-life [8]. Thus, CVD has often been assumed to be a disease of men, despite the fact that the mortality rate due to CVD in women increases similar to men across the lifespan [9, 10]. The rate of diabetes is higher among men than women until 60 years of age, when the rate exceeds men [11]. Gender-based differences in the timing and development of
Menopause among middle-aged Chinese women

chronic diseases, particularly in the menopausal transition for women, need to be investigated further. There is a risk that lack of research into menopause and associated health risks puts women at risk for a compromised quality of life and increased disease burden [12].

The aim of the research reported in this paper was to determine the association between MetS risk factors and correlated diseases among women before and after the menopause. Our specific aims were as follows:

1. Determine the prevalence of MetS among pre- and post-menopausal women 48–56 years of age;
2. Determine the prevalence of diabetes, stroke, hypertension, and hyperlipidemia in pre- and post-menopausal women 48–56 years of age; and
3. Consider the metabolic risks for women posed by the menopause.

Methods

Study design and population

This cross-sectional study was conducted to compare the rates of MetS in 3 age cohorts (born in 1956, 1960–1961, and 1964 in Yuci District, Jinzhong City, Shanxi Province, China). These age cohorts were chosen as part of a larger study comparing individuals born in 1960–1961 with individuals born before and after the famine (1954 and 1956). Data was collected in the latter one-half of 2008 and 2012, respectively, in Yuci District (population = 300,000). No menopausal data was collected in 2008, thus the present paper reports on the cross-sectional data collected in 2012. Yuci is a satellite city to the provincial capital of Taiyuan, and while accommodating many rural migrants into the city in recent years, immigration from outside the province is limited. At the time of the survey, participants were required to have been born in Jinzhong City, not currently under treatment for tuberculosis or cancer, not currently taking corticosteroids, and not currently pregnant.

Two-thirds of the participants were recruited through 16 of 19 community health centers (CHCs) in Yuci District using the Health Record Database of each CHC, which contains the names of all enrolled individuals in the capitation area. Participants were recruited by telephone invitation, posters in the community and word of mouth. The intensity of recruitment varied by center, as did the participation rate, with up to 80% participation at one center, but an average response rate of approximately 10%. Centers with a high population of residents born outside Jinzhong were not included in the data collection. The remaining one-third of the participants was recruited through the Jinzhong Hospital Health Examination Center. Individuals examined at this facility were primarily healthy individuals whose employer arranges an annual physical examination. Informed consent was obtained from each participant before data collection.

A total of 806 people completed the cohort study in 2008, of which 13 were excluded due to failure to meet the inclusion criteria. A total of 659 people completed the follow-up study in 2012, with a loss-to-follow up rate of 16.9%. Two hundred and nineteen males were excluded, leaving 440 female participants for the data analysis. This paper will only analyze the 2012 data.

Data collection

Laboratory: Overnight fasting blood samples were drawn by venipuncture to measure serum glucose, total cholesterol, triglycerides, high density lipoprotein (HDL)-cholesterol, and low-density lipoprotein (LDL)-cholesterol. All samples were analyzed within 3 h at the Jinzhong People’s Hospital Laboratory on a Roche Diagnostics Modular P800 Analyzer (Roche Diagnostics, Mannheim, Germany) using the reagents imported from Roche Diagnostics.

Anthropometric measurements: Weight, height, and waist circumference were measured by trained staff according to a standard protocol. Participants were weighed (without shoes), but with light summer clothing, and when the season changed, 1–2 kg was deducted to adjust for heavier fall and winter clothing. Standing height was measured in meters (without shoes) with a stadiometer attached to a scale (Su Hong Medical Equipment Company, Limited, Jiangsu, China). Measurements were taken to the nearest 0.1 cm.

Waist circumference was measured with the participant standing erect using a standard tape measure. Measurement was taken at the umbilicus, with the tape being horizontal and passing just above the iliac crest.
**Blood pressure measurement:** At least two blood pressure measurements were obtained 1 min apart by trained nurses and physicians. The protocol was adapted from the American Heart Association recommendations [13]. The blood pressure was the last procedure completed to ensure that the participants had 30 min of rest after any exercise or smoking. A standard mercury sphygmomanometer was used, and calibrated at the Jinzhong People’s Hospital Medical Equipment Department twice during the study period. For this Chinese population, the standard cuff was suitable for all participants. All measurements were averaged.

**Survey**
A 47-item survey was designed by 2 Chinese and 2 American MetS and chronic disease experts. The survey was pilot-tested to ensure face validity. The survey was administered by trained research staff to all participants, assessing demographic data, personal and family medical histories of hypertension, diabetes, stroke, and heart disease, exercise (moderate and vigorous activity done for >10 min at a time, including activities associated with commuting, working, and leisure), smoking (never smoked, quit >1 year, and smoked at least 1 cigarette a day), alcohol intake volume and frequency (never, occasional, quit, and ≥twice a week), menopausal status (post-menopause defined as 12 months without menses), and self-reported health score (1=poor, 2=fair, 3=good, and 4=excellent).

**Definition of MetS**
The primary outcome measure was rate of MetS, as defined by the revised NCEP ATP III criteria [14], using the Asian criteria for waist circumference [15].

MetS is the presence of ≥3 of the following risk determinants:
1) increased waist circumference (≥90 cm for men, ≥80 cm for women [Asian standards]);
2) elevated triglycerides (≥1.7 mmol/L [150 mg/dL]) or treatment for this lipid abnormality;
3) low HDL-cholesterol (<1.03 mmol/L [<40 mg/dL] in men and <1.29 mmol/L [50 mg/dL] in women), or treatment for this lipid abnormality;
4) hypertension (≥130/≥85 mm Hg) or treatment for hypertension; and
5) impaired fasting glucose (≥5.6 mmol/L [100 mg/dL]) or treatment for elevated blood glucose.

**Data analysis**
Responses from 440 female participants for 2012 were analyzed. Data on sociodemographic characteristics (gender, age, education, and income), lifestyle (exercise, alcohol drinking, and smoking), menopausal status, and health status were described using percentages, means, standard deviations, and compared using ANOVA or chi-square tests. Multinomial logistic regression analysis was used to determine the odds ratios (ORs) and 95% confidence intervals (CIs) between menopausal status and the above variables. Model fitting likelihood ratio and chi-square test (significance) values were 13.595 (0.009) and 93.801 (0.000), as shown in Tables 3 and 4, respectively. A 0.05 significance level was used for all tests. All analyses were performed using the statistical software (SPSS 20.0 for Windows).

**Results**
The participants in this study had an average age of 48.72 and 53.77 years among pre- and post-menopausal women, respectively (Table 1). The median age of menopause was 50 years and the average duration of menopausal symptoms was 4.70±3.6 years. Post-menopausal women had a higher prevalence of MetS, and a higher number of chronic diseases than pre-menopausal women (Table 1). No difference in self-assessed health was observed between the two groups, with a mean self-assessed score for both groups representing health between fair and good. Pre- and post-menopausal women had a mean exercise time of 274.32 and 276.59 min per week, respectively, both of which exceeded the target of 150 min per week.

The prevalence of MetS was 37.82%, 46.05%, and 53.29% for women 48, 52, and 56 years of age, respectively (p=0.035). Table 2 shows the prevalence of the five components that make up the MetS for each of the 3 age cohorts (48, 52, and 56 year). Increased waist circumference and a low HDL-cholesterol level were the two MetS components that contributed most significantly to the presence of MetS in each age cohort. Elevated blood pressure and fasting blood glucose were two components that showed an increase with each increase in age increment.

Post-menopausal women had significantly higher rates of hyperlipidemia and hypertension than pre-menopausal women.
The prevalence of stroke and diabetes was also higher for post-menopausal than pre-menopausal women, but the difference was not statistically significant at the 0.05 level. The average number of chronic diseases (total of 4) was 0.319 and 0.568 for pre- and post-menopausal women, respectively, even after adjusting for age ($p=0.000$).

Regression analysis showed that the presence of MetS was significantly associated with the presence of chronic diseases in a gradient fashion (Table 4). Being post-menopausal was significant for the presence of two or three chronic diseases, but not for the presence of only one chronic disease. Physical activity was protective against the presence of chronic diseases, with an OR of 0.831 and 0.676 for 1 and 2–3 chronic diseases, respectively, but neither were statistically significant.

### Discussion

In this study, the prevalence of MetS was higher among post-menopausal women, regardless of age. MetS is a known predictor of diabetes and CVD, thus the results reported here...
most significantly contributing to the presence of MetS in this cohort of women. Limiting weight gain during menopause is difficult, but extremely important because abdominal fat is a major contributor to insulin resistance. Abdominal obesity, particularly visceral adiposity, contributes to insulin resistance and eventual diabetes [26]. The prevalence of elevated glucose in women increased steadily from 48 to 56 years of age, while the prevalence of elevated blood glucose for men was constant across the 3 age cohorts.

The results from other studies are inconsistent with respect to weight gain among women due to aging or menopause. Women tend to gain weight and accumulate visceral adipose tissue during the transition through menopause [27–29]. Estrogen deficiency has been shown to partially contribute to excessive visceral fat accumulation, insulin resistance, and increasing risks of cardiovascular diseases among post-menopausal women [27, 28]. It has been suggested that estrogen acts on android fat to enhance lipolysis and on gynoid fat to suppress lipolysis, but enhance lipoprotein lipase activity. Thus, estrogen promotes mobilization of android fat and deposition of gynoid fat [30]. Estrogen has favorable effects on the lipid profile and insulin sensitivity [31–33], thus offering a protective effect against metabolic disorders.

The prevalence of diabetes, hypertension, hyperlipidemia, and stroke is higher among post-menopausal women than pre-menopausal women; however, being post-menopausal was only associated with the presence of chronic diseases in a statistically significant manner among women with two or three chronic diseases. This suggests the possibility that the end of menses contributes to the increased presence of chronic diseases among a distinct segment of at-risk women, but not among all women. Therefore, particular attention should be paid to early identification of at-risk women by the utilization of a MetS screening tool at the time when the metabolic profile of women begins to change remarkably (approximately 44 years of age [34, 35]).

Although mortality due to CVD among women at 45 years of age is one-half that of men, the mortality rate increases 4-fold in women between age 45 and 55 years of age and is higher among menopausal women than men of comparable age [34, 35]. Among men and women, Ford et al. [21] reported MetS rates to increase with age in a linear fashion before leveling out at 60 years of age. In agreement with these findings

<table>
<thead>
<tr>
<th>Number of chronic diseases</th>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Presence of MetS</td>
<td>3.390 (1.477, 7.779)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Post-menopausal</td>
<td>1.462 (0.772, 2.770)</td>
<td>0.244</td>
</tr>
<tr>
<td></td>
<td>Physical activity &gt;150 min/week</td>
<td>0.831 (0.521, 1.325)</td>
<td>0.251</td>
</tr>
<tr>
<td>2–3</td>
<td>Presence of MetS</td>
<td>13.483 (6.127, 29.673)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Post-menopausal</td>
<td>4.134 (1.540, 11.100)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Physical activity &gt;150 min/week</td>
<td>0.676 (0.347, 1.317)</td>
<td>0.437</td>
</tr>
</tbody>
</table>

Referent is no chronic diseases, adjusted for age and smoking.

suggest the possibility of elevated risk for diabetes and CVD after menopause. Although it has been erroneously viewed as a disease primarily of men, CVD is the primary cause of death in women in Western countries [16]. Menopause has been shown to predict MetS in non-Western countries [17, 18], but the results have been inconsistent [19]. It is known that women develop chronic disease approximately 10 years later than men, with a marked increase through the menopausal years [20–22].

A hallmark of the menopausal transition is the dramatic reduction in estradiol levels. With this reduction, there is a progressive shift toward androgen dominance in the hormonal milieu [23]. Little is known about how this hormonal shift influences CVD risk [24], for the replacement of estrogen does not protect against CVD [23].

The proportion of women in this study in whom blood pressure and fasting blood glucose exceeded the criteria used in determining MetS increased with each age increment. A higher risk of elevated blood pressure may reflect the loss of circulating estrogen associated with menopause. It is possible that post-menopausal women exhibit poorer control of blood pressure than pre-menopausal women, but unlikely. The relationship between menopause and blood pressure is still unclear worldwide [25].

The women in this study already had a high rate of increased waist circumference at all ages, which was the component
and studies in other Asian populations [36], our study showed that prevalence of MetS increased in men in their 40s and decline after 50 years of age, and in women the rates sharply increase between 48 and 52 years of age [3]. By 56 years of age, the prevalence of MetS in women approximate those of men of the same age due to higher rates of extreme central adiposity and elevated blood pressure.

This group of Chinese women faced rapidly worsening health status, with an increasing burden created by menopause and the cost of managing the symptoms. This epidemiologic phenomenon will occur in a population of women with a rather unique history. To appreciate the impact, it is important to better understand this population of women.

Women are universally healthier than men in their 40s due to better lifestyles and the protective effects of estrogen. One could assume that chronic diseases are more of a concern for men than women. Additionally, women tend to delay seeking health care longer than men, in part because of the sense that they are the family caregiver and do not have time to take sick leave from the family [37, 38]. Gender roles and health-seeking behavior are controversial [39], but there is consistent evidence globally for a lack of attention paid to women and CVD. While there has been increased attention to the need for women to receive classic gynecologic preventive services, such as mammograms and cervical cancer screenings, women need to receive increased screenings for metabolic disorders in the menopausal period. Women shown to be pre-diabetic or women with elevated cholesterol or blood pressure should be treated aggressively to prevent CVD. Although hormone replacement therapy gives protection against menopausal symptoms and osteoporosis, hormone replacement therapy has been shown to increase rates of breast cancer and myocardial infarction, so hormone replacement therapy is recommended for short-term use only. Culturally- and gender-sensitive medical care for menopausal women is needed in China, and around the world.

Limitations
As a cross-sectional study, it is not possible to determine with certainty the temporal relationship between menopause and the onset of the reported diseases. This study is part of an 8-year longitudinal study, however, so these questions will be elucidated with time.

This study was limited by low response rates in each age cohort, particularly among the men, and the localized nature of the surveyed population. The survey instrument was not validated, so misclassification bias was a possibility. The generalizability of this study was limited to middle-aged, lower middle income urban women in Shanxi Province, China. Selection bias was unavoidable as the study participants chose to participate in the study and may not be representative of the community at large, although whether or not the general population is healthier than this group is unknown. Recall bias was also present as questions required recall of habits in the previous month or longer. Only 16.9% of the participants were lost to follow-up from the first phase of this longitudinal study, but the self-perceived health scores of these individuals was higher, thus compromising the generalizability of the results to all populations.

Future research
Current preventive health guidelines should take into consideration menopausal status. While there is the risk of medicalizing menopause, or over-treating menopause, chronic disease screening for women needs to be attentive to the potential increase in the risk for metabolic disorders in the postmenopausal stage of life. Another question to be further investigated is the role of hormone replacement therapy to improve the metabolic profile, such as lower rates of weight gain, hypertension, and insulin sensitivity. As a longitudinal study, the eventual completion of this research will allow elucidation of the development of MetS by age and gender. Finally, early age at menarche is associated with all-cause mortality [40], so it would be valuable to know whether or not early menopause also predicts early mortality.

Conclusions
The prevalence of MetS and associated chronic diseases, including diabetes, stroke, hypertension, and hyperlipidemia, was higher among post- than pre-menopausal women. Menopause should be considered a critical time to screen women for the presence of risk factors known to predict cardiovascular disease. In particular, the MetS screen is an easy and highly sensitive tool to be used. Health screenings for women in China should consider the increased risk of
metabolic disorders in the postmenopausal stage of life, and provide cultural-sensitive services to this at-risk population of women.

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**Conflict of Interest**
The authors report no conflicts of interest.

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Menopause among middle-aged Chinese women