Original Article

Normal-weight central obesity is associated with metabolic disorders in Chinese postmenopausal women

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Background and Objectives: This cross-sectional study examined whether normal-weight central obesity, defined as a high waist-to-height ratio (WHtR), is associated with metabolic disorders in Chinese postmenopausal women. **Methods and Study Design:** We recruited 634 community-dwelling postmenopausal women with a normal body mass index (BMI) who participated in an annual health checkup. Normal-weight obesity (NWO) was defined as a normal BMI and WHtR in the highest tertile of the study population. The updated National Cholesterol Education Program/Adult Treatment Panel III criteria were used to assess metabolic abnormalities, and binary logistic regression models were employed to estimate the associations between NWO and metabolic disorders. **Results:** The prevalence of each metabolic disorder showed a graded increase (p<0.05) across the WHtR tertiles in the study population. NWO was significantly associated with some non-adipose components of metabolic syndrome (MetS) (p<0.05) after adjusting for age, smoking status, drinking status, inflammatory markers, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), body fat percentage (BF%), and the remaining non-adipose MetS components. Participants in the highest WHtR tertile had a higher odds ratio [2.00 (1.19–3.33), p<0.01] for the presence of at least two non-adipose MetS components than those in the lowest tertile after adjusting for age, lifestyle factors, inflammatory markers, TC, LDL-c, and BF%. **Conclusions:** NWO is significantly associated with metabolic disorders, suggesting that a clinical assessment of abdominal obesity indices should be conducted in postmenopausal women, even in those with a normal BMI.

Key Words: normal-weight obesity, waist-to-height ratio, metabolic disorder, metabolic syndrome, body mass index

INTRODUCTION

Metabolic syndrome (MetS) and obesity are major risk factors for cardiovascular disease (CVD). The prevalence of obesity has increased worldwide over the past decades.[1,2] Body mass index (BMI) has many advantages as a surrogate of body fat (BF), such as simplicity and reproducibility, and epidemiologic studies have shown an association between extreme BMI values and increased mortality.[3-6] However, BMI has significant limitations; for example, it does not always reflect true body fatness, and it does not indicate the risk of obesity-related diseases in individuals with low muscle mass and high BF, particularly in those with high BF and a normal BMI.[7-11]

Ruderman et al described a specific type of obesity called metabolically obese normal-weight (MONW) individuals. Affected individuals were characterized by a normal body weight and BMI but presented with hyperinsulinemia and insulin resistance and were predisposed to type 2 diabetes, hypertriglyceridemia, and CVDs.[12,13] Subsequently, the term normal-weight obesity (NWO) was used to identify individuals with a normal body weight and BMI, high BF%, and total lean mass deficiency.[14,15]

Body fat percentage (BF%) is most commonly used in clinical practice. Some previous studies have found that a high BF% is associated with an increased cardiovascular (CV) risk, regardless of BMI.[16,17] However, the measurement of BF% cannot differentiate subcutaneous adipose tissue from visceral adipose tissue. The accumulation of visceral fat, as opposed to subcutaneous fat, increases the risk of metabolic disease and CVD.[18] Therefore, it is currently accepted that the distribution of BF, rather than the total amount of adipose tissue, is a crucial determinant of metabolic abnormalities.[19] Moreover, waist circumference (WC), an essential diagnostic component of MetS and a

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typical anthropometric parameter reflecting central obesity, has been recommended as a more favorable indicator of abdominal visceral fat and an appropriate indicator of metabolic disorders.[20,21] However, a recent systematic review demonstrated that the waist-to-height ratio (WHtR) is a significantly more favorable screening tool for adult metabolic risk factors than are BMI and WC.[22] Our previous study also suggested that WHtR and waist-to-hip ratio (WHR), which are frequently used obesity indices, are the optimal indicators of MetS development in Chinese postmenopausal women.[23]

Several studies have reported associations between NWO and metabolic disorders. [14,24-28] Some of these studies have defined NWO as a normal BMI but high BF%.[24,25] A recent study in Brazil defined NWO as a normal BMI with the sum of sub-scapular and triceps skin folds above the 90th percentile of the study population.[26] In addition, several studies have used WHtR to assess the central obesity status and related cardio metabolic risk profile in children and younger adults with normal weight.[27,28] However, to the best of our knowledge, few studies have specifically examined the associations between normal-weight central obesity, defined as a high WHtR, and metabolic disorders in postmenopausal women in China. Postmenopausal women accumulate more fat in the intra-abdominal region than premenopausal women and subsequently have a higher risk of developing metabolic complications associated with obesity.[29] Therefore, it is crucial for physicians to pay attention to metabolic disorders in postmenopausal women, even in those with a normal BMI. The present study evaluated the association between normal-weight central obesity and metabolic disorders in Chinese postmenopausal women who underwent a health check up.

MATERIALS AND METHODS

From January to June 2013, a total of 634 non-obese (BMI=18.5–23.9 kg/m^2) postmenopausal women who voluntarily visited the Medical Examination Center of Peking Union Medical College Hospital, China Academic Medical Science and Peking Union Medical College (Beijing, China), for a health check up were recruited for this study. All participants were of Han ethnicity and dwelled in communities of Beijing, China. Participants were naturally postmenopausal women who had amenorrhea for 12 months after their final menstruation and did not have any pathological cause of amenorrhea. The exclusion criteria were as follows: 1) evidence of liver or renal insufficiency or malignancy, 2) a medication history of corticosteroids or hormone replacement therapy (HRT) in the previous 6 months, 3) those on a weight-loss program or had lost ≥5% of their body weight in the previous 12 months, and 4) current hyperthyroidism.

This study was approved by the Ethics Committee of Peking Union Medical College Hospital, China Academic Medical Science. All participants provided written informed consent before participating in this study.

Procedure

Trained physicians administered a standard questionnaire to collect information on age, smoking status (yes/no), drinking status (yes/no), last menstrual cycle, weight status, medical history, and medication use. Routine physical examinations were then performed for all participants. Two blood pressure recordings (rounded to the nearest 2 mmHg) were obtained from the right arm of the participants while seated after 30 minutes of rest. The final measurement was the average of these two recordings.

Anthropometric measurements

Participants were requested to wear light clothing and take off their shoes for the measurement of their anthropometric characteristics, which was performed by well-trained examiners. Height was measured (rounded to the nearest 0.1 cm) using a portable stadiometer. Body weight was measured (rounded to the nearest 0.1 kg) using a calibrated scale with the participant in an upright position. BMI was calculated by dividing the weight (kg) by the height squared (m^2). WC was measured (rounded to the nearest 0.1 cm) at the end of normal expiration at the midpoint between the lower borders of the rib cage and the iliac crest. Total BF% was measured using a multi frequency bioelectric impedance analyzer (Inbody 720; eight contact points; 5, 50, 250, and 500 kHz; Biospace Co. Ltd., Seoul, Korea). Four electrodes were placed on the palm and thumb of both hands, and four electrodes were placed on the anterior and posterior aspects of the soles of both feet.

Biochemical measurements

Blood samples were collected from the peripheral vein of all participants in the morning after a fasting period of 10–12 h. After collection, the samples were immediately centrifuged at 4°C. The plasma was assayed for the lipid profile [including total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c)], fasting blood glucose (FBG), and high-sensitivity C-reactive protein (hs-CRP) by using an automated analyser (Olympus AU5800, Japan).

Definition of metabolic syndrome, metabolic abnormalities, and normal-weight obesity

According to the updated National Cholesterol Education Program/Adult Treatment Panel III (NCEP-ATP III) criteria, the metabolic risk factors were as follows: WC ≥80 cm, TGs ≥1.7 mmol/L, HDL-c <1.30 mmol/L, blood pressure ≥130/85 mmHg or current antihypertensive medication use, and fasting glucose ≥5.6 mmol/L, type 2 diabetes mellitus previously diagnosed by a physician, or current antidiabetic medication use.[30] NWOwas defined as a normal BMI (18.5–23.9 kg/m^2) and WHtR in the highest tertile (≥0.50) of the study population.

Statistical analyses

Statistical analyses were performed using SPSS version 11.5 (SPSS, Chicago, IL, USA). Data are expressed as means and standard deviations (SDs) for continuous variables and frequency and percentages for categorical variables. In this study, normal-BMI participants were divided into three groups according to the WHtR tertiles. Univariate analysis was used to compare the continuous variables of the three groups after adjusting for age, with WHtR tertiles as the fixed factor. Categorical variables

were examined using the chi-squared test. Binary logistic regression analysis was performed to estimate the association between NWO and the presence of MetS and ≥2 nonadipose MetS components (including high TG, low HDL-c, high blood pressure, and high blood glucose). Results with $p<0.05$ were considered statistically significant.

RESULTS

Table 1 lists the characteristics of the study population. All data are presented according to the three pre-established WHtR tertiles. After age was controlled, a significant increase was observed in BMI, WC, BF%, WHtR, systolic blood pressure (SBP), diastolic blood pressure (DBP), TC, TG, LDL-c, and FBG with an increase in the WHtR tertile ($p<0.01$). In addition, significant differences in age and HDL-c and hs-CRP levels were only observed between the highest and the lowest tertiles of WHtR.

Among participants, 19.6% (n=124) were diagnosed with MetS according to the updated NCEP-ATP III criteria for Asian Americans. The prevalence of MetS and all its components showed a graded increase ($p<0.05$) across the WHtR tertiles in all the participants (Table 2 and Figure 1).

As shown in Table 3, the binary logistic regression analysis revealed that postmenopausal women in the highest WHtR tertile had a higher odds ratio (OR) for the presence of at least 2 non-adipose MetS components compared with those in the lowest tertile after adjusting for age, smoking status, and drinking status (Model 1). Moreover, the higher OR was maintained even after further adjustment for TC, LDL-c, hs-CRP (Model 2), and BF% (Model 3). Significant associations were observed between normal-weight central obesity and some nonobese MetS components in all the participants, even after adjusting for age, smoking status, drinking status, TC, LDL-c, hs-CRP, BF%, and the remaining non-adipose MetS components [high TG (OR=2.13; 95% confidence interval 1.11–4.12, $p<0.05$) and high blood pressure (OR=2.06; 95% confidence interval 1.09–3.90, $p<0.05$)]. In addition, women in the highest WHtR tertile had a higher OR for the presence of high blood glucose compared with those in the lowest tertile in Models 1 and 2. However, the OR became non-significant after further adjustment for BF% (Model 3).

DISCUSSION

In our cross-sectional study, NWO, defined as a normal BMI and WHtR in the highest tertile of the study population, was associated with metabolic disorders in Chinese postmenopausal women. This finding suggests that the

Table 1. Characteristics of all participants with a normal body mass index according to WHtR tertiles. Data are expressed as mean (standard deviation) or number (%).

Variables (n=634)	Tertile 1 (n=214)	Tertile 2 (n=222)	Tertile 3 (n=198)	p_{adj} for trend
Age†, years	52.7 (5.9)	53.7 (7.9)	59.0 (9.0)** ††	<0.01
BMI, kg/m^2	20.8 (1.4)	22.8 (1.2)**	23.6 (1.1)** ††	<0.01
WC, cm	72.7 (2.5)	77.0 (2.0)**	80.0 (2.1)** ††	<0.01
Body fat,%	24.1 (4.8)	27.9 (4.6)**	31.2 (3.9)** ††	<0.01
WHtR	0.44 (0.01)	0.48 (0.01)**	0.51 (0.02)** ††	<0.01
SBP, mmHg	114 (13.4)	117 (15.9)**	125 (20.2)** ††	<0.01
DBP, mmHg	68.7 (7.2)	70.3 (8.0)**	72.0 (9.4)** ††	<0.01
TC, mmol/L	5.11 (0.85)	5.14 (0.98)**	5.37 (0.93)** ††	<0.01
TG, mmol/L	1.13 (0.49)	1.38 (0.83)**	1.53 (0.86)** ††	<0.01
HDL-c, mmol/L	1.47 (0.31)	1.43 (0.34)	1.39 (0.31)*	0.08
LDL-c, mmol/L	3.10 (0.74)	3.13 (0.81)*	3.30 (0.80)** ‡	<0.01
FBG, mmol/L	5.1 (0.9)	5.2 (1.1)**	5.4 (1.3)** ††	<0.01
Hs-CRP, mg/L	0.92 (1.12)	1.01 (1.51)	1.55 (1.92)** ††	<0.01
Current smoker,%	24 (11.2)	30 (13.5)	32 (16.2)	0.34
Current drinker,%	37 (17.3)	46 (20.7)	49 (24.7)	0.18

BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglyceride; hs-CRP: high-sensitivity C-reactive protein; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; FBG: fasting blood glucose; WHtR: waist-to-height ratio.
†By one-way analysis of variance.
Compared with tertile 1 of WHtR, *$p<0.05$, **$p<0.01$.
Compared with tertile 2 of WHtR, ‡$p<0.05$, ††$p<0.01$.

Table 2. Metabolic syndrome and its components in all participants with a normal body mass index according to WHtR tertiles. Data are given as number (%).

Variables (n=634)	Tertile 1 (n=214)	Tertile 2 (n=222)	Tertile 3 (n=198)	p_{adj} for trend
High waist circumference	0 (0.0)	12 (5.4)	98 (48.5)	<0.01
High triglycerides	26 (12.1)	54 (24.3)	64 (32.3)	<0.01
Low HDL-c	67 (31.3)	77 (34.7)	88 (44.4)	0.02
High blood pressure	27 (12.6)	48 (21.6)	70 (35.4)	<0.01
High blood glucose	27 (12.6)	45 (20.3)	62 (31.3)	<0.01
Metabolic syndrome	12 (5.6)	37 (16.7)	75 (37.9)	<0.01

HDL-c: high density lipoprotein cholesterol.

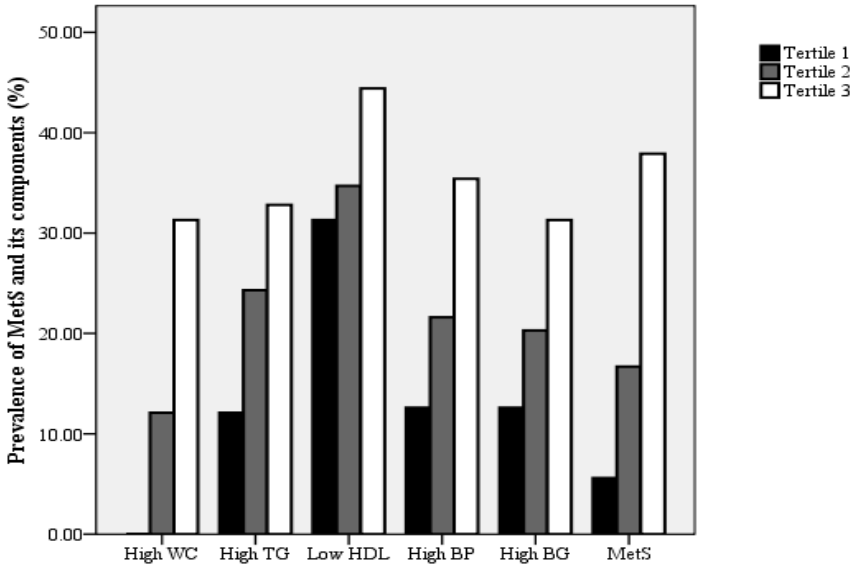

Figure 1. Prevalence of metabolic syndrome and its components according to the WHtR tertiles. WC: waist circumference; TG: triglycerides; HDL: high density lipoprotein; BP: blood pressure; BG: blood glucose; MetS: metabolic syndrome.

Table 3. Adjusted odds ratio of the relationship of metabolic syndrome and metabolic disorders with waist-to-height ratio tertiles.

Variables (n=634)	Tertile 1	Tertile 2	Tertile 3
High triglycerides†			
Model 1	Reference	2.23 (1.33-3.74)**	2.72 (1.60-4.62)**
Model 2	Reference	1.91 (1.08-3.37)*	2.16 (1.21-3.86)**
Model 3	Reference	1.89 (1.04-3.45)*	2.13 (1.10-4.12)*
High blood pressure†			
Model 1	Reference	1.70 (0.99-2.92)	2.08 (1.21-3.57)**
Model 2	Reference	1.61 (0.93-2.79)	1.91 (1.09-3.33)*
Model 3	Reference	1.69 (0.94-3.03)	2.06 (1.09-3.90)*
High blood glucose†			
Model 1	Reference	1.64 (0.97-2.78)	2.17 (1.27-3.70)**
Model 2	Reference	1.40 (0.81-2.40)	1.78 (1.03-3.09)*
Model 3	Reference	1.22 (0.69-2.17)	1.44 (0.77-2.68)
Low HDL-c†			
Model 1	Reference	1.46 (0.99-2.18)	1.57 (1.02-2.41)*
Model 2	Reference	0.93 (0.52-1.67)	1.03 (0.62-1.70)
Model 3	Reference	0.94 (0.49-1.79)	1.04 (0.61-1.75)
≥2 of non-adipose components††			
Model 1	Reference	1.75 (1.14-2.67)**	2.18 (1.40-3.41)**
Model 2	Reference	1.75 (1.14-2.69)**	2.08 (1.33-3.27)**
Model 3	Reference	1.71 (1.09-2.69)*	2.00 (1.19-3.33)**

HDL-c: high-density lipoprotein cholesterol.
†Model 1, adjusted for age, smoking status ,drinking status; Model 2, adjusted for all variables in Model 1 plus total cholesterol, LDL-c, high sensitivity C-reactive protein, and the remainding non-adipose MetS components; Model 3, adjusted for all variables in Model 2 plus body fat percentage.
††Model 1, adjusted for age, smoking status, drinking status; Model 2, adjusted for all variables in Model 1 plus total cholesterol, LDL-c, and high-sensitivity C-reactive protein; Model 3, adjusted for all variables in Model 2 plus body fat percentage.
*$p<0.05$; **$p\leq0.01$

use of only BMI to identify postmenopausal women at risk of metabolic disorders may fail to identify a crucial fraction of the women who, despite having a normal BMI, are at a higher risk of metabolic disorders (compared with the general population) because of the accumulation of more fat, particularly in the intra-abdominal region. NWO has been previously defined; however, its prevalence has not been studied in the general population.[24] A large perspective population-based study reported that NWO was associated with a four-fold increase in the prevalence of MetS, and women with NWO had an increased independent risk of cardiovascular mortality after a median follow-up of 8.8 years; that study defined NWO as a normal BMI and a BF% in the highest BF% tertile (>33.3%).[24] In addition, the impact of central obesity was examined using tertiles of WC. Notably, that population-based study reported that an increased WC was similarly associated with a CV risk. Another study that included only women showed that NWO was associated with abnormalities in the components of MetS.[31] De Lorenzo et al reported that plasma interleukin and CRP levels, regarded as inflammatory biomarkers, were significantly higher in women

with NWO than in those without NWO.[32]

Supporting our current observations, several recent studies have reported that subjects with normal-weight central obesity determined on the basis of WHtR have a significantly adverse CV risk profile and a significantly higher prevalence of MetS compared with a group of controls.[27,28] In the present study, we found that the participants in the highest WHtR tertile (≥0.5) had a higher OR for the presence of at least 2 non-adipose MetS components compared with those in the lowest tertile after adjusting for age, smoking status, drinking status, TC, LDL-c, hs-CRP, and BF%. This finding suggests that normal-weight central obesity is significantly associated with the presence of MetS, because WC, as a component of MetS (according to the NCEP-ATP III criteria), is strongly associated with other obesity indices.[23,33] The significant associations between normal-weight central obesity and the presence of MetS and its components (high blood pressure and high TG) were maintained even after adjusting for BF%. This result suggests that a WHtR of 0.5 or higher might be independently associated with the presence of MetS in Chinese postmenopausal women, regardless of BF%. Notably, a systematic review demonstrated that WHtR could be a screening tool for predicting CVD and diabetes, and a WHtR of 0.5 could be a suitable global boundary value.[34]

WC is a common anthropometric parameter for assessing central obesity and is a diagnostic component of MetS; it is strongly related to CVD.[35] WHtR, another anthropometric parameter for evaluating central obesity, is a favorable indicator of MetS development in postmenopausal women.[23] In addition, WHtR is significantly associated with an adverse cardiovascular risk profile, even in normal-BMI subjects.[27,28] A recent systematic review reported that compared with BMI, WC improved the discrimination of adverse CV risk outcomes by 3%, and WHtR improved discrimination by 4–5%.[22] Moreover, statistical analysis of the within-study differences in the area under the curve (AUC) showed that WHtR was significantly more favorable than WC for diabetes, hypertension, and CVD in men and women, suggesting the superiority of WHtR over WC and BMI for detecting cardio metabolic risk factors in both sexes. A recent study reported that WHtR might be an effective index for identifying CV risk factors in Chinese individuals with a normal BMI and WC, particularly women.[36] Therefore, the aforementioned results and our findings reveal that normal-weight central obesity determined using WHtR is significantly associated with metabolic disorders.

Our study has several limitations. First, we could not demonstrate the cause and effect of normal-weight central obesity on MetS and its components in postmenopausal women because of the cross-sectional design. Therefore, prospective studies should be conducted to fully understand their causal relationship. Second, we did not evaluate the level of insulin resistance; thus, we could not provide any mechanistic explanation for our results. Third, we did not evaluate the physical activity level in each participant. Finally, all the participants of this study were of Chinese ethnicity and residents of Beijing and were recruited from a single hospital; therefore, it is unclear whether our results are applicable to other ethnic groups, and this requires further investigation.

Conclusion

Despite the limitations of the present study, we conclude that normal-weight central obesity is significantly associated with metabolic disorders. This result suggests that the clinical assessment of abdominal obesity indices, particularly WHtR, should be conducted in postmenopausal women, even in those with a normal BMI.

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AUTHOR DISLOSURES

All the authors had full access to the data and participated in the conceptualization, design, and drafting of this manuscript. The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper. This work has not been published elsewhere.

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