Body mass index, waist circumference, and waist-to-height ratio for prediction of multiple metabolic risk factors in Chinese elderly population

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The purpose of this study was to compare the predictive ability of five obesity indices, including body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHtR), waist-to-hip ratio (WHpR) and body adiposity index (BAI), to predict multiple non-adipose metabolic risk factors, including elevated blood pressure (BP), elevated fasting plasma glucose (FPG), elevated triglyceride (TG), reduced high-density lipoprotein cholesterol (HDL-C), elevated serum uric acid (SUA) and non-alcoholic fatty liver disease (NAFLD), in an elderly Chinese population. A total of 5685 elderly Chinese subjects (≥60 years) were recruited into our community-based cross-sectional study. Receiver operating characteristic curve (ROC) analyses were used to compare the predictive ability as well as determine the optimal cut-off values of the obesity indices for multiple metabolic risk factors. According to the areas under the receiver operating characteristic curve (AUC), BMI, WC and WHtR were able to similarly predict high metabolic risk in males (0.698 vs. 0.691 vs. 0.688), while in females, BMI and WC were able to similarly predict high metabolic risk (0.676 vs. 0.669). The optimal cut-off values of BMI, WC and WHtR in males were, respectively, 24.12 kg/m², 83.5 cm and 0.51, while in females, the values were 23.53 kg/m² and 77.5 cm.

Metabolic syndrome (MetS) is a complex disease spectrum with a clustering of metabolic and cardiovascular risk factors1. MetS has a high general prevalence of 33.9% among Chinese adults5. According to the diagnosis criteria proposed by the International Diabetes Federation (IDF) and the American Heart Association (AHA)/National Heart, Lung and Blood Institute (NHLBI) in 20099, obesity, elevated blood pressure (BP), elevated fasting plasma glucose (FPG), elevated triglyceride (TG) and reduced high-density lipoprotein cholesterol (HDL-C) are the main components of MetS. In addition to these factors, numerous studies support the hypothesis that elevated serum uric acid (SUA)4–7 and non-alcoholic fatty liver disease (NAFLD)8–10 are also risk factors for MetS. Uric acid is the end-product of purine metabolism in humans, and an altered SUA level is associated with glucose and lipid metabolism11,12. In numerous studies, hyperuricemia is considered to be a risk factor for MetS or metabolic disorders4–7. NAFLD is a clinicopathological condition characterized by abnormal lipid deposition in hepatocytes13 and has been suggested to be a hepatic manifestation of MetS14,15. Therefore, obesity, elevated BP, elevated FPG, elevated TG, reduced HDL-C, elevated SUA and NAFLD are considered to be the common and important metabolic risk factors for MetS in our study.

Obesity is already a serious public health burden worldwide16. Up to 50% of elderly Chinese have an abnormally high body mass index, causing a large disease-related healthcare burden17. Various obesity-related
Results

Baseline characteristics of study subjects. As shown in Table 1, there were no significant statistical differences by gender for age and BMI. In contrast, WC and WHR were greater in males compared to females, while female subjects had greater WHR and BAI compared to males (P value < 0.001). Among the multiple metabolic risk factors, the prevalence of elevated BP, elevated FPG and NAFLD did not differ by gender. The prevalence of elevated TG was greater in females compared to males, while male subjects had greater WHtR and BAI compared to females ($P$ value < 0.001). Among the multiple metabolic risk factors in both genders, we adopted the five commonly used obesity indices to predict high metabolic risk in males and females. The AUC, optimal cut-off values, sensitivity, specificity and Youden index of the five obesity indices for predicting high metabolic risk are shown in Table 3. BMI had the strongest predictive ability for the elevated TG of males. WHtR had the strongest predictive ability for the elevated SUA of females. WC had the strongest predictive ability for reduced HDL-C of both genders as well as for the elevated TG of females. WHR had the strongest predictive ability for the elevated SUA of females.

AUC of obesity indices for multiple metabolic risk factors. Table 3 shows the areas under the receiver operating characteristic curve (AUC) for BMI, WC, WHR, WHR and BAI for each multiple metabolic risk factor in both genders using receiver operating characteristic curve (ROC) analyses. BMI had the strongest predictability for elevated BP, elevated FPG and NAFLD in both genders; for the elevated SUA of males; and for the elevated TG of females. WHR had the strongest predictive ability for reduced HDL-C of both genders as well as for the elevated TG of males. WHR had the strongest predictive ability for the elevated SUA of females.

ROC analyses were applied to compare the predictive ability of obesity indices to predict the presence of a high metabolic risk population that had ≥3 non-adipose metabolic risk factors. Figure 1 shows the ROC curves for the five obesity indices to predict high metabolic risk in males and females. The AUC, optimal cut-off values, sensitivity, specificity and Youden index of the five obesity indices for predicting high metabolic risk are shown in

Table 1. Baseline characteristics of study subjects. Data are expressed as mean± standard deviation, median (interquartile range 25–75%), or counts (percentages). WC: waist circumference; BMI: body mass index; WHR: waist-to-height ratio; WHpR: waist-to-hip ratio; BAI: body adiposity index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; SUA: serum uric acid; BP: blood pressure; NAFLD: non-alcoholic fatty liver disease.

Table 2 shows the association of metabolic risk factors and obesity indices. BMI, WC, WHR, WHpR and BAI showed an increase in the number of metabolic risk factors in both genders. As shown in Table 2, 2653 elderly subjects (1115 men and 1538 women) had ≥3 non-adipose metabolic risk factors. We estimated that approximately half of the elderly subjects (46.67% in total, 43.85% in males and 48.95% in females) in our study had high metabolic risk.

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Table 4 shows the association of metabolic risk factors and obesity indices. BMI, WC, WHR, WHpR and BAI showed an increase in the number of metabolic risk factors in both genders. As shown in Table 4, 2653 elderly subjects (1115 men and 1538 women) had ≥3 non-adipose metabolic risk factors. We estimated that approximately half of the elderly subjects (46.67% in total, 43.85% in males and 48.95% in females) in our study had high metabolic risk.

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| Variable | Total (n = 5683) | Male (n = 2543) | Female (n = 3142) | $P$ value |
|----------|-----------------|----------------|------------------|-----------|
| Age (years) | 70.16 ± 7.50 | 70.05 ± 7.27 | 70.24 ± 7.67 | 0.333 |
| Height (cm) | 161.23 ± 7.62 | 167.36 ± 5.55 | 156.26 ± 5.02 | < 0.001 |
| Weight (kg) | 63.14 ± 10.96 | 68.14 ± 10.33 | 59.10 ± 9.73 | < 0.001 |
| WC (cm) | 81.70 ± 9.19 | 83.41 ± 8.99 | 80.32 ± 9.12 | < 0.001 |
| BMI (kg/m²) | 24.22 ± 3.43 | 24.29 ± 3.23 | 24.16 ± 3.59 | 0.175 |
| WHR | 0.51 ± 0.06 | 0.50 ± 0.05 | 0.51 ± 0.06 | < 0.001 |
| WHpR | 0.88 ± 0.06 | 0.89 ± 0.06 | 0.86 ± 0.06 | < 0.001 |
| BAI | 27.63 ± 4.07 | 25.26 ± 3.06 | 29.54 ± 3.77 | < 0.001 |
| SBP (mmHg) | 138.45 ± 22.40 | 138.62 ± 22.06 | 138.32 ± 22.67 | 0.621 |
| DBP (mmHg) | 82.19 ± 12.39 | 81.66 ± 12.66 | 82.63 ± 12.16 | 0.003 |
| FPG (mmol/L) | 5.6(5.2–6.3) | 5.6(5.2–6.4) | 5.6(5.2–6.2) | 0.001 |
| TG (mmol/L) | 1.20(0.84–1.83) | 1.21(0.86–1.72) | 1.36(1.01–1.91) | < 0.001 |
| HDL–C (mmol/L) | 1.25(1.07–1.44) | 1.16(1.02–1.35) | 1.31(1.13–1.50) | < 0.001 |
| SUA (μmol/L) | 320.2(271.1–378.3) | 356.0(304.5–410.3) | 294.7(252.4–343.7) | < 0.001 |
| Elevated BP | 3902 (68.64%) | 3928 (69.19%) | 3142 (67.95%) | 0.316 |
| Elevated FPG | 2997 (52.72%) | 3176 (54.11%) | 1621 (51.59%) | 0.059 |
| Elevated TG | 1688 (29.69%) | 1760 (29.59%) | 1028 (32.72%) | < 0.001 |
| Reduced HDL-C | 2218 (39.01%) | 2311 (39.96%) | 1507 (47.96%) | < 0.001 |
| Elevated SUA | 764 (13.44%) | 759 (13.98%) | 205 (6.52%) | < 0.001 |
| NAFLD | 2409 (42.37%) | 2416 (43.70%) | 1373 (43.70%) | 0.025 |

Table 1. Baseline characteristics of study subjects. Data are expressed as mean± standard deviation, median (interquartile range 25–75%), or counts (percentages). WC: waist circumference; BMI: body mass index; WHR: waist-to-height ratio; WHpR: waist-to-hip ratio; BAI: body adiposity index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; SUA: serum uric acid; BP: blood pressure; NAFLD: non-alcoholic fatty liver disease.
The strengths of our study include the sample size, the specificity of our population, and the additional use of obesity indices with multiple metabolic risk factors and to focus on a Chinese elderly population. The results showed that BMI, WC and WHR were more useful for predicting multiple metabolic risk factors, in line with Wang et al’s research.15 We also found that WHtR had the same predictive ability as BMI and WC for predicting the high metabolic risk population in males. A European study suggested that BMI, WC and WHtR were associated with clustered cardiometabolic risk factors and that the magnitudes of the associations were similar.
for BMI, WC and WHtR using mixed-effect regression and ROC analyses. Liu et al. have found that the BMI, WC and WHtR values were able to equivalently predict the presence of multiple metabolic risk factors using ROC analyses in a general Chinese adult population. Our results validated these findings in elderly males, while we found that BMI and WC had more significant predictive value than WHtR in elderly females. Moreover, we found that both WHpR and BAI in either gender was a much weaker predictor, supporting Yu et al.’s research.

In the present study, the optimal cut-off values of the appropriate obesity indices were determined to predict the high metabolic risk population according to gender among the Chinese elderly. The BMI values for both genders were approximately 24 kg/m², in line with Wang et al.’s research in north China, and were higher than Liu et al.’s research, which was conducted in a general adult population in northeast China. The WC values in both genders were lower than in Wang et al.’s results (88.05 and 87.10 cm in males and females), Liu et al.’s results (91.3 and 87.1 cm in males and females) and Guan et al.’s results conducted in Chinese rural adults (85 and 80 cm in males and females). The WHR value in males was in line with Liu et al.’s results and was higher than that of Guan et al.’s results (0.50 in males). Wang et al.’s research suggested that the obesity indices for the prediction of MetS changed with age distribution. Our study focuses on elderly Chinese people aged 60 years and above in Shanghai, and the differences in the results may be due to the age and regional distributional differences of the samples. As these obesity indices change with age and gender, “one for all” cut-off values of obesity indices for all age groups are not appropriate to assess multiple metabolic risk factors.

There are, however, several limitations of this study. The subjects in this study were all from Shanghai, and the sample may not fully reflect all Chinese elderly. This study included quite a large number of Chinese elderly, but we only enrolled subjects who had completed the comprehensive health check study, which may have biased our primary findings. Further studies with multi centers and a larger sample size are needed to identify the association of obesity indices with more comprehensive metabolic risk factors.

**Table 4.** AUC, optimal cut-off values, sensitivity, specificity and Youden index of obesity indices to predict the high metabolic risk population. *P value < 0.05. **P value < 0.01. The obesity indices were able to similarly predict ≥3 metabolic risk factors using MedCalc statistical software with the algorithm developed by DeLong’s research team.
Methods

Study subjects. This study is a community-based cross-sectional investigation for the elderly population in Shanghai, China. A total of 5736 residents from Zhangjiang community of Shanghai aged ≥ 60 years were recruited into our study between April and July 2015. The study was performed according to the guidelines of the Helsinki Declaration. A standard protocol was designed by Shanghai innovation center of TCM health service and was approved by the Ethics Committee of Shanghai University of Traditional Chinese Medicine. Written informed consents were obtained from all subjects.

The inclusion criteria included age ≥ 60 years, local residents in Shanghai, complete data measurements and informed consents. Subjects with mental disorders, malignant tumors or incomplete recorded information were excluded from this project based on their medical records. After investigation, 51 subjects were excluded from the study. A total of 5685 Chinese elderly subjects (2543 males and 3142 females) with complete data were finally included in this study.

Data measurements. The anthropometric indices included WC, hip circumference (HC), height and weight. WC and HC were measured to the nearest 0.1 cm using a flexible metric measuring tape (Pudong CDC; Shanghai, China). Height and weight were measured to the nearest 0.1 cm and 0.1 kg using electronic measurement instrument (Shengyuan; Zhengzhou, China). All subjects were measured wearing light clothing without hats and shoes. BMI was calculated as bodyweight (kg)/height\(^2\) (m\(^2\)). WHtR was calculated as WC (cm)/height (cm). WHR\(p\)R was calculated as WC (cm)/HC (cm). BAI was calculated as HC (cm)/height\(^{1.5}\) (m) minus 18\(\text{cm}\).

Blood pressure was measured with electronic sphygmomanometers (Biospace; Cheonan, South Korea) using the standard recommended procedures. Blood samples were obtained from the antecubital vein in the morning after an overnight fasting period. FPG, TG, HDL-C and SUA were measured using an automatic biochemistry analyzer (Hitachi; Tokyo, Japan). The color ultrasound system (TOSHIBA; Tokyo, Japan) was used by two experienced radiologists to screen for fatty liver.

Criteria for multiple metabolic risk factors and the “high metabolic risk population”. According to the diagnosis criteria of MetS in 2009\(^1\), the multiple non-adipose metabolic risk factors included the following items: (a) elevated BP: systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg, or ongoing antihypertensive medications; (b) elevated FPG: FPG ≥ 5.6 mmol/L, or ongoing anti-diabetic treatment; (c) elevated TG: TG ≥ 1.7 mmol/L; and (d) reduced HDL-C: HDL-C < 1.30 mmol/L in males and HDL-C < 1.50 mmol/L in females. In addition to the regular MetS components, we also enrolled: (e) elevated SUA: SUA > 420 μmol/L according to the diagnosis criteria of hyperuricemia in 2000\(^2\); (f) NAFLD: no history of heavy drinking, liver ultrasound imaging for diffuse fatty liver, and no drug-induced liver disease or viral hepatitis according to the diagnosis criteria of NAFLD in 2012\(^{24}\). Subjects with three or more of the six non-adipose metabolic risk factors were defined as the “high metabolic risk population” in present study.

Statistical analyses. All of the descriptive statistics for all of the variables were calculated. Continuous variables were expressed as mean ± standard deviation and compared using two-sided \(t\) tests. Categorical variables were expressed as counts or percentages and compared using Pearson’s \(\chi^2\) tests. To compare the predictive ability and determine the optimal cut-off values of the obesity indices for predicting multiple metabolic risk factors, ROC analyses were used. AUCs were calculated, and the optimal cut-off values were identified from the maximum Youden index (sensitivity plus specificity-1) to determine the appropriate obesity indices. \(P\) values < 0.05 were set as significant for all of the statistical tests for bilateral contrasts. All statistical analyses were conducted using SPSS version 17.0 (SPSS; Chicago, USA). The statistical significance of the differences in the AUCs was analyzed using MedCalc version 17.1.0 (MedCalc; Ostend, Belgium) with the algorithm developed by DeLong’s research team\(^{35}\).

References

1. Alberti, K. G., Zimmet, P. & Shaw, J. Medical syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 23, 469–480 (2006).
2. Lu, J. et al. Metabolic Syndrome Among Adults in China: The 2010 China Noncommunicable Disease Surveillance. J Clin Endocrinol Metab 102, 507–515 (2017).
3. Alberti, K. G. et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120, 1640–1645 (2009).
4. Kowbara, M. et al. Asymptomatic Hyperuricemia Without Comorbidities Predicts Cardiometabolic Diseases: Five-Year Japanese Cohort Study. Hypertension 69, 1036–1044 (2017).
5. Khichar, S. et al. Serum uric acid level as a determinant of the metabolic syndrome: A case control study. Diabetes Metab Syndr 11, 19–23 (2017).
6. Yang, T. et al. Uric acid level as a risk marker for metabolic syndrome: a Chinese cohort study. Atherosclerosis 229, 525–531 (2012).
7. Lin, W. Y. et al. In addition to insulin resistance and obesity, hyperuricemia is strongly associated with metabolic syndrome using different definitions in Chinese populations: a population-based study (Taichung Community Health Study). Ann Rheum Dis 67, 432–433 (2008).
8. Naderian, M. et al. Assessment of Lean Patients with Non-alcoholic Fatty Liver Disease in a Middle Income Country; Prevalence and Its Association with Metabolic Disorders: A Cross-sectional Study. Arch Iran Med 20, 211–217 (2017).
9. Lee, S. W. et al. The association of non-alcoholic fatty liver disease and metabolic syndrome in a Chinese population. Hepatobiliary Pancreat Dis Int 16, 176–180 (2017).
10. Caserta, C. A. et al. Association of non-alcoholic fatty liver disease and cardiometabolic risk factors with early atherosclerosis in an adult population in Southern Italy. Ann Ist Super Sanita 53, 77–81 (2017).
11. Chizynski, K. & Rozycka, M. Hyperuricemia. Pol Merkur Lekarski 19, 693–696 (2005).
12. Kanbay, M. et al. Uric acid in metabolic syndrome: From an innocent bystander to a central player. Eur J Intern Med 29, 3–8 (2016).
13. Brunt, E. M. Nonalcoholic steatohepatitis: definition and pathology. Semin Liver Dis 21, 3–16 (2001).
14. Gianotti, G. et al. Diastolic dysfunction and cardiovascular risk in old subjects: possible association with NAFLD? Arch Gerontol Geriatr 58, 188–195 (2014).
15. Dowman, J. K., Tomlinson, J. W. & Newsome, P. N. Systematic review: the diagnosis and staging of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Aliment Pharmacol Ther 33, 525–540 (2011).
16. Ng, M. et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 384, 766–778 (2014).
17. Zhang, M., Jiang, Y., Li, Y., Wang, L. & Zhao, W. [Prevalence of overweight and obesity among Chinese elderly aged 60 and above in 2010], Zhonghua Liu Xing Bing Xue Za Zhi 35, 365–369 (2014).
18. Guan, X. et al. Associations between metabolic risk factors and body mass index, waist circumference, waist-to-height ratio and waist-to-hip ratio in a Chinese rural population. J Diabetes Investig 7, 601–606 (2016).
19. Wang, F. et al. Waist circumference, body mass index and waist to hip ratio for prediction of the metabolic syndrome in Chinese. Nutr Metab Cardiovasc Dis 19, 542–547 (2009).
20. Zhang, Z. Q. et al. Comparison of various anthropometric and body fat indices in identifying cardiometabolic disturbances in Chinese men and women. PLoS One 8, e70893 (2013).
21. Liu, Y., Tong, G., Tong, W., Lu, L. & Qin, X. Can body mass index, waist circumference, waist-hip ratio and waist-height ratio predict the presence of multiple metabolic risk factors in Chinese subjects? BMC Public Health 11, 35 (2011).
22. Guasch-Ferre, M. et al. Waist-to-height ratio and cardiovascular risk factors in elderly individuals at high cardiovascular risk. PLoS One 7, e43275 (2012).
23. Baumgartner, R. N., Heymsfield, S. B. & Roche, A. F. Human body composition and the epidemiology of chronic disease. Obes Res 3, 73–95 (1995).
24. Budimir, D. et al. Sex-specific association of anthropometric measures of body composition with arterial stiffness in a healthy population. Med Sci Monit 18, CR65–71 (2012).
25. Bennasar-Veny, M. et al. Body adiposity index and cardiovascular health risk factors in Caucasians: a comparison with the body mass index and others. PLoS One 8, e63999 (2013).
26. Bergman, R. N. et al. A better index of body adiposity. Obesity (Silver Spring) 19, 1083–1089 (2011).
27. Sardinha, L. B. et al. A Comparison between BMI, Waist Circumference, and Waist-To-Height Ratio for Identifying Cardio-Metabolic Risk in Children and Adolescents. PLoS One 11, e0149351 (2016).
28. Yu, J. et al. Optimal cut-off of obesity indices to predict cardiovascular disease risk factors and metabolic syndrome among adults in Northeast China. BMC Public Health 16, 1079 (2016).
29. Reas, D. L., Nygard, J. F., Svensson, E., Sorensen, T. & Sandanger, I. Changes in body mass index by age, gender, and socio-economic status among a cohort of Norwegian men and women (1990-2001). BMC Public Health 7, 269 (2007).
30. Fang, J. & Alderman, M. H. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971–1992. National Health and Nutrition Examination Survey. JAMA 283, 2404–2410 (2000).
31. Chalasani, N. et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 142, 1592–1609 (2012).
32. DeLong, E. R., DeLong, D. M. & Clarke-Pearson, D. L. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 44, 837–845 (1988).

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Author Contributions
G.J., L.Z., B.C.L., D.L., and Z.G. designed research, B.C.L., Y.L.H., P.H.Z., J.Y.W., and X.J.H. performed experiments, Z.G. and H.Y.H. analyzed the data, Z.G. wrote the main manuscript text. All authors reviewed the manuscript.

Additional Information
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