Analysis of the Predictive Value of the Cardiometabolic Index for Abnormal Metabolic Phenotypes in Normal-Weight Populations: Postprint

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Abstract

Background: Cardiometabolic index (CMI) is a simple indicator for measuring blood lipids and is closely associated with diabetes and stroke. Individuals with the metabolically obese normal weight (MONW) phenotype have higher risks of morbidity and mortality from diabetes and cardiovascular and cerebrovascular diseases. Correct identification of individuals with the MONW phenotype is crucial for the prevention and control of metabolism-related diseases. However, few studies have investigated the predictive value of CMI for the MONW phenotype.

Objective: To explore the relationship between CMI and the MONW phenotype and to evaluate the predictive value of CMI for the MONW phenotype.

Methods: The study population comprised 30,408 adults (43.45% male) aged $ 18*years*with*BMI*between*18.5 − 24*kg*/*m*^{2}$ from the 2017-2018 Nanjing Adult Chronic Disease Risk Factor Surveillance data. Robust Poisson regression models were used to analyze the relationship between CMI and the MONW phenotype in different gender groups. Receiver operating characteristic (ROC) curves were used to evaluate the predictive performance of CMI for the MONW phenotype by gender and age.

Results: The crude prevalence of the MONW phenotype was 22.09% (23.34% in males, 21.13% in females). After multivariate adjustment, a positive dose-response relationship between the MONW phenotype and CMI levels was observed in both genders (P for trend <0.001). Compared with the low CMI level group, the prevalence ratio (PR) values for the association between high CMI level group and MONW phenotype were 5.09 (95%CI: 4.68-5.53), 3.76 (95%CI:

3.28-4.10), and 6.94 (95%CI: 6.17-7.80) in the total population, males, and females, respectively. ROC curve analysis showed that the AUC values of CMI for predicting the MONW phenotype were 0.767 (95%CI: 0.757-0.778) in males and 0.809 (95%CI: 0.801-0.818) in females, both superior to WHtR, TG/HDL-C, WC, and BMI (P<0.001). Furthermore, the predictive performance of CMI was highest in the 18-34 age group, with AUC values of 0.835 (95%CI: 0.818-0.852) in males and 0.832 (95%CI: 0.817-0.847) in females.

Conclusion: CMI is positively associated with the risk of MONW phenotype, and CMI has strong predictive performance, making it an effective tool for identifying the MONW phenotype in normal-weight populations, particularly in younger individuals.

Full Text

Preamble

Predictive Value of Cardiometabolic Index for Metabolic Phenotype in Normal Weight Population

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Abstract

Background: The cardiometabolic index (CMI) is a simple lipid-related metric that is closely associated with diabetes and stroke. Individuals with the metabolically obese normal weight (MONW) phenotype exhibit higher risks of diabetes, cardiovascular and cerebrovascular diseases, and mortality. Correctly identifying individuals with the MONW phenotype is essential for the prevention and control of metabolism-related diseases. However, few studies have examined the predictive value of CMI for the MONW phenotype.

Objective: To investigate the association between CMI and the MONW phenotype and to evaluate the predictive value of CMI for identifying MONW individuals.

Methods: The study population comprised 30,408 normal-weight adults (BMI 18.5–24 kg/m^2, aged $ $18 years, 43.45% male) from the 2017–2018 Nanjing

Adult Chronic Disease Risk Factor Surveillance data. Robust Poisson regression models were used to analyze the relationship between CMI and MONW phenotype by sex. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive accuracy of CMI, stratified by sex and age.

Results: The crude prevalence of MONW phenotype was 22.09% (23.34% in men, 21.13% in women). After multivariate adjustment, a positive dose-response relationship was observed between MONW phenotype and CMI levels in both sexes (P for trend <0.001). Compared with the lowest CMI quartile, the prevalence ratios (PRs) for the highest quartile were 5.09 (95%CI: 4.68–5.53) for the total population, 3.76 (95%CI: 3.28–4.10) for men, and 6.94 (95%CI: 6.17–7.80) for women. ROC analysis showed that CMI predicted MONW phenotype with AUC values of 0.767 (95%CI: 0.757–0.778) for men and 0.809 (95%CI: 0.801–0.818) for women, significantly outperforming WHtR, TG/HDL-C, WC, and BMI (all P<0.001). The predictive performance of CMI was highest in the 18–34 age group, with AUC values of 0.835 (95%CI: 0.818–0.852) for men and 0.832 (95%CI: 0.817–0.847) for women.

Conclusion: CMI is positively associated with MONW phenotype risk and demonstrates strong predictive performance, making it an effective tool for identifying MONW individuals in normal-weight populations, particularly among younger adults.

Keywords: Cardiometabolic index; Metabolically obese normal weight; Receiver operating characteristic curve; Predictive value

Introduction

Obesity is a well-established risk factor for cardiovascular disease, and at the population level, overweight and obesity are associated with multiple metabolic abnormalities [1-2]. However, substantial individual variation exists. Approximately 20–30% of individuals with normal body weight exhibit metabolic abnormalities typically associated with overweight and obesity, a condition known as the metabolically obese normal weight (MONW) phenotype [3-4]. Because these individuals have normal weight, they are often overlooked in screening programs and fail to receive timely intervention. Studies have shown that compared with metabolically healthy normal weight (MHNW) individuals, those with MONW phenotype have a 2- to 8-fold increased risk of diabetes, cardiovascular and cerebrovascular diseases, and mortality [5-6]. Therefore, accurate identification of MONW individuals is critical for preventing and controlling metabolism-related diseases. Currently, visceral fat and insulin resistance are widely used as key indicators for identifying MONW phenotype [7], but their low feasibility and high cost limit practical application. Previous studies have demonstrated that the cardiometabolic index (CMI) is closely related to diabetes and stroke, suggesting its potential predictive value for metabolic diseases [8-9]. However, the predictive utility of CMI for MONW phenotype remains unclear. This study

utilizes data from the 2017–2018 Nanjing Adult Chronic Disease Risk Factor Surveillance to examine the relationship between CMI and MONW phenotype and assess its predictive value.

1.1 Study Population

From January 1, 2017, to June 30, 2018, a total of 61,089 permanent residents aged $ $18 years were surveyed in Nanjing using a multistage stratified cluster sampling method. The inclusion criteria for this analysis were age $ $18 *years and BMI between* 18.5 *kg/m^{2}* $ and 24.0 kg/m^2, yielding 32,381 eligible individuals. We excluded participants with missing data on height, weight, waist circumference (WC), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), or low-density lipoprotein cholesterol (LDL-C) (n=593), those using lipid-lowering medications (n=1,113), and those with malignant tumors (n=267). The final analytic sample comprised 30,408 participants. This study was approved by the Ethics Committee of Nanjing Municipal Center for Disease Control and Prevention (PJ2017002), and all participants provided informed consent before enrollment.

1.2 Research Methods

Data collection consisted of three components: questionnaire survey, physical examination, and laboratory testing. The questionnaire covered demographic and socioeconomic information, chronic disease risk factors, and medical history. Physical measurements included height, weight, WC, and blood pressure. Blood pressure was measured three times consecutively using an Omron HBP-1300 device with at least one minute between measurements; the average of the last two readings was used. Height was measured with a calibrated stadiometer in the standing position. WC was measured at the midpoint between the iliac crest and the lower border of the 12th rib in the horizontal plane with the participant standing upright, feet approximately 30 cm apart, and weight evenly distributed; measurements were taken at the end of expiration using a flexible tape with 0.1 cm precision, snug against but not compressing soft tissue. Laboratory tests required all participants to fast for 12 hours before morning venous blood collection. Fasting plasma glucose (FPG), TG, and HDL-C were measured using an automatic analyzer.

1.3 Diagnostic Criteria and Definitions

1. **Normal weight** was defined as BMI 18.5–24.0 kg/m^2 for Chinese adults according to the Working Group on Obesity in China [10]; BMI $ 24.0 *kg/m^{2}* $ was classified as overweight/obesity.
2. **Metabolic abnormality** was defined as having $ $2 of the following criteria based on the revised National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) guidelines [7]: (i) systolic blood pressure (SBP) $ $130 mmHg or diastolic blood pressure (DBP) $ $85 mmHg or self-reported hypertension or antihypertensive medication use; (ii) TG

$ $1.7 mmol/L; (iii) HDL-C <1.04 mmol/L in men or <1.30 mmol/L in women; (iv) FPG >5.6 mmol/L. Due to collinearity between BMI and WC (correlation coefficient r=0.75, P<0.001), WC was not included in the metabolic abnormality criteria. Based on these definitions, MHNW was defined as normal weight with normal metabolism, and MONW as normal weight with metabolic abnormalities [11].

3. **CMI** was calculated as: CMI = TG (mmol/L) / HDL-C (mmol/L) × WHtR [8].
4. **Waist-to-height ratio (WHtR)** = WC (cm) / height (cm).
5. **Current smoking** was defined as smoking $ $1 cigarette per day for $ $6 months at the time of survey [12].
6. **Alcohol consumption** was defined as drinking at least once per month on average and still drinking at the time of survey.
7. **Physical activity level** was quantified as metabolic equivalent hours per day (MET-h/day) based on reported duration and type of activities [13].
8. **Sedentary behavior time** was defined as total daily time spent sitting, reclining, or lying down (excluding sleep) [14].
9. **Dietary intake** of red meat, fruits, and vegetables over the past 12 months was assessed for frequency and amount. High red meat intake was defined as $ $75 g/day; low fruit and vegetable intake was defined as $ $500 g/day [15].
10. **Hypertension** was defined as self-reported diagnosis by community/township-level or higher hospital, or antihypertensive medication use within the past two weeks, and/or average SBP $ $140 mmHg and/or DBP $ $90 mmHg [16].
11. **Diabetes** was defined as self-reported diagnosis by community/township-level or higher hospital, or use of glucose-lowering medication (insulin or oral agents) within the past two weeks, and/or FPG $ $7.0 mmol/L [17].
12. **Dyslipidemia** was defined as meeting any of the following: TC $ $6.2 mmol/L, TG $ $2.3 mmol/L, LDL-C $ $4.1 mmol/L, HDL-C <1.0 mmol/L, or self-reported diagnosis, or lipid-lowering medication use within the past two weeks [18].

1.4 Statistical Analysis

Data were analyzed using SPSS web version and Stata 15.0. Normally distributed continuous variables were expressed as mean ± standard deviation and compared using ANOVA; non-normally distributed variables were expressed as median (P25–P75) and compared using Kruskal-Wallis H test. Categorical variables were expressed as percentages and compared using ^{2} tests. Participants were divided into four groups based on CMI quartiles. Robust Poisson regression models were used to estimate prevalence ratios (PRs) and 95% confidence intervals (CIs) for MONW phenotype across CMI groups [19], with sequential adjustment for covariates: Model 1 adjusted for age, education, and occupation; Model 2 additionally adjusted for current smoking, alcohol consumption, physical activity, sedentary behavior, high red meat intake, and low fruit/vegetable

intake; Model 3 further adjusted for hypertension, diabetes, dyslipidemia, antihypertensive medication, and diabetes medication. Because CMI was skewed, log transformation was applied when analyzing the effect per 1-SD increase. ROC curves were constructed to calculate area under the curve (AUC), maximum Youden index, sensitivity, and specificity for CMI, WHtR, TG/HDL-C, WC, and BMI in predicting MONW phenotype. AUCs were compared using DeLong's method [20], and diagnostic value was examined by sex and age strata. All tests were two-sided, with $P<0.05$ considered statistically significant.

Results

2.1 Baseline Characteristics

The final analytic sample included 30,408 participants (13,213 men: 10,129 MHNW and 3,084 MONW; 17,195 women: 13,562 MHNW and 3,633 MONW). The crude prevalence of MONW phenotype among normal-weight adults was 22.09% (23.34% in men, 21.13% in women). Significant differences between MHNW and MONW groups were observed for education, occupation, current smoking, alcohol consumption, sedentary time, disease history, medication use, height, WC, BMI, TC, TG, HDL-C, LDL-C, SBP, DBP, FPG, TG/HDL-C, WHtR, and CMI (all $P<0.001$). No significant differences were found for physical activity in men ($P=0.101$), low fruit/vegetable intake in men ($P=0.266$), high red meat intake in women ($P=0.118$), low fruit/vegetable intake in women ($P=0.815$), or low fruit/vegetable intake in the total sample ($P=0.806$). Detailed baseline characteristics are presented in .

2.2 Sex-Stratified Multivariable Robust Poisson Regression Analysis

After adjusting for relevant covariates (Model 3), a positive dose-response relationship was observed between MONW phenotype and CMI levels in both sexes (P for trend <0.001). Using the lowest CMI quartile as reference, the PRs for the highest quartile were 5.09 (95%CI: 4.68–5.53) for the total population, 3.76 (95%CI: 3.28–4.10) for men, and 6.94 (95%CI: 6.17–7.80) for women. For each 1-SD increase in log-transformed CMI, the PRs for MONW phenotype were 1.68 (95%CI: 1.64–1.73) for the total population, 1.56 (95%CI: 1.51–1.62) for men, and 1.81 (95%CI: 1.74–1.89) for women. These results are summarized in .

2.3 ROC Curve Analysis

In men, the AUC values for predicting MONW phenotype were 0.767 (95%CI: 0.757–0.778) for CMI, 0.630 (95%CI: 0.619–0.641) for WHtR, 0.755 (95%CI: 0.745–0.766) for TG/HDL-C, 0.601 (95%CI: 0.590–0.612) for WC, and 0.588 (95%CI: 0.577–0.599) for BMI, with all differences being statistically significant ($P<0.001$). The maximum Youden index for CMI was 0.432 at a cutoff value of 0.548, yielding sensitivity of 82.9% and specificity of 60.3%. In women, the corresponding AUC values were 0.809 (95%CI: 0.801–0.818) for CMI, 0.638 (95%CI: 0.628–0.648) for WHtR, 0.796 (95%CI: 0.787–0.805) for TG/HDL-C,

0.616 (95%CI: 0.606–0.626) for WC, and 0.611 (95%CI: 0.601–0.621) for BMI (all P<0.001). The maximum Youden index for CMI was 0.477 at a cutoff of 0.487, with sensitivity of 81.6% and specificity of 66.1%. CMI demonstrated superior predictive performance in women compared with men. Detailed results are presented in .

2.4 Age-Stratified ROC Analysis

When stratified by age group, both men and women aged 18–34 years showed the highest AUC values (both P<0.05): 0.835 (95%CI: 0.818–0.852) for men and 0.832 (95%CI: 0.817–0.847) for women. These findings are illustrated in [Figure 1: see original paper].

2.5 Sensitivity Analysis

To verify the stability of our estimates, we conducted sensitivity analyses by excluding participants using diabetes or antihypertensive medications at baseline (n=3,736) and by expanding the BMI inclusion criteria to 18.5–25.0 kg/m^2 (n=37,734). The results remained essentially unchanged (data not shown).

Discussion

The prevalence of MONW phenotype has been increasing in China in recent years [11,21]. Multiple studies have demonstrated that individuals with MONW have substantially higher risks of diabetes, hypertension, cardiovascular and cerebrovascular diseases, and mortality compared with MHNW individuals [5-6,22]. The TG/HDL-C ratio is a simple indicator reflecting diabetic dyslipidemia and insulin resistance [23], while WHtR reflects the degree of subcutaneous and visceral fat accumulation [24]. CMI combines these two parameters into a novel metric for assessing obesity and metabolic abnormalities that is more easily obtainable than direct measures of visceral fat or insulin resistance. This study aimed to explore low-cost, high-feasibility predictive indicators for MONW phenotype, examine the relationship between CMI and MONW, and evaluate its predictive value to improve identification and enable early intervention for MONW individuals, thereby reducing or delaying the onset of metabolic diseases.

Previous research has confirmed that CMI is closely associated with diabetes, atherosclerosis, and stroke [8-9]. Liu et al. [25] found a positive association between CMI levels and MONW phenotype, with an odds ratio (OR) of 71.2 for the highest versus lowest CMI group. However, when outcome frequency is high, ORs may overestimate the effect of exposure on outcomes [19]. Using robust Poisson regression models, our study demonstrated a positive dose-response relationship between CMI and MONW phenotype risk, with a 68% increase in MONW risk per 1-SD increase in CMI, indicating its utility for screening metabolic risk factors in the population.

Our findings revealed a stronger association between CMI and MONW phenotype in women (PR=6.94) than in men (PR=3.76), consistent with previous studies [8,26-27]. This sex difference may be attributed to the effects of sex hormones, particularly estrogen, on fat distribution [28]. The predictive performance of CMI was also higher in women, as evidenced by greater AUC values. Another possible explanation relates to sex differences in free fatty acid metabolism, as visceral fat lipolysis contributes more to hepatic non-esterified fatty acid delivery in women [29]. Additionally, our results showed that CMI' s predictive performance was superior in younger adults, peaking in the 18–34 age group, suggesting that age-related changes in metabolism, body composition, and comorbidities may influence CMI' s predictive value [30], though the underlying mechanisms require further investigation.

The primary mechanism underlying metabolic disorders in normal-weight individuals is visceral fat accumulation [3-4]. Previous studies have evaluated the predictive value of various anthropometric and lipid measures for MONW phenotype. Stefan et al. [7] noted that BMI and WC cannot fully reflect body fat distribution or differentiate fat types, potentially leading to misclassification of MONW phenotype. Research on Korean adults showed that WHtR predicted metabolic syndrome better than BMI and WC [31]. Gu et al. [32] found that TG/HDL-C was superior to BMI for predicting metabolic disorders in Chinese adults. Since CMI combines WHtR and TG/HDL-C, it may outperform either measure alone in identifying MONW phenotype. CMI has demonstrated good predictive value for various metabolic diseases including diabetes, atherosclerosis, and stroke [8-9,25]. Our results confirm that CMI predicted MONW phenotype with AUC values of 0.767 in men and 0.809 in women, outperforming WHtR, TG/HDL-C, WC, and BMI. Given that MONW individuals are often overlooked due to their "deceptive" normal weight, and considering that WHtR and TG/HDL-C are routinely available in general health check-ups and basic public health services, CMI represents a simple and practical assessment tool that warrants attention for early identification of MONW risk.

This study has several strengths, including a large sample size and good representativeness, as well as sex- and age-stratified analyses that provide detailed evidence for translating CMI into a screening tool. However, limitations should be acknowledged. First, the cross-sectional design precludes establishing causal relationships between CMI and MONW phenotype, which requires further prospective studies. Second, we used modified NCEP-ATP III criteria to define metabolic abnormalities, and different definitions may yield varying results, though no universal standard for MONW phenotype currently exists. Additionally, because CMI components overlap with MONW diagnostic criteria, mathematical coupling may inflate regression coefficients and AUC values, warranting cautious interpretation of our findings.

In conclusion, CMI is significantly and positively associated with increased risk of MONW phenotype. With its strong predictive performance, CMI serves as an effective tool for identifying MONW individuals among normal-weight

populations, particularly in younger adults.

Author Contributions: CHEN Yijia conceived and designed the study and drafted and revised the manuscript; QI Shengxiang and DU Jinlin performed formal analysis; WANG Chenchen and ZHOU Hairong collected literature and data; YE Qing and QIN Zhenzhen organized literature and data; SU Jian and WU Ming reviewed and edited the manuscript; HONG Xin supervised quality control and is responsible for the overall content.

Conflict of Interest: The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.