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Original Article

Underweight but metabolically abnormal phenotype: Metabolic features and its association with cardiovascular disease

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ABSTRACT

Background: Previous studies revealed that among people with normal and high body mass index (BMI), metabolic abnormalities contribute to the increased risk of cardiovascular disease (CVD). However, studies investigating the metabolic features and its association with CVD are limited.
Methods: A national representative sample of adult population in China was used. Underweight was defined as BMI < 18.5 kg/m^2. Participants who had less than 2 criteria of metabolic syndrome were classified as metabolically healthy; those who had 2 or more criteria of metabolic syndrome were classified as metabolically abnormal. Presence of CVD and albuminuria were compared among groups stratified by BMI and metabolic status.
Results: Among 46 308 participants, 2267 (4.6%) were classified as underweight; and 372 (16.4%) of them were identified as metabolically abnormal. Metabolic features were comparable between underweight but metabolically abnormal participants and obese participants. Compared with participants with normal weight and normal metabolic features, the underweight but metabolically abnormal participants were more likely to have CVD and albuminuria, with an adjusted odds ratio of 2.33 (95% confidence interval (CI) 1.34–4.05) and 2.56 (95% CI 1.86–3.52), respectively. Among underweight participants, factors associated with metabolic abnormal phenotype included leisure time physical inactivity, mild occupational physical activity, and waist circumference.
Conclusions: Metabolically abnormal phenotype is not rare among underweight population in China, and preventive strategy against CVD should also be considered in that population.

1. Introduction

The association between body mass index (BMI) and cardiovascular risk factors has always been an important public health concern [1–3]. An improved understanding of their relationship may help to identify high-risk population of cardiovascular disease (CVD). Compelling evidence has confirmed that overweight and obesity often accompany with multiple cardiovascular risk factors [1,2]. Hence, screening and intervention of cardiovascular risk factors are mainly focused on the population with high BMI. However, observational studies have revealed that population with low BMI could also have high mortality from CVD [4–7]. Therefore, the risk factors of CVD among them deserve further investigation, especially in some regions of Asia and Africa, where a substantial number of individuals with low BMI lives [8–10].

Previous studies have demonstrated that the metabolic abnormalities could contribute to the increased CVD risk and death [11,12]. For example, a considerable proportion of normal weight people express metabolic abnormalities and terms "normal weight obesity." Individuals of this phenotype are associated with increased risk of future cardiovascular events [11,13]. In addition, a subset of obese people have a favorable metabolic profile, who are described as "metabolically healthy obese" [14]. These individuals have a relatively lower cardiovascular risk compared with that of the "metabolically abnormal" obese peers [11,15–17].

However, the metabolic profile as well as its association with CVD in low BMI population has not been investigated. Therefore, we initiate the present study using data from a national representative sample of adult population in China, with the specific aim to investigate the characteristics of metabolically abnormal phenotype in underweight population, as well as its association with CVD.

2. Subjects and methods

2.1. Study participants

The sampling method has been described in detail elsewhere [18]. In brief, a multistage stratified sampling method was used to

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obtain a representative sample of people 18 years or older in the general population. Altogether, 47 204 people completed the survey and examination. The response rate was 93%.Of them, a total of 896 participants were excluded from present analyses due to missing data for height or weight, which left 46 308 participants for the present analyses. The ethics committee of Peking University First Hospital approved the study. All participants gave written informed consent before data collection.

2.2. Data collection

All on-site screenings were done between September 2009 and September 2010. Data were collected in examination centers at local health stations or community clinics in participants' residential areas. All participants completed a questionnaire documenting sociodemographic status, personal and family health history, and lifestyle with the assistance of medical students, trained general practitioners, and nurses. Anthropometric measurements were obtained including items of height, weight, and waist circumference. Height and waist circumference were accurate to 0.1 cm, and weight was accurate to 0.1 kg. All study investigators and staff members completed a training program that taught the methods and process of the study.

Serum samples were collected in the morning after an overnight fast of at least 10 hours. The measured items included fasting blood glucose (FBG), serum lipids, and uric acid. FBG was measured enzymatically with a glucose oxidase method. Serum total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and uric acid were measured with commercially available reagents. The laboratories used a timed-end point colourimetric method to measure LDL-C and HDL-C. Urine albumin and creatinine were measured from a fresh morning spot urine sample or morning urine sample stored at 4 °C for less than 1 week. Urine albumin was measured with immunoturbidimetric tests. Urinary creatinine was measured with Jaffe's kinetic method. The urinary albumin-to-creatinine ratio (ACR; mg/g creatinine) was calculated. All blood and urine samples were analyzed at the central laboratory in each province. All the study laboratories successfully completed a standardization and certification program.

2.3. Definition of underweight and classification of BMI

BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). According to the recommendation by Working Group on Obesity in China [19], individuals were classified as being underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–23.9 kg/m^2), or obese (BMI ≥28.0 kg/m^2).

2.4. Metabolic features

Four criteria to define metabolic syndrome were used in our study: high BP (≥130/85 mmHg) or current use of antihypertensive medication; high TG (≥150 mg/dL (1.7 mmol/L)); low HDL-C (<40 mg/dL (1.03 mmol/L) and <50 mg/dL (1.29mmol/L) in men and women, respectively); high FBG level (≥100 mg/dL(5.6mmol/L) or previously diagnosed diabetes). According to previous literatures [16,17], participants who met less than 2 items were classified as metabolically healthy, who met 2 or more items were classified as metabolically abnormal. It should be noted that the waist circumference was not included as an item of metabolically abnormality. Firstly, our study population was stratified by BMI in addition to the metabolic status. Since BMI has the interaction with waist circumference, it might be inappropriate to compare the waist circumference among different BMI groups. Secondly, the major purpose of our study was to investigate the metabolic features of underweight population, among which only 2.6% has central obesity (defined as waist circumference >90 cm and >80 cm for men and women, respectively) according to the criteria of metabolic syndrome.

Blood pressure was measured 3 times at 5-minute intervals by sphygmomanometer. The mean value of the 3 readings was calculated unless the difference between the readings was >10 mmHg, in which case the mean value of the 2 closest measurements was used. Hypertension was defined as a systolic BP ≥140 mmHg or/and diastolic BP ≥90 mmHg, or use of antihypertensive medication in the past 2 weeks irrespective of the BP. Diabetes was defined as fasting plasma glucose of 100 mg/dL (7.0 mmol/L) or more, or use of hypoglycemic agents, or self-reported history of diabetes. Dyslipidemia was defined by presence of at least one of following: serum TC level ≥200 mg/dL (5.2 mmol/L), TG ≥150 mg/dL (1.7 mmol/L), LDL-C ≥130 mg/dL (3.4 mmol/L), and HDL-C <40 mg/dL (1.0 mmol/L) [20].

2.5. CVD and albuminuria

Presence of CVD was defined as self-reported history of myocardial infarction (MI) or stroke. Albuminuria was defined as urinary albumin concentration of more than 20 mg/L or ACR greater than 30 mg/g and was used as a biomarker for CVD risk [21,22].

2.6. Other covariates

Family history of premature hypertension, diabetes, and CVD were defined as the first-degree relatives suffered from hypertension, diabetes, and stroke/coronary heart disease, respectively, and the onset age of corresponding diseases was before 55 years for men and before 65 years for women. Three lifestyle behaviors were identified through questionnaire: habitual drinking (defined as drinking every day), leisure time physical inactivity (defined as exercising <3.5 hours per week), and mild occupational physical activity. The degree of occupational physical activity was divided into three levels (mild (75% of working hours were spent on sitting or standing); moderate; heavy (40% of working hours were spent on sitting or standing)).

2.7. Statistical analysis

Synthesized weights, which were calculated by the product of sampling weight, nonresponse weight, and population weight, were used to estimate the prevalence of underweight in the Chinese adult population [18].

Besides underweight population, we included two other groups as references: the normal weight and metabolically healthy participants as the "theoretically healthiest group" and the obese participants as the "theoretically unhealthiest group." According to the BMI classification and metabolic status, participants were divided into four groups: underweight and metabolically healthy, underweight but metabolically abnormal, normal weight and metabolically healthy, and obese. Relevant characteristics were described and compared among the four groups. Continuous data were presented as mean (standard deviation) except for ACR, which was presented as median (inter-quartile range) due to the high skewness. Categorical variables were presented as percentage (95% confidence intervals [CI])). ANOVA was used for comparison between groups, and differences in proportion between groups were tested by the χ^2 test.

Logistic regression model was used to analyze the association between the underweight but metabolically abnormal phenotype and presence of CVD, as well as albuminuria. The age- and sex-adjusted, and multivariable adjusted odds ratios (ORs) with 95% CIs were reported. Covariates included in the multivariable logistic regression models were age (by increased by 10 years), sex, education level (≥high school vs. <high school), family history of premature hypertension, diabetes, and CVD (yes vs. no). ACR (as continuous variable) was included in the analysis of presence of CVD.