Obesity and novel cardiovascular markers in a population without diabetes and cardiovascular disease in China

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ABSTRACT

Objective. To investigate associations of novel cardiovascular markers with obesity in a general population.

Methods. A total of 9361 individuals without diabetes or cardiovascular disease were studied between 2009 and 2012 in China. High-sensitivity cardiac troponin T (hs-cTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), brachial-ankle pulse wave velocity (baPWV), pulse pressure, and central systolic blood pressure (cSBP) were assessed according to body mass index (BMI) levels and different BMI/metabolic syndrome (MetS) combinations.

Results. 'Levels of hs-cTnT, baPWV, pulse pressure, and cSBP increased across BMI levels. Obesity was positively associated with these markers in multivariate models ($P < 0.05$ for all). When stratified by MetS, these associations remained significant in the non-MetS group, and compared with normal weight participants, the obese participants had 1.87 (95% confidence interval: 1.48, 2.36), 1.27 (1.02, 1.57), 1.89 (1.39, 2.57), and 2.71 (2.11, 3.47) fold risks for having elevated hs-cTnT, baPWV, pulse pressure, and cSBP, respectively, and had 1.61 (1.26, 2.05), 1.75 (1.27, 2.42), 2.45 (1.46, 4.11), and 3.14 (2.13, 4.62) fold risks for having 1, 2, 3, and 4 elevated cardiovascular markers, respectively; while no relationship was observed between obesity and these novel markers in the MetS group, after multivariate adjustment. These results were unchanged when using a waist-hip ratio, body fat per cent, and visceral adiposity index to redefine obesity.

Conclusions. Obesity was positively associated with novel cardiovascular markers (except NT-proBNP) in participants without MetS rather than in participants with MetS. Obese participants without MetS also had higher odds of having more number of elevated cardiovascular markers.

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1. Introduction

The prevalence of obesity has rapidly increased over the past four decades worldwide. Between 1980 and 2013, the proportion of adults who are overweight or obese increased from 28.8% to 36.9% in men and from 29.8% to 38.0% in women (Ng et al., 2014). Although obesity is associated with an increased risk of cardiovascular disease (CVD)

and all-cause mortality (Arnlov et al., 2010), recent studies show that obese patients with CVD or diabetes survive longer than their leaner counterparts with the same CVD or diabetes, and this is referred to as obesity paradox (Shah et al., 2014; Turer et al., 2012).

Obesity has long been recognized as a risk factor for metabolic abnormalities (Luna-Luna et al., 2015), while metabolic abnormalities are associated with an increased risk of developing atherosclerotic CVD (Arnlov et al., 2010; Kuk and Ardern, 2009). Previous studies reported that metabolic abnormalities played an important role in the effect of obesity on CVD (Fitchett, 2015; Shah et al., 2014), suggesting that the obesity paradox may be partly caused by a lower cardiovascular risk in some obese patients without metabolic abnormalities than in their leaner counterparts with metabolic abnormalities (Du et al., 2015; Kuk and Ardern, 2009). However, the different effects of obesity on cardiovascular risk between individuals with and without metabolic abnormalities in a general population are still unknown.

Furthermore, a large number of epidemiological studies used body mass index (BMI) as the primary indicator of obesity (Ng et al., 2014;

Twig et al., 2016). Although BMI is proven to be related to health risks (Bhaskaran et al., 2014; Tobias et al., 2014), several studies reported limitations when using BMI to measure obesity (Heymsfield and Cefalu, 2013; Rothman, 2008). For instance, using BMI fails to differentiate between an elevated body fat content and an increased lean mass (Heymsfield and Cefalu, 2013). Thus, the possible bias from the measurement of obesity may result in the obesity paradox and affect the relationship between obesity and CVD.

In recent years, several novel cardiovascular markers, such as high-sensitivity cardiac troponin T (hs-cTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), pulse wave velocity (PWV), pulse pressure, and central systolic blood pressure (cSBP), identifying early cardiac injury and subclinical atherosclerosis in a general population (Kaess et al., 2012; Neeland et al., 2013a), have been used to evaluate long term cardiovascular risk in primary prevention (Saunders et al., 2011; Welsh et al., 2013). Analyses of associations of these markers with obesity may bring new perspectives to obesity-related cardiovascular risk. However, limited data are available on associations of obesity with these markers in the general population.

In the present study, we tested whether obesity is associated with these novel markers in the general population. Given the important links between metabolic abnormalities and CVD, we further tested whether metabolic abnormalities affect associations between obesity and these novel markers. Considering that BMI is still the most widely used measurement of obesity, it was used as the primary indicator to assess obesity and more measures of adiposity, such as waist-hip ratio (WHR), body fat per cent (BF%), and visceral adiposity index (VAI), were used in a series of sensitivity analyses.

2. Methods

2.1. Study population

We analyzed data from the Disease Risk Evaluation and Health Management (DREHM) study (Zeng et al., 2013), in which a total of 10,145 individuals were recruited and administered standardized questionnaires, a routine physical examination, and measurements of novel cardiovascular markers between 2009 and 2012 in Beijing and Hangzhou. For the current study, 183 individuals with incomplete demographic information were excluded. Individuals with previously known CVD ($n = 394$), diabetes ($n = 153$), chronic kidney disease estimated by a glomerular filtration rate of <60 ml/min ($n = 38$), a BMI <18.5 kg/m^2 ($n = 76$), and acute or chronic inflammatory disease ($n = 128$) were also excluded. Participants provided written informed consent, and the protocol was approved by the Institutional Review Board of Chinese PLA General Hospital (Beijing, China) and the Second Affiliated Hospital of Medical College of Zhejiang University (Zhejiang, China).

Data about education level, smoking status, and physical activity were collected. Physical activity levels were assessed using metabolic equivalent (MET) hours per week (MET-h/week). Family history of CVD was obtained from a standardized medical history questionnaire. The details are shown in the Supplemental material.

Blood samples were collected after the patients fasted overnight. Triglyceride, high-density lipoprotein cholesterol, fasting glucose, and creatinine were measured by routine laboratory methods. Insulin levels were measured with the Pharmacia insulin radioimmunoassay kit (Pharmacia Diagnostics, Sweden). Homeostasis model assessment (HOMA) was calculated to evaluate insulin resistance (IR) using the formula (fasting glucose [mmol/l] × (fasting insulin [μU/ml]) / 22.5) (Wildman et al., 2008).

2.2. Anthropometric measurements and body fat distribution

BMI, WHR, BF%, and VAI were used to measure body fat distribution. Weight and height were measured, and the BMI was calculated.

BMI cutoffs for normal weight (18.5–24 kg/m^2), overweight (24–27.9 kg/m^2), and obese (≥28 kg/m^2) were used according to the recommendation by the Working Group on Obesity in China (Zhou, 2002). WHR was calculated as waist circumference divided by hip circumference. An elevated WHR was defined by the upper sex-specific quartile of WHR (≥0.98 in men and ≥0.90 in women). Body fat was measured using a bioelectrical impedance analyzer (ARTEMIS, Seoul, South Korea) (details are given in the Supplemental material). An excess in BF% was defined by the highest sex-specific tertile of the BF% (≥27.8 in men and ≥36.8 in women) (Romero-Corral et al., 2010). VAI was calculated by the published formula: (Amato et al., 2010) (waist circumference / (39.68 + 1.88 × BMI)) × (triglyceride / 1.03) × (1.31 / high-density lipoprotein cholesterol) in men and (waist circumference / (36.58 + 1.89 × BMI)) × (triglyceride / 0.81) × (1.52 / high-density lipoprotein cholesterol) in women. An elevated VAI was defined by the upper sex-specific quartile of the VAI (≥3.46 in men and ≥2.46 in women).

2.3. Measurements of novel cardiovascular markers

In the present study, the novel cardiovascular markers included pulse pressure, cSBP, PWV, hs-cTnT, and NT-proBNP. The systolic and diastolic blood pressures were measured, and the pulse pressure was calculated. The cSBP and PWV measurement were described previously (Zeng et al., 2014). The details are presented in the Supplemental material.

The hs-cTnT concentration was measured by a high-sensitivity assay on an Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, Indiana), with an interassay coefficient of variation of 8% at 10 pg/ml and 2.5% at 100 pg/ml. The limit of detection is 3 pg/ml. The NT-proBNP levels were measured using an electrochemiluminescence-immunoassay (Elecsys proBNP, Roche Diagnostics, Indianapolis, Indiana), with an analytical range from 5 to 35,000 pg/ml. The coefficient of variation for the assay was 2% to 5%.

2.4. Definition of metabolic abnormalities

Metabolic abnormalities were defined as metabolic syndrome (MetS) in the present study. The definition of MetS, as released in the latest joint statement (Alberti et al., 2009), was met when three or more of the following criteria were present: (1) systolic blood pressure/diastolic blood pressure ≥ 130/85 mm Hg; (2) triglyceride ≥150 mg/dl; (3) high-density lipoprotein cholesterol <40 mg/dl in men or <50 mg/dl in women; (4) fasting glucose ≥100 mg/dl; and (5) WC ≥90 cm in men or ≥80 cm in women.

2.5. Statistics

All normally distributed continuous variables are expressed as the mean ± standard deviation (SD), nonnormally distributed continuous variables as the median (interquartile range), and categorical variables as percentages. The differences between the continuous variables and the categorical variables were tested with a one-way analysis of variance and χ^2 tests, respectively. Nonnormally distributed variables were log transformed before the analyses. The interaction terms between the BMI levels and MetS were calculated in unadjusted regression models for each cardiovascular marker and stratified analyses were performed due to the presence of an interaction.

Firstly, novel cardiovascular markers were analyzed as continuous variables. of the hs-cTnT and NT-proBNP markers were log transformed due to their skewed distribution. For those with an undetectable hs-cTnT, we assigned a value equal to half of the lower limit of detection (D'Angelo et al., 2008). Several multivariate linear regression models were used to assess the associations of these markers with the BMI levels and to compare the levels of the markers between different BMI/MetS combinations.