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Nontraditional risk factors for cardiovascular disease and visceral adiposity index among different body size phenotypes

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Abstract *Background and aims:* Increased cardiovascular disease and mortality risk in metabolically healthy obese (MHO) individuals remain highly controversial. Several studies suggested risk while others do not. The traditional cardiovascular risk factors may be insufficient to demonstrate the complete range of metabolic abnormalities in MHO individuals. Hence, we aimed to compare the prevalence of elevated lipoprotein (a), apolipoprotein B, and uric acid (UA) levels, apolipoprotein B/apolipoprotein A1 ratio, and visceral adiposity index (VAI) scores, and low apolipoprotein A1 levels among 6 body size phenotypes (normal weight with and without metabolic abnormalities, overweight with and without metabolic abnormalities, and obese with or without metabolic abnormalities).
Methods and results: We conducted a cross-sectional analysis of 7765 Chinese adults using data from the nationwide China Health and Nutrition Survey 2009. MHO persons had intermediate prevalence of elevated apolipoprotein B and UA levels, apolipoprotein B/apolipoprotein A1 ratio and VAI scores, and low apolipoprotein A1 levels between metabolically healthy normal-weight (MHNW) and metabolically abnormal obese individuals ($P < 0.001$ for all comparisons). Elevated apolipoprotein B and UA concentrations, apolipoprotein B/apolipoprotein A1 ratio, and VAI scores were all strongly associated with the MHO phenotype (all $P < 0.01$).
Conclusions: Prevalence of elevated apolipoprotein B and UA levels, apolipoprotein B/apolipoprotein A1 ratio and VAI scores, and low levels of apolipoprotein A1 was higher among MHO persons than among MHNW individuals. The elevated levels of the nontraditional risk factors and VAI scores in MHO persons could contribute to the increased cardiovascular disease risk observed in long-term studies.

Introduction

Obesity is a complex disorder with heterogeneous adiposity phenotypes. One recognized phenotype is the metabolically healthy obese (MHO) individual who, despite having excessive body fatness, seems to be protected from adipose-associated metabolic abnormalities [1]. Another phenotype is the metabolically abnormal obese (MAO) individual who is obese and expresses deleterious metabolic profile characterized by insulin resistance, hypertension, impaired glucose tolerance, and dyslipidemia [2]. The potential implications of these phenotypes for disease risk have triggered interest in exploring whether differential future risks of incident diabetes, cardiovascular disease (CVD) occurred in different body size phenotypes [2,3]. There is no consensus on how to define the MHO phenotype. Similarly, conflicting results regarding the outcomes were observed

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and associations between MHO phenotype and CVD outcomes were definition dependent [2–5]. Even if the same definition was used to define the MHO phenotype, conflicting evidence regarding the outcomes was still noted [4,5]. In addition, MHO persons experienced increased risk for metabolic alterations [6]. Taken together, MHO should not be regarded as benign condition. The conventional CVD risk factors may be insufficient to demonstrate the complete range of metabolic abnormalities in MHO individuals. It is possible that some other effective indicators of CVD may predispose MHO individuals to an increased CVD risk. Elevated lipoprotein (a), apolipoprotein B (apo B), and uric acid (UA) levels, and apoB/apolipoprotein A1 (apoA1) ratio, and low apoA1 levels have been reported to be associated with an increased CVD risk [7,8]. Few epidemiologic data examined lipoprotein (a), apoA1, apoB and UA levels, and apoB/apoA1 ratio in each of the 6 body size phenotypes (normal weight with and without metabolic abnormalities, overweight with and without metabolic abnormalities, MHO, and MAO). Visceral adiposity is independently associated with incident CVD incidence [9]. Although imaging techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT), are required for direct measurement of visceral adiposity, they cannot be used in daily practice due to practical, ethical and economic reasons. Recent studies have indicated that the visceral adiposity index (VAI) is a good indicator of visceral fat accumulation [10]. No data on VAI scores in each of the 6 body size phenotypes was available. Hence, we took advantage of the large cohort of Chinese adults who participated in the China Health and Nutrition Survey (CHNS) 2009 to examine the prevalence of elevated lipoprotein (a), apoB, and UA levels, apoB/apoA1 ratio and VAI scores, and decreased apoA1 levels among the 6 body size phenotypes.

Methods

China health and nutrition survey 2009 and its participants

The CHNS is the only large-scale longitudinal, household-based survey in China. Full details of the study have been described elsewhere [11] and in Supplemental Appendix 1. Each participant provided a written informed consent and the study was approved by the institutional review committees of the University of North Carolina at Chapel Hill, the National Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention, and the China–Japan Friendship Hospital, Ministry of Health.

Since fasting blood samples were initially collected in 2009, this study is a cross-sectional study using the data from CHNS 2009 (2011 data collection is done, updating longitudinal datasets with 2011 data is underway). A total of 10,038 adult respondents were surveyed at the 2009 exam, 1423 did not give blood, 402 were not fasting before blood collection, and 62 were pregnant, resulting in a total of 8151 individuals with fasting blood samples. Participants aged ≥18 years and with BMI ≥18.5 kg/m^2 were included in the present analysis. Exclusion criteria included lipid-lowering medication use, blood pressure (BP)-lowering medication use, no information on age, anthropometry information, and five components of metabolic syndrome. Ultimately, 7765 participants (3655 men and 4110 women) were included in current analysis. There were no statistically significant differences in the total 2009 sample vs the analytical sample in sex or metabolic risk (data not shown).

All participants were asked to complete a structured questionnaire which provided information on educational attainment, cigarette smoking and alcohol consumption habits, histories of current and previous illness, and medical treatment. Relevant definitions were shown in Supplemental Appendix 2.

Measurements and definitions

Weight was measured with participants wearing light clothing on a calibrated beam scale and height was measured without shoes using a portable stadiometer. Body mass index (BMI) was calculated by the formula: weight/height^2 (kilograms/meters^2). According to the World Health Organization criteria for Asians [12], subjects were classified as normal weight (BMI of 18.5–22.9 kg/m^2), overweight (BMI of 23.0–27.4 kg/m^2), and obesity (BMI ≥27.5 kg/m^2). Waist circumference (WC) was measured with an inelastic tape at a midpoint between the bottom of the rib cage and the top of the iliac crest at the end of exhalation. Seated systolic/diastolic BP was measured by trained technicians in triplicate after a 10-min rest, using mercury manometers. The three readings were averaged in our data analysis.

Blood was collected after an at least 8-h overnight fast. Whole blood was immediately centrifuged and plasma or serum samples were then frozen, and stored at −86 °C for later laboratory analysis. All samples were analyzed in a national central lab in Beijing, with strict quality control. Fasting plasma glucose (FPG) was measured by the GOD-PAP method (Randox Laboratories Ltd, UK]. All lipids (total cholesterol [TC], triglyceride [TG], low and high density lipoprotein cholesterol [LDL-C and HDL-C]) were directly measured with Hitachi 7600 automated analyzer (Hitachi Inc., Tokyo, Japan). TC, LDL-C, and HDL-C were measured enzymatically (Kyowa, Japan). Non-HDL-C was calculated as TC minus HDL-C. TG was measured by GPO-PAP method (Kyowa, Japan). ApoA1 and apoB were measured by immunoturbidimetric method (Randox Laboratories Ltd, UK). Abnormal apo levels were defined as apoA1 <15th percentile value (1.1 g/L), apoB ≥85th percentile value (1.3 g/L) [13], and apoB/apoA1 ≥0.8 [8]; Lipoprotein (a) was determined with an immunoturbidimetric method (Denka Seiken, Japan). Elevated lipoprotein (a) was defined as lipoprotein (a) ≥85th percentile value (28.4 mg/dl) [13]. UA was measured by enzymatic colorimetric method (Randox Laboratories Ltd, UK). Elevated UA was defined as UA ≥ 6 mg/dl (357 mmol/l) for women and ≥7 mg/dl (416 mmol/l) for men [14].

The VAI was calculated by the published formula [10]: Males: [WC/39.68 + (1.88 × BMI)] × (TG/1.03) × (1.31/HDL); Females: [WC/36.58 + (1.89 × BMI)] × (TG/