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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.

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Keywords

Apolipoprotein A1; apolipoprotein B; metabolically abnormal and obese; metabolically healthy but obese

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 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.

Materials and 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, 1,423 did not give blood, 402 were not fasting before blood collection, and 62 were pregnant, resulting in a total of 8,151 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-hour 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 (357mmol/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/0.81) × (1.52/HDL), where both TG and HDL levels are expressed in mmol/l.

Subjects were classified as metabolically abnormal by having any 2 of the following, consistent with the Adult Treatment Panel-III (ATP III) metabolic syndrome definition [15]: WC ≥ 90/80 cm for men/women, systolic/diastolic BP ≥130/85 mmHg, TG ≥1.7 mmol/l (150 mg/dl), FPG ≥5.6 mmol/l (100 mg/dl) or use of diabetes medications, HDL-C ≥1.0/1.3 mmol/l (40/50 mg/dl) for men/women. Subjects were classified as metabolically healthy by having 0 or 1 risk factor. Based on cross-classification of BMI categories and metabolic status, participants were categorized into 6 mutually exclusive six body size phenotypes: metabolically healthy normal-weight (MHNW), metabolically abnormal normal-weight (MANW), metabolically healthy overweight (MHOW), metabolically abnormal overweight, MHO, and MAO.

The Framingham risk score (FRS) was calculated according to the ATP III algorithm [16] based on age, TC, HDL-C, systolic BP (categorized according to their values), smoking status (categorized into “current smokers” and “non-smokers”), and sex. According to FRS, individuals were categorized into 3 risk groups (low [<10%], intermediate [10–20%], and high [≥20%]).

Statistical analysis

All statistical analyses were conducted using SPSS software (version 12.0 for windows; SPSS, Chicago, IL, USA). Continuous variables were presented as medians and interquartile ranges (IQR) due to their skewed distribution. Differences in characteristics across BMI categories, for metabolically healthy and metabolically abnormal groups, separately, were tested for significance by Kruskal-Wallis one-way analysis of variance or Cochran-Mantel-Haenszel chi-square statistics as appropriate. Bonferroni correction was made based on 15 different comparisons between metabolically healthy and metabolically abnormal groups, when necessary, thus, a two-tailed P value of 0.05 divided by 15, 0.003, was considered significant. The interactions between BMI and metabolic status in variables listed in Table 1 and Table 2 were tested by logistic regression models and general linear models, respectively. Among 7641 participants without taking any medication for diabetes, receiver operating characteristic (ROC) curve analysis was used to determine optimal VAI cut-point for predicting diabetes as defined by FPG ≥7.0 mmol/l. We then defined elevated VAI scores as VAI ≥ the optimal VAI cut-point. Odds ratios (OR) with 95% CI from multinomial logistic regression models were used to assess odds for each nontraditional risk factor by body size phenotypes. The MHNW phenotype was used as the reference. Breslow-Day test was used to test the trends for ORs across the 6 body size phenotypes.

Results

Characteristics of the study group were shown in supplementary Table 1. Prevalence of lifestyle variables and traditional CVD risk factors in six body size phenotypes was indicated in Table 1. Significant trends were observed for all variables listed in Table 2, with the exception of lipoprotein (a), among groups with or without metabolic abnormality (all parameters: P <0.01). Compared to MHNW and MAO individuals, the MHO individuals had intermediate metabolic profiles (including traditional CVD risk factors except for LDL-C, and non-traditional CVD risk factors except for lipoprotein (a) and apoA1, and VAI scores) (all P <0.001). All variables listed in Table 2 except for age, BMI, WC, TC, LDL-C, apoB, were worse in MANW individuals than in MHO individuals (all P <0.001). None of the interaction terms (BMI*metabolic status) in all variables listed in Table 2, with the exception of systolic and diastolic BP, LDL-C, apoB, was statistically significant (all P >0.05), indicating that most of the variables were independently related to increasing BMI and being metabolically abnormal.

According to the ROC curve analysis, the optimal VAI cutoff point for detecting diabetes was 1.8. Hence, VAI scores were defined as elevated if VAI ≥1.8.

The prevalence of all nontraditional risk factors studied, except elevated lipoprotein (a) levels, increased progressively with worsening BMI status regardless of metabolic status (all P for trend <0.01) (Figure 1). The prevalence of low apoA1 levels, and elevated apoB, and UA concentrations, apoB/apoA1 ratio and VAI scores in MHO group was intermediate between that observed in MHNW and MAO persons (P <0.001 for all comparisons). The most frequent metabolic risk factor within all body size phenotypes was elevated apoB/apoA1 ratio. The prevalence of all these risk factors studied was higher in MANW participants than in MHO individuals.

Logistic regression analysis was carried out to evaluate the interactions between sex and body size phenotypes on ORs for each of the evaluated risk factors. No significant sex *body size phenotypes interactions were noted, except for UA. Hence, models were sex pooled to increase precision. Models were also performed by stratification of the data by sex (Table 3).

After adjustment for age, sex, educational attainment, smoking status, and alcohol use, elevated apoB, and UA levels, apoB/apoA1 ratio and VAI scores were all associated with the MHO and MANW phenotype (all parameters: P <0.01) (Table 4). After adjustment for educational attainment, alcohol use, and FRS score, elevated apoB, and UA levels, apo B/apo A1 ratio and VAI scores were still associated with the MHO and MANW phenotype (all parameters: P <0.01). Although MHOW subjects experienced risks for elevated apoB, and UA levels, apoB/apoA1 ratio and VAI scores similar to MHO subjects, there were significant trends for these adjusted ORs across the 6 body size phenotypes.

Discussion

In the current study, MHO individuals have a traditional and nontraditional CVD risk profile, and VAI score that is intermediate between those observed in MHNW and MAO

persons. Furthermore, the MHO phenotype remained a significant risk factor independent of the FRS for elevated apoB, and UA concentrations, apoB/apoA1 ratio and VAI scores, which may possibly explain the increased risk of CVD in MHO persons.

ApoB reflects the entire spectrum of pro-atherogenic circulating lipoproteins. ApoA1 is the main structural protein of HDL particles. Therefore, the apoB/apoA1 ratio has been regarded as a reliable atherogenic parameter that reflects lipid disorder [17]. Increasing apoB concentrations have been reported to be related to a greater risk of fatal myocardial infarction [8]. Evidence showed that reduction in serum apoB was associated with reduced inflammation and insulin resistance [18]. Moreover, the apoB/apoA1 ratio is a better predictor of CVD risk than traditional lipid parameters [19]. The apoA1 and apoB levels in MHO and MAO phenotypes have been investigated in a limited number of studies [20, 21]. Unfortunately, prior studies with apo levels yielded mixed results and are limited by small selected samples of obese women, and thus had limited generalizability [20, 21]. Karelis et al. reported similar apoB and apoA1 levels in obese postmenopausal women with or without insulin resistance [20]. Messier et al. compared the serum apoB and apoA1 levels among 26 MHO women with those of 86 MAO women, and found that serum apoB levels were significantly higher while apoA1 levels were significantly lower in MAO women than in MHO women [21]. Our present study showed that the MHO phenotype carries intermediate apoB, levels, and apoB/apoA1 ratio compared with MAO and MHNW individuals. In addition, more than half of the MHO persons present an elevated apoB/apoA1 ratio. The unfavorable lipid profile may expose MHO persons to poor health outcomes in view of the independent predictive value of elevated apoB levels and apoB/apoA1 for CVD risk [17, 19].

The present study has also shown that MHO persons had intermediate UA levels between MAO and MHNW individuals. Furthermore, about 1 in 10 MHO persons suffered from hyperuricemia. At present, only a few studies have investigated UA levels across the spectrum of body size phenotypes [22]. Mangge et al. reported that MHO persons had an intermediate UA levels between MHNW and MAO persons [22]. This study also indicated that UA emerged as a significant discriminator between the MHO and MAO phenotypes [22]. Increased UA levels have been shown to play a mechanistic role in vascular smooth muscle cell proliferation, inhibition of the nitric oxide pathway, and inflammation, which may in turn promote lipid oxidation. In addition, UA becomes a strong oxidant that can increase oxygen radicals in the environment of obesity [23]. Thus, increased UA levels and obesity may have synergistic effects on poor CVD outcomes among MHO persons.

Visceral adiposity is more pathogenic than subcutaneous adiposity because of its greater endocrine activity. Several epidemiological studies have indicated that the VAI, a mathematical model that uses anthropometric (BMI and WC) and metabolic (TG and HDL-C) parameters, is a good indicator of the visceral fat accumulation measured by MRI or CT [10], and is independently correlated with the rate of peripheral glucose utilization during the euglycemic-hyperinsulinemic clamp [10]. Moreover, several prospective studies have identified a positive association between the VAI scores and CVD risk [10]. Hence, the VAI, offering advantages of a reduced economic burden and no radiation exposure, may indirectly reflect other non-classical risk factors, i.e. increased adipokine production, and

proinflammatory activity as accumulating evidence identifies inflammation as a potential mechanism linking adipose tissue and cardiometabolic risk [24]. Recent studies also show that MHO persons possess abnormal levels of inflammatory markers such as interleukin-6, fibrinogen, and plasminogen activator inhibitor-1 [25, 26]. In our current study, we documented that approximately 1 in 8 MHO persons had elevated VAI scores. From a clinical perspective, VAI might serve to predict the future CVD risk.

Significant trends in ORs for nontraditional CVD risk factors and VAI scores were observed across the 6 body size phenotypes, indicating that both obesity and metabolic abnormalities are associated with cardiovascular abnormalities. The present data seem to argue that caution is warranted when using the term “healthy obese”. Moreover, the MHOW persons demonstrate similar ORs for nontraditional CVD risk factors and VAI scores to MHO persons, suggesting that MHOW persons may experience multiple CVD risk factors similar to MHO persons. Given that the proportion of MHOW subjects was much larger than MHO subjects, it is important to identify MHOW persons early to prevent or delay CVD incidence.

Asians are prone to have a greater amount of visceral adiposity and a higher prevalence of metabolic abnormalities than other ethnic populations at a given BMI. This ethnic difference may predispose Asians to be metabolically abnormal even at normal weight [27]. MANW individuals often elude screening as they are perceived as healthy persons. However, increasing evidence has noted an increase in incidences of diabetes and CVD in MANW individuals [2, 5, 28]. Our current study indicates that these individuals have a higher prevalence of most of the nontraditional risk factors, despite their lower BMI, than MHO persons. These factors may mediate poorer health outcomes in MANW individuals. Hence, it is particularly important to identify these persons as early intervention may help in attenuating or delaying the onset of overt disease.

There are several important public health and clinical implications of our results. The current analysis highlights a poor non-traditional risk factor profile and increased VAI scores in MHO/MHOW persons. Such a profile is strongly predictive of the risk of future CVD morbidity and mortality [8, 17, 19, 29]. Our results provide additional impetus for clinical suspicion and investigation for a potential existence of these risk factors in MHO/MHOW persons. In addition, given the poor CVD risk profile in MANW persons, it is important to monitor carefully and treat these individuals to reduce the disease burden.

There are several limitations. First, the study population is comprised of only Chinese adults, thus, extrapolating results to other racial or ethnic population should be interpreted cautiously. Second, other nontraditional CVD risk factors such as inflammatory markers, which would increase in MHO/MHOW persons, were not considered. Third, the cross-sectional design implies that no potential temporal relations between the non-traditional risk factors for CVD and the body size phenotypes can be drawn.

In conclusion, the current study has documented that a considerable proportion of MHO/MHOW persons possess low apoA1 levels, elevated serum apoB, and UA levels, apoB/apoA1 ratio and VAI scores. The elevated levels of the nontraditional risk factors and VAI

scores in MHO/MHOW persons could contribute to the increased CVD risk observed in relevant studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Highlights

- MHO persons had intermediate nontraditional risk profile between MHNW and MAO persons
- MHO persons had intermediate VAI scores between MHNW and MAO persons
- All nontraditional risk factors studied and VAI scores were strongly associated with MHO phenotype
- MONW persons had poorer nontraditional risk profile than MHO persons
- All nontraditional risk factors studied and VAI scores were strongly associated with MONW phenotype

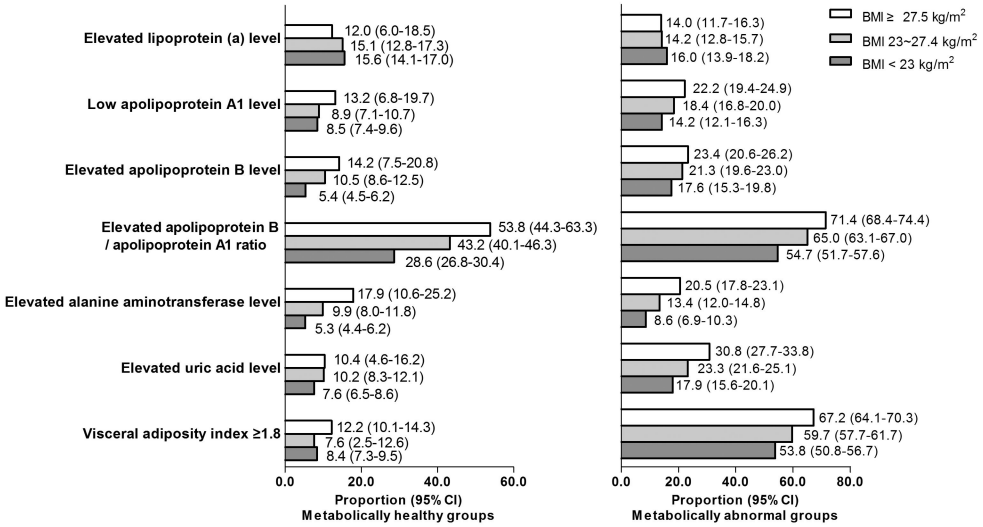

Figure 1.

The prevalence of nontraditional risk factors for cardiovascular disease and elevated VAI scores in body size phenotypes according to the Adult Treatment Panel-III definition

Table 1

Characteristics of the study participants in six body size phenotypes according to ATP III criterion

	Metabolically healthy			P*	Metabolically abnormal			p*	P for interaction†
	BMI < 23 kg/m^2	BMI 23-27.4 kg/m^2	BMI ≥ 27.5 kg/m^2		BMI < 23 kg/m^2	BMI 23-27.4 kg/m^2	BMI ≥ 27.5 kg/m^2		
n	2464	968	106	...	1092	2251	884	...	...
Male (%)	48.5	48.8	47.2	0.9500	43.0	47.9	44.2	0.4332	0.2050
Current smokers, %	30.7	28.5	26.4	0.1368	27.3	27.5	21.6	0.0070	0.5191
Current drinkers, %	12.3	13.8	13.2	0.2718	14.3	14.9	12.0	0.1830	0.6360
Less than primary school, %	40.8	38.2	37.7	0.2560	55.2	45.9	49.8	<.0001	0.0450
Coronary heart disease, %	1.7	2.0	2.8	0.5301	4.7	4.1	4.2	0.0426	0.9735
Stroke, %	0.7	0.6	0.9	0.8969	2.2	2.0	1.6	0.3362	0.8024
Glucose lowering medications, %	0.2	0.1	0.0	0.4413	2.5	4.0	6.7	<.0001	0.2998
Hypertension, %	1.9	8.6	11.9	<.0001	33.1	37.5	49.6	<.0001	<.0001
Diabetes, %	1.0	1.0	1.9	0.6056	12.7	11.9	19.0	0.0002	0.9534

Data are percentages.

*P for trend across BMI categories within metabolic risk factor category

†P for interaction terms (BMI × metabolic risk factor status) were assessed by logistic regression analysis.

Table 2

Characteristics of the study participants in six body size phenotypes according to ATP III criterion

	Metabolically healthy			P*	Metabolically abnormal			p*	P for interaction†
	BMI < 23 kg/m²	BMI 23-27.4 kg/m²	BMI ≥ 27.5 kg/m²		BMI < 23 kg/m²	BMI 23-27.4 kg/m²	BMI ≥ 27.5 kg/m²		
Age, y	45.2 (35.3-57.3)	46.2 (39.0-55.2)	43.5 (34.3-51.5)	0.0121	56.9 (46.4-67.6)	54.6 (45.1-63.0)	52.5 (43.5-62.1)	<.0001	<.0001
BMI, kg/m²	20.9 (19.9-21.9)	24.3 (23.6-25.4)	28.6 (27.8-29.9)	<.0001	21.6 (20.5-22.3)	25.1 (24.1-26.2)	29.3 (28.2-30.8)	<.0001	0.3588
Waist circumference, cm	75.0 (71.0-79.0)	82.2 (78.0-86.8)	92.0 (84.5-98.0)	<.0001	81.1 (77.0-86.0)	88.0 (84.0-93.0)	97.0(92.0-102.0)	<.0001	0.3120
Systolic blood pressure, mmHg	116.0 (108.0-122.0)	119.0 (110.0-122.0)	118.7 (110.0-122.0)	<.0001	129.3 (119.3-140.0)	130.0 (120.0-140.7)	133.3 (121.0-149.3)	<.0001	0.0042
Diastolic blood pressure, mmHg	76.0 (70.0-80.7)	78.7 (70.7-81.0)	79.2 (74.7-80.0)	<.0001	81.3 (76.0-90.0)	83.3 (79.3-90.0)	86.7 (80.0-96.0)	<.0001	<.0001
Fasting glucose level, mmol/l	4.8 (4.5-5.2)	4.9 (4.6-5.2)	5.0 (4.7-5.3)	0.0056	5.3 (4.8-6.0)	5.3 (4.9-6.0)	5.5 (5.0-6.2)	<.0001	0.9063
Total cholesterol, mmol/l	4.5 (4.0-5.1)	4.7 (4.2-5.4)	4.8 (4.4-5.6)	<.0001	4.9 (4.2-5.6)	5.0 (4.4-5.7)	5.1 (4.5-5.8)	<.0001	0.0505
Triglycerides, mmol/l	1.0 (0.7-1.2)	1.1 (0.8-1.4)	1.1 (0.9-1.4)	<.0001	1.6 (1.0-2.3)	1.7 (1.2-2.4)	1.9 (1.3-2.7)	<.0001	0.0844
LDL cholesterol, mg/dl	105.6 (86.2-127.2)	116.4 (94.7-137.7)	120.6 (101.3-152.0)	<.0001	113.7 (88.2-139.6)	117.9 (94.7-143.1)	119.9 (95.5-143.9)	0.0005	0.0005
HDL cholesterol, mmol/l	1.5 (1.3-1.8)	1.5 (1.3-1.7)	1.4 (1.2-1.6)	<.0001	1.3 (1.1-1.6)	1.2 (1.1-1.5)	1.2 (1.0-1.4)	<.0001	0.8650
Non-HDL-C, mmol/l	2.9 (2.5-3.4)	3.2 (2.7-3.7)	3.5 (3.0-3.9)	<.0001	3.7 (3.0-4.5)	4.0 (3.3-4.7)	4.3 (3.5-5.1)	<.0001	0.7333
Lipoprotein (a), mg/dl	8.0 (4.0-17.0)	7.9 (4.4-16.9)	6.9 (4.0-15.4)	0.7245	8.3 (3.9-18.1)	7.9 (4.1-16.0)	7.1 (3.7-15.3)	0.0588	0.6392
Apo A1, g/l	1.1 (1.0-1.3)	1.1 (1.0-1.3)	1.0 (1.0-1.3)	0.0169	1.1 (0.9-1.3)	1.1 (0.9-1.2)	1.0 (0.9-1.2)	<.0001	0.5022
Apo B, g/l	0.8 (0.7-0.9)	0.9 (0.7-1.0)	0.9 (0.8-1.1)	<.0001	0.9 (0.8-1.1)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	<.0001	0.0043
Apo B / Apo A1	0.7 (0.5-0.8)	0.8 (0.6-0.9)	0.8 (0.7-1.0)	<.0001	0.8 (0.6-1.0)	0.9 (0.7-1.1)	0.9 (0.8-1.2)	<.0001	0.6900
Uric Acid, mmol/l	271.0 (221.0-329.0)	280.0 (231.0-341.0)	287.0 (248.0-356.0)	0.0006	304.0 (243.0-367.0)	316.0 (255.0-387.0)	337.0 (277.0-405.5)	<.0001	0.4686
Visceral Adiposity Index	0.9 (0.7-1.3)	1.1 (0.8-1.5)	1.2 (0.9-1.5)	<.0001	2.0 (1.2-3.0)	2.2 (1.4-3.4)	2.5 (1.6-4.1)	<.0001	0.0501

Data are median (interquartile range).

*P for trend across BMI categories within metabolic risk factor category

†P for interaction terms (BMI × metabolic risk factor status) were assessed by generalized linear model.

Table 3

Odds ratios (95% confidence intervals)[*] of nontraditional risk factors associated with body size phenotypes[†]

	Metabolically healthy			Metabolically abnormal			P for interaction[‡]
	BMI < 23 kg/m^2	BMI 23-27.4 kg/m^2	BMI ≥ 27.5 kg/m^2	BMI < 23 kg/m^2	BMI 23-27.4 kg/m^2	BMI ≥ 27.5 kg/m^2	
High serum lipoprotein (a) level							
Men	1	0.9 (0.6-1.2)	0.8 (0.3-2.0)	0.9 (0.7-1.2)	0.7 (0.6-0.9)	0.6 (0.4-0.9)	0.0077
Women	1	1.0 (0.8-1.4)	0.7 (0.3-1.7)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	1.0 (0.7-1.3)	
Low serum apolipoprotein A1 level							
Men	1	1.2 (0.9-1.7)	1.3 (0.6-2.8)	2.2 (1.6-2.9)	2.5 (2.0-3.2)	3.9 (2.9-5.2)	0.3937
Women	1	0.9 (0.5-1.4)	2.0 (0.8-4.7)	2.6 (1.9-3.8)	3.9 (2.9-5.2)	3.8 (2.7-5.4)	
High serum apolipoprotein B level							
Men	1	2.3 (1.5-3.4)	2.5 (1.6-5.7)	3.3 (2.3-4.7)	4.9 (3.6-6.7)	5.2 (3.6-7.4)	0.8128
Women	1	1.7 (1.2-2.5)	3.2 (1.5-6.8)	2.6 (1.9-3.5)	3.0 (2.3-4.0)	3.7 (2.7-5.2)	
Apolipoprotein B/apolipoprotein A 1 ≥ 0.8							
Men	1	2.1 (1.7-2.6)	2.6 (1.4-4.6)	2.4 (2.0-3.0)	4.9 (4.1-5.9)	7.8 (5.9-10.2)	0.9267
Women	1	1.7 (1.4-2.1)	3.1 (1.8-5.3)	3.2 (2.6-3.9)	3.9 (3.3-4.7)	4.8 (3.8-6.1)	
Uric acid ≥ 6mg/dl in women or ≥ 7mg/dl in men							
Men	1	1.5 (1.1-2.0)	1.6 (1.3-2.4)	2.2 (1.6-2.9)	3.6 (2.9-4.6)	4.6 (3.5-6.0)	0.0021
Women	1	1.1 (0.6-1.8)	2.1 (1.6-5.2)	3.2 (2.2-4.6)	3.6 (2.6-5.1)	6.8 (4.8-9.7)	
Visceral adiposity index ≥ 1.8							
Men	1	2.0 (1.3-2.9)	2.1 (1.4-3.1)	18.3 (13.2-25.2)	25.1 (18.8-33.6)	38.3 (27.3-53.7)	0.0517
Women	1	1.3 (1.0-1.8)	1.8 (1.3-1.9)	11.5 (9.0-14.7)	14.2 (11.4-17.6)	17.2 (13.2-22.5)	

[*] Adjusted for age, educational attainment, smoking status, and alcohol use.

[†] Abnormal levels of each nontraditional risk factor were defined in the Definition section.

[‡] P for interaction terms (Sex × body size phenotypes) were assessed by logistic regression analysis.

Table 4

Odds ratios (95% confidence intervals) of nontraditional risk factors associated with body size phenotypes*

	Metabolically healthy			Metabolically abnormal			P for trend**
	BMI < 23 kg/m^2	BMI 23-27.4 kg/m^2	BMI ≥ 27.5 kg/m^2	BMI < 23 kg/m^2	BMI 23-27.4 kg/m^2	BMI ≥ 27.5 kg/m^2	
Multivariate adjusted odds ratios (95% confidence interval)†							
High serum lipoprotein (a) level	1	1.0 (0.8-1.2)	0.8 (0.4-1.4)	0.9 (0.8-1.1)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.189
Low serum apolipoprotein A1 level	1	1.1 (0.8-1.4)	1.6 (0.9-2.8)	2.3 (1.9-2.9)	3.0 (2.5-3.7)	3.8 (3.1-4.7)	<0.001
High serum apolipoprotein B level	1	2.0 (1.5-2.7)	3.1 (1.7-5.5)	3.1 (2.4-3.9)	4.0 (3.3-5.0)	4.8 (3.8-6.0)	<0.001
Apolipoprotein B/apolipoprotein A 1 ≥ 0.8	1	1.9 (1.6-2.2)	3.0 (2.0-4.5)	2.9 (2.5-3.4)	4.5 (4.0-5.1)	6.2 (5.2-7.4)	<0.001
Uric acid ≥ 6mg/dl in women or ≥ 7mg/dl in men	1	1.4 (1.1-1.8)	1.8 (1.2-2.7)	2.7 (2.1-3.3)	3.7 (3.1-4.5)	5.8 (4.7-7.2)	<0.001
Visceral adiposity index ≥ 1.8	1	1.6 (1.2-2.0)	1.9 (1.4-1.8)	14.1 (11.7-17.1)	18.4 (15.5-21.9)	25.3 (20.6-31.1)	<0.001
Framingham Risk Score-adjusted odds ratios (95% confidence interval)‡							
High serum lipoprotein (a) level	1	1.0 (0.8-1.2)	0.8 (0.4-1.4)	1.0 (0.8-1.2)	0.9 (0.7-1.0)	0.8 (0.7-1.1)	0.202
Low serum apolipoprotein A1 level	1	1.1 (0.8-1.4)	1.7 (0.9-3.0)	1.8 (1.4-2.2)	2.3 (2.0-2.8)	3.0 (2.4-3.7)	<0.001
High serum apolipoprotein B level	1	2.1 (1.6-2.8)	3.1 (1.7-5.5)	3.3 (2.6-4.2)	4.2 (3.4-5.2)	4.8 (3.8-6.1)	<0.001
Apolipoprotein B/apolipoprotein A 1 ≥ 0.8	1	2.0 (1.7-2.3)	3.1 (2.1-4.6)	2.7 (2.4-3.2)	4.3 (3.8-4.8)	5.7 (4.8-6.8)	<0.001
Uric acid ≥ 6mg/dl in women or ≥ 7mg/dl in men	1	1.4 (1.1-1.8)	1.6 (1.3-2.8)	2.4 (2.0-3.0)	3.4 (2.8-4.0)	5.1 (4.1-6.3)	<0.001
Visceral adiposity index ≥ 1.8	1	1.5 (1.2-1.9)	1.7 (1.4-1.9)	12.7 (10.5-15.3)	16.3 (13.8-19.3)	22.4 (18.3-27.4)	<0.001

*Abnormal levels of each nontraditional risk factor were defined in the Definition section.

†Adjusted for age, sex, educational attainment, smoking status, and alcohol use.

‡Adjusted for educational attainment, alcohol use and Framingham Risk Score (low, intermediate, and high).

**Trends for ORs across the 6 body size phenotypes were tested using Breslow-Day test.

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