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Metabolically healthy obese phenotype and risk of cardiovascular disease: Results from the China Health and Retirement Longitudinal Study

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ABSTRACT

Background: Epidemiologic evidence on metabolically healthy obese (MHO) phenotype and cardiovascular diseases (CVD) risk remains controversial.
Aims: We aim to examine the relationship between MHO and risk of CVD among the Chinese population.
Methods: The China Health and Retirement Longitudinal Study is a prospective cohort study of 7849 participants aged ≥45 years without CVD at baseline. Metabolic health status was assessed based on blood pressure, triglycerides, high-density lipoprotein cholesterol, glycated hemoglobin, fasting glucose, and C-reactive protein. A cutoff point of body mass index of 24.0 kg/m^2 was used to define over-weight/obesity (≥24.0 kg/m^2) or normal weight (< 24.0 kg/m^2). CVD was based on self-reported doctor's diagnosis of heart problems and stroke. Incidence rate ratio (IRR) with 95% confidence interval (CI) was deduced from modified Poisson regression.
Results: During a mean 3.6 years of follow-up, 880 incident CVD events were recorded. 789 (10.05%) were identified MHO among 3321 (42.3%) obese individuals. Compared with metabolically healthy normal weight individuals, the multivariable adjusted IRR of CVD was 1.33 (95%CI: 1.19–1.49) for MHO, 1.29 (95%CI: 1.22–1.38) for metabolically unhealthy normal weight, and 1.61 (95%CI: 1.51–1.75) for metabolically unhealthy obese in the full adjusted model.
Conclusions: MHO individuals are associated with the increased risk of cardiovascular diseases among the Chinese population.

1. Introduction

In China, between 1980 and 2015, prevalence of obesity had significantly increased from 1.23% to 10.53% in adults aged 20 years or older. Furthermore, China had the highest numbers of obesity adults in 2015 in the worldwide (Collaborators et al., 2017). Epidemiologic studies and meta-analysis have demonstrated that, obesity are associated with a wide range of adverse health outcomes including cardiovascular disease (Song et al., 2016; Twig et al., 2016), stroke (Song et al., 2016), diabetes mellitus (Tobias et al., 2014), cancer (Caleyachetty et al., 2017; Song et al., 2016) as well as all-cause mortality (Afzal, Tybjaerg-Hansen, Jensen, & Nordestgaard, 2016; Aune et al., 2016; Song et al., 2016). However, a subgroup of obese individuals has a favorable metabolic profiles such as normal glucose, blood pressure and free of dyslipidemia, those individuals are at lower risk of cardiovascular diseases (CVD), termed as metabolically healthy obese (MHO) (Phillips, 2013; Stefan, Haring, Hu, & Schulze, 2013).

Recently, metabolically healthy obesity has evolved into a hot subject of debate whether it increases the risk of cardiovascular diseases in the field of medicine and public health. However, there is a considerable controversy surrounds this issue and lack of a consistent definition of metabolic health status (Hinnouho et al., 2013; Phillips, 2013; Seo & Rhee, 2014). The prevalence of MHO phenotype varied generally in different study population and definition of metabolic health (Appleton et al., 2013; Caleyachetty et al., 2017; Calori et al., 2011). Several studies showed that MHO was not associated with an increased risk of cardiovascular diseases and all-cause mortality (Aung, Lorenzo, Hinojosa, & Haffner, 2014; Dhana et al., 2016; Hamer &

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Stamatakis, 2012; Katzmarzyk, Janssen, Ross, Church, & Blair, 2006; Seo & Rhee, 2014), while other studies (Caleyachetty et al., 2017; Hansen et al., 2017; Hinnouho et al., 2015; Lassale et al., 2017; Wildman et al., 2008) and meta-analysis (Kramer, Zinman, & Retnakaran, 2013; Zheng, Zhou, & Zhu, 2016) showed a higher risk for a range of adverse outcomes. For example, a recently published article by Caleyachetty et al. had demonstrated that, compared with metabolically healthy with normal weight individuals, MHO individuals had a 1.5-fold risk of coronary heart disease among 3.5 million U.K. population (Caleyachetty et al., 2017). However, this paper maybe overlook several potential confounding factors, especially depression (Hare, Toukhsati, Johansson, & Jaarsma, 2014), cognitive function (Picano, Bruno, Ferrari, & Bonuccelli, 2014) and activities of daily living (ADL) (Forman et al., 2017), those confounder may modify the relationship between MHO and CVD among the elderly. To the best of our knowledge, the pattern and prevalence of obesity and cardiovascular diseases in Chinese population is different from that in Western population (Yang et al., 2012). And, very few prospective cohort studies have been conducted in Chinese populations to investigate the association between metabolically healthy obesity and the risk of cardiovascular diseases.

Therefore, based on the China Health and Retirement Longitudinal Study (CHRLS), a large-scale national representative epidemiological data, we aim to examine the association of the MHO and metabolically unhealthy normal weight (MUH-NW) phenotype with incident CVD among 7849 individuals aged over 45 years free of CVD at baseline.

2. Methods

2.1. Study design and population

The China Health and Retirement Longitudinal Study (CHRLS) is a national population-based prospective cohort study of 17,708 men and women aged 45 years or older from 28 provinces in China. A multistage probability sampling method was used to obtain a nationally representative sample. The study design and sampling procedure of CHRLS have been published previously (Zhao, Hu, Smith, Strauss, & Yang, 2014). In brief, the first examination of participants took place during the 2011–2012 period, with two follow-up visits taking place, each approximately every 2 years. In the present study, 11,847 participants who had stored whole-blood samples were available for measurement of metabolic health status. We excluded participants who had a history of cardiovascular disease, as well as those who had missing data for height or weight or body mass index (BMI) < 18.5 kg/m^2. Our final sample size was 7849 persons. The study CHRLS protocol was approved by the ethical review committee at the Peking University and the Chinese Center for Disease Control and Prevention, and written informed consent was obtained from all participants.

2.2. Assessment of body mass index

Participants' body weight was measured by using Omron™ HN-286 electronic scale [Seca Trading (Hangzhou) Co., LTD., Hangzhou, China] in underwear and height was measured using Seca™213 stadiometer [Krell Precision (Yangzhou) Co. LTD., Yangzhou, China] in the Frankfort plane with standing erect in bare feet with head. BMI was calculated as weight in kilograms dividing by the square of height in meters (kg/m^2). According to the standard classification of general adiposity measured by BMI specific for Chinese adluts (Lee et al., 2007), participants were categorized as follows: normal weight (18.5–23.9 kg/m^2), overweight/obese (≥24.0 kg/m^2). For the current analysis, participants with underweight (BMI < 18.5 kg/m^2) were excluded (n = 594).

2.3. Assessment of metabolic factors

Systolic and diastolic blood pressure (BP) was measured with an Omron™ HEM-7200 Monitor [Omron (Dalian) Co., LTD., Dalian, China] by certified health workers or nurses in the sitting position after 5-min rest between each reading. Three times BP measurements were taken with a 45-s interval and then were averaged to represent individuals' average level of BP. Participants had been fasting overnight before the health examination and blood samples were taken from the antecubital vein. Serum total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) were measured using an enzymatic colorimetric test. Blood glucose was measured using the glucose oxidase method. Glycosylated hemoglobin (HbA1c) was measured using the affinity high performance liquid chromatography (HPLC) method. High-sensitivity C-reactive protein (hsCRP) was determined using an immunoturbidimetric assay. These assays were performed at the Youanmen Center for Clinical Laboratory of Capital Medical University. This laboratory has a regular external quality assessment organized by the Chinese Ministry of Health.

2.4. Assessment of metabolic health status

There is not yet a standardized definition of metabolic health status. According to the existing criteria and availability of data, 5 metabolic abnormalities were defined as (Hamer, Batty, & Kivimaki, 2012): elevated blood pressure (Systolic/diastolic BP ≥ 130/85 mm Hg, or physician-diagnosed or antihypertensive medication use), impaired glycemic control (fasting glucose level ≥100 mg/dL or doctor's diagnosed diabetes or antidiabetic medication use, or HbA1c ≥6.0%), high triglycerides (≥150 mg/dL or lipid-lowering drugs use), decreased HDL-C (< 40 mg/dL for men or < 50 mg/dL for women) and diabetes), systemic inflammation (hsCRP ≥3 mg/L).

Based on the combined of BMI categories (normal weight, overweight/obesity) and metabolic health status (metabolically healthy: having 0–1 metabolic abnormality), and metabolically unhealthy: having 2 or more metabolic abnormalities), participants were then categorized into four groups: metabolically healthy normal weight (MHNW); metabolically healthy overweight or obese (MHO); metabolically unhealthy normal weight (MUNW); metabolically unhealthy overweight or obese (MUO).

2.5. Assessment of covariates

Data on social and demographic characteristics were obtained from the standard questionnaire in the baseline survey as follows: age, sex (male, female), region (rural, urban), marital status (married, unmarried), education level (no formal education, primary, and middle or high school or above). Self-reported health behaviors included smoking status (never, former, and current smoker), frequency of alcohol consumption in the past year (never, less than once a month, and more than once a month), and physical activity (yes, no). Trained health workers collected information about physician-diagnosed hypertension, diabetes mellitus, dyslipidemia, lung diseases, asthma and arthritis and collected information on prescribed medication. History of fall was asked for each participant. Depressive symptoms were assessed with the 10 items-Center for Epidemiologic Studies Depression scale (CES-D), which has been widely used and validated in prior studies (Shrout & Yager, 1989). Participants who met ≥10 scores were considered as elevated depressive symptoms (Bjorgvinsson, Kertz, Bigda-Peyton, McCoy, & Aderka, 2013). Cognitive function consisted of immediate and delayed recall of a 10-word list (20 points), serial 7 subtraction (5 points), orientation (1 point each for year, month, date, day of the week and season) and drew the picture (1 point). We combined scores ranged 0–31 with higher scores indicating better cognitive function. Physical impairments were defined as ≥1 dependency in activities of daily

living (ADLs) including dressing, bathing, eating, getting out of bed, using the toilet and continence; and instrumental activities of daily living (IADLs), including doing housework, preparing meals, shopping, managing bills, and taking medications (Quinn, McArthur, Ellis, & Stott, 2011).

2.6. Outcomes ascertainment

Cardiovascular diseases were based on self-reported doctor's diagnosis of heart diseases (including heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems) and stroke.

2.7. Statistical analysis

Baseline characteristics of the study population were reported using percentages for categorical variables and mean (SD) or median (IQR) for continuous variables as appropriate. We compared the characteristics differences between BMI-metabolic status phenotypes described above with analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables and the chi-squared test for categorical variables.

Person-years was calculated from the baseline health examination (May 1, 2011) until the occurrence of first cardiovascular disease events, death, loss to follow-up, or the end of follow-up (May 31, 2015), whichever came first. Incidence rates of CVD were calculated per 1000 person-years. Incidence rate ratio (IRR) were estimated from a modified Poisson regression with robust error variance (Hoffmann et al., 2008; McNutt, Wu, Xue, & Hafner, 2003). MHNW individuals were used as referent category. The three core models were as follows: Model 1 was adjusted for age, gender, residence. Model 2 was adjusted for age, gender, residence, educational level, marital status, smoking status, alcohol use, and physical activity. Finally, model 3 was adjusted for all the variables in model 2 plus history of arthritis, asthma and history of fall, physical impairments in ADL and IADL, and cognition score, total cholesterol, high-density cholesterol levels. For the current analyses involving more than two exposure categories, the floating absolute risk method (Arbogast, 2005) was used to calculate all categories of IRR (including the reference category). The 95% confidence interval (CI) for each log IRR of BMI-metabolic status phenotypes was estimated by adding ± 1.96 times the floated standard error of each log IRR (Easton, Peto, & Babiker, 1991).

Stratified analyses were conducted a priori to assess whether the association between BMI-metabolic status phenotypes and cardiovascular diseases varied among different demographic variables including sex (male vs. female), age group (< 65 years vs. ≥ 65 years), and residence (rural vs. urban). The cutoff value of 65 years was according to the pervious definition of "elderly" (Orimo et al., 2006). Therefore, we re-fitted the full adjusted model included the multiplicative interaction terms between BMI-metabolic status phenotypes and those effect modifiers, and likelihood ratio test were used to test whether the interaction terms were significant. Sensitivity analysis was also conducted: metabolically healthy individuals were defined as having none of the metabolic risk factors.

The statistical analyses were performed using Stata (version 14.1, StataCorp, College Station, Texas) and the R statistical package, versions 3.4.2 (https://www.r-project.org/). All P values were 2-side and statistical significance was set as $P < 0.05$.

3. Results

A total of 11,847 participants attended the blood examination and 3998 were excluded for one or more of the following reasons: missing data on BMI (n = 1987), BMI < 18.5 kg/m^2 (n = 681), prevalent CVD (n = 1239), or age < 45 (n = 91) (Fig. 1). The final sample consisted of 7849 individuals free of CVD had data both on BMI and metabolic factors. The participants included in the analytic sample compared with those who were excluded were more likely to be older (59.88 ± 10.82 vs. 58.76 ± 9.19; $P < 0.001$), male (47.20% vs. 45.06%; $P = 0.032$) and living in urban (40.01% vs. 34.59%; $P < 0.001$) (Supplementary materials Table S1). Although these differences were statistically significant, but the absolute differences were small. In the analytic sample, 37.52% (n = 2945) of the participants were metabolically healthy; and 789 (n = 10.05%) individuals were MHO. Baseline characteristics of the study population according to the BMI-metabolic status phenotypes are shown in Table 1. MHO individuals were more likely to be younger, female, high education level compared with metabolically unhealthy obese individuals.

During the mean follow-up of 3.67 years corresponding 28,922 person-years, 880 adjudicated CVD cases were documented, corresponding to an incidence rate of 30.43 (95% CI: 28.48–32.50) per 1000 person-years. Table 2 shows the associations between BMI-metabolic status phenotypes and the risk of CVD with the MHNW group as the reference. In analyses adjusted for age, sex and area, the metabolically healthy overweight or obese individuals experienced a 40% increased risk of CVD (IRR: 1.40, 95% CI: 1.25–1.56). These associations were attenuated in the fully adjusted model (IRR: 1.33, 95% CI: 1.19–1.49). Individuals who were MUNW had an increased risk of CVD compared to normal weight individuals without metabolic abnormalities after adjustment for potential confounders (IRR: 1.29, 95% CI: 1.22–1.38). Fig. 2 showed the incidence risk ratio for heart diseases and stroke analyzed separately rather than a composite CVD outcome. The results did not essentially change. Subgroup analyses were conducted and showed in Fig. 3. There was no evidence that the risk of CVD in MHO individuals differed significantly by age, sex and area (all P interaction > 0.05). Sensitivity analysis also showed that MHO increased the risk of CVD (IRR: 1.94, 95% CI: 1.18–3.20) (Table S2).

4. Discussion

In this prospective cohort study of Chinese adults initially free of cardiovascular diseases from the China Health and Retirement Longitudinal Study, we explore the combined effect of BMI-metabolic status on the occurrence of CVD with a mean 3.67 years of follow-up. Our findings showed that metabolically healthy overweight or obese and metabolically unhealthy normal weight individuals were significantly associated with a higher risk of developing CVD compared with individuals who was metabolically healthy normal weight. These associations seemed to be similar both in those aged < 65 and ≥ 65 years, in male and female, and in urban and rural resident area.

It is well known that overweight and obesity strongly increases risk of CVD and mortality (Twig et al., 2016). In contrast to almost previous studies conducted among Western populations (Caleyachetty et al., 2017; Hinnouho et al., 2015; Lassale et al., 2017), overweight and obesity were more serious and challenge. The overall prevalence of overweight and obesity in China among 45 years or older adults in 2011 was 31.43% and 11.87%, respectively. Our present result was consistent with the results from previous studies (Thomsen & Nordestgaard, 2014; Twig et al., 2016) that obese adults were at high risk of cardiovascular disease. Several prospective studies had previously reported the association of MHO phenotype with risk of CVD, but showing inconsistent results (Aung et al., 2014; Caleyachetty et al., 2017; Dhana et al., 2016; Hamer & Stamatakis, 2012; Hansen et al., 2017; Hinnouho et al., 2015; Lassale et al., 2017; Thomsen & Nordestgaard, 2014). For example, in the Rotterdam Study included 5314 individuals aged 55 years or older, no significant association was observed an increased CVD risk in MHO individuals (HR: 1.07, 95% CI: 0.75–1.53) over 14 years of follow-up. Additionally, Espinosa et.al found that there was no difference in the risk of CVD between MHO and MHNW in 18,071 individuals over 15 years of follow-up in Olmsted County (Espinosa De Ycaza, Donegan, & Jensen, 2018). However, in a large cohort study of 3.5 million UK adults over 5.4 years of follow-up, individuals who were overweight without metabolic abnormalities had an increased risk of coronary heart disease (HR: 1.30, 95% CI:

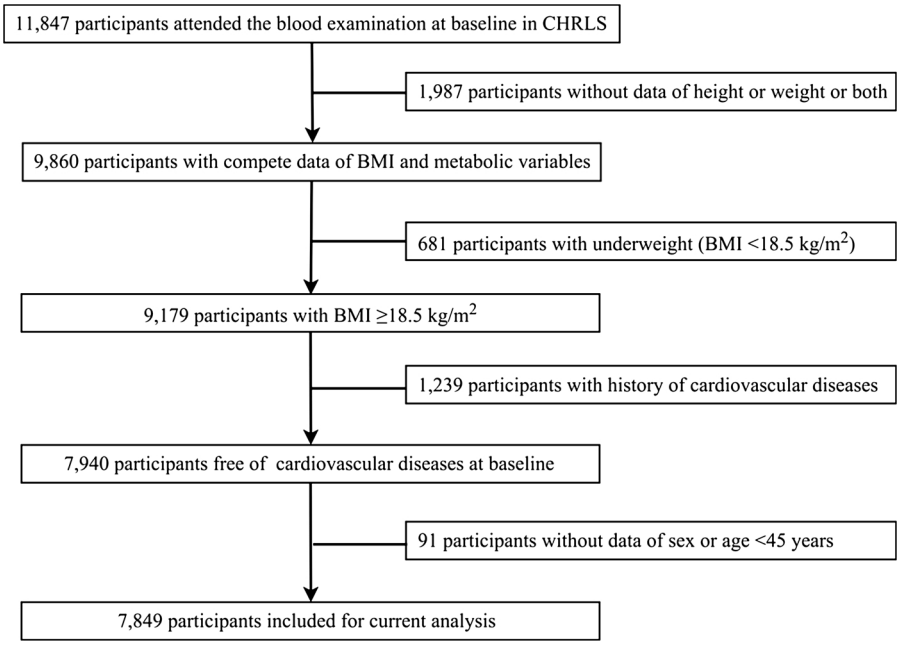

Fig. 1. Flow chart for selection of study participants.

Table 1
Baseline Characteristics of the Study Participants According to Body Mass Index-Metabolic Heath Status.

Characteristic*	MHNW	MHO	MUNW	MUO	p-value
n (%)	2156 (27.47)	789 (10.05)	2372 (30.22)	2532 (32.26)	
Age (yr)	58.16 ± 8.98	55.29 ± 8.10	61.23 ± 9.64	58.02 ± 8.69	< 0.001
Female sex (%)	948 (43.97)	474 (60.08)	1165 (49.11)	1557 (61.49)	< 0.001
Urban residence (%)	623 (28.90)	291 (36.88)	720 (30.35)	1081 (42.69)	< 0.001
Middle school or above	628 (29.13)	295 (37.39)	605 (25.51)	864 (34.12)	< 0.001
Married (%)	1928 (89.42)	736 (93.28)	1978 (83.39)	2301 (90.88)	< 0.001
Current smoker	846 (39.24)	169 (21.42)	851 (35.88)	552 (21.80)	< 0.001
Drinking ≥ 1 times/month	679 (31.49)	199 (25.22)	652 (27.49)	535 (21.13)	< 0.001
Physical activity (%)	738 (34.23)	285 (36.12)	807 (34.02)	859 (33.93)	0.047
Physician-diagnosed disease (%)					
Hypertension	125 (5.80)	76 (9.63)	548 (23.10)	974 (38.47)	< 0.001
Diabetes	20 (0.93)	10 (1.27)	125 (5.27)	224 (8.85)	< 0.001
Dyslipidemia	21 (0.97)	11 (1.39)	171 (7.21)	384 (15.17)	< 0.001
Lung diseases	199 (9.23)	52 (6.59)	235 (9.91)	198 (7.82)	0.007
Asthma	54 (2.50)	14 (1.77)	87 (3.67)	85 (3.36)	0.016
Arthritis	706 (32.75)	283 (35.87)	802 (33.81)	881 (34.79)	0.320
History of fall (%)	346 (16.05)	124 (15.72)	351 (14.80)	412 (16.27)	0.520
Depression (%)	806 (37.38)	243 (30.80)	888 (37.44)	784 (30.96)	< 0.001
Physical impairments in ADL (%)	291 (13.50)	108 (13.69)	374 (15.77)	355 (14.02)	0.130
Physical impairments in IADL (%)	351 (16.28)	123 (15.59)	544 (22.93)	440 (17.38)	< 0.001
Cognitive score	14.43 ± 5.25	15.55 ± 5.17	13.61 ± 5.41	15.13 ± 5.28	< 0.001
Systolic blood pressure	119.65 ± 16.95	123.07 ± 17.42	135.60 ± 21.63	137.80 ± 21.28	< 0.001
Diastolic blood pressure	70.31 ± 10.49	73.89 ± 11.20	77.12 ± 11.86	80.51 ± 11.95	< 0.001
Body mass index (Kg/m^2)	21.33 ± 1.48	26.38 ± 3.01	21.66 ± 1.49	27.27 ± 3.15	< 0.001
Total cholesterol (mg/dl)	187.63 ± 34.74	193.50 ± 33.20	194.71 ± 40.21	199.79 ± 41.90	< 0.001
LDL-C (mg/dl)	113.09 ± 31.15	121.85 ± 29.86	116.06 ± 36.53	119.60 ± 38.06	< 0.001
HDL-C (mg/dl)	59.40 ± 14.18	54.94 ± 11.49	49.23 ± 15.44	43.72 ± 12.46	< 0.001
Triglycerides (mg/dl)	79.65 (61.95, 105.32)	91.15 (69.92, 114.17)	117.71 (80.54, 175.23)	146.91 (101.78, 210.63)	< 0.001
Fasting glucose (mg/dl)	97.47 ± 18.62	97.78 ± 22.21	117.61 ± 44.20	118.72 ± 41.56	< 0.001
Glycated Hemoglobin (%)	5.10 (4.80, 5.30)	5.10 (4.80, 5.30)	5.10 (4.90, 5.40)	5.20 (4.90, 5.60)	< 0.001
C-Reactive Protein (CRP) (mg/l)	0.70 (0.43, 1.27)	0.83 (0.51, 1.36)	1.15 (0.57, 3.03)	1.47 (0.78, 2.99)	< 0.001

Abbreviation: MHNW means metabolically healthy normal weight, MHO means metabolically healthy overweight or obese, MUNW means metabolically unhealthy normal weight, MUO means metabolically unhealthy overweight or obese, ADL means activities of daily living, IADL means instrumental activities of daily living, LDL-C means low-density lipoprotein cholesterol and HDL-C means high-density lipoprotein cholesterol.

* Values were expressed as mean ± SD, median (IQR), or n (%) when appropriate.

1.27–1.34) (Caleyachetty et al., 2017). Similarly, our study also showed metabolically healthy overweight or obese individuals had increased of 33% risk of CVD (IRR: 1.33, 95% CI: 1.19–1.49). Most importantly, we had carefully adjusted for most potential confounding variables including depression, cognitive function and activities of daily living (ADL), which had most impacts on the risk of CVD in the late-life for the elderly.

Previous studies had proven that metabolically healthy obesity was a temporary condition and not a benign condition (Kramer et al., 2013; Stefan et al., 2013). Metabolic risk factors were a key point that

Table 2
Incidence Risk Ratio for Cardiovascular Disease Associated with Body Mass Index-Metabolic Status.

	MHNW (n = 2156)	MHO (n = 789)	MUNW (n = 2372)	MUO (n = 2532)
Number of incidence CVD	168	82	270	360
Number of person-year	8088	2934	8696	9204
Incidence rate per 1000 person-year	20.77	27.95	31.05	39.11
Model 1: Incidence Risk Ratio[a]	1.00	1.40	1.33	1.76
95% CI, without floating absolute risk	*Ref.*	1.09–1.80	1.10–1.59	1.48–2.10
95% CI, with floating absolute risk	0.93–1.08	1.25–1.56	1.25–1.41	1.67–1.86
Model 2: Incidence Risk Ratio[b]	1.00	1.39	1.31	1.72
95% CI, without floating absolute risk	*Ref.*	1.08–1.79	1.09–1.58	1.44–2.04
95% CI, with floating absolute risk	0.93–1.08	1.26–1.57	1.24–1.40	1.65–1.83
Model 3: Incidence Risk Ratio[c]	1.00	1.33	1.29	1.61
95% CI, without floating absolute risk	*Ref.*	1.02–1.72	1.07–1.55	1.31–1.97
95% CI, with floating absolute risk	0.92–1.09	1.19–1.49	1.22–1.38	1.51–1.75

[a] Model 1: Adjusted for age, gender, residence.
[b] Model 2: Adjusted for age, gender, residence, educational level, marital status, smoking status, alcohol use, and physical activity.
[c] Model 3: Adjusted for factors in Model 2 plus history of arthritis, asthma, lung disease and fall, physical impairments in ADL and IADL, cognitive score, total cholesterol, LDL cholesterol.

overweight or obesity contributed to the development of CVD. Compared with normal weight individuals, HDL-C cholesterol was decreased and blood pressure, triglycerides, CRP, and fasting plasma glucose was increased for overweight or obesity. Our finding that high blood pressure (Rapsomaniki et al., 2014), high triglycerides (Patel et al., 2004), elevated CRP (Wakugawa et al., 2006) increased the risk of CVD and stroke was consistent with previous studies. In accordance with our study, in the Whitehall II cohort study with a 17-year follow-up, metabolically unhealthy individuals had an increased risk of incident CVD (HR: 1.97, 95% CI: 1.72–2.27) (Hinnouho et al., 2015). Similarly, in the Copenhagen General Population Study of 71,527 individuals, individuals with metabolic syndrome were increasing cumulative incidences of CHD (Thomsen & Nordestgaard, 2014).

Our study has several strengths, including a nationally representative study and the availability of detailed information on multiple laboratory variables, which allowed us to define metabolic health more objectively and accurately. In addition, the questionnaire used in CHARLS was accordance with Health and Retirement Study (Sonnega et al., 2014) and English Longitudinal Study of Ageing (Steptoe, Breeze, Banks, & Nazroo, 2013), and the data collection was accurate and comprehensive to give us a chance to adjust potential confounding variables. Several limitations of our study need to be considered. First, the relatively small fraction of MHO phenotype, a low number of CVD events and short follow-up may not have enough statistical power to discriminate differences in risk for CVD. However, we had confirmed metabolically healthy overweight/obese individuals were at a higher risk of CVD. Second, previous studies had reported that cardiorespiratory fitness (CRF) modified the relation between obesity and CVD (Jae et al., 2017; Ortega, Cadenas-Sanchez, Sui, Blair, & Lavie, 2015), however, CRF measurement was not available for CHARLS. Third, metabolic factors and BMI was only measured at baseline, metabolic change and weight loss or gain in our study could not completely be controlled. Finally, our study was conducted in a relatively older Chinese adult, and the generalizability of our finding to other populations needed to be more cautious, particularly other age or race/ethnicity groups.

5. Conclusions

In summary, in our population-based study of middle-aged and elderly adults, metabolically healthy overweight/obesity individuals were associated with higher risk of cardiovascular diseases.

Competing interests

The authors declare that they have no competing interests.

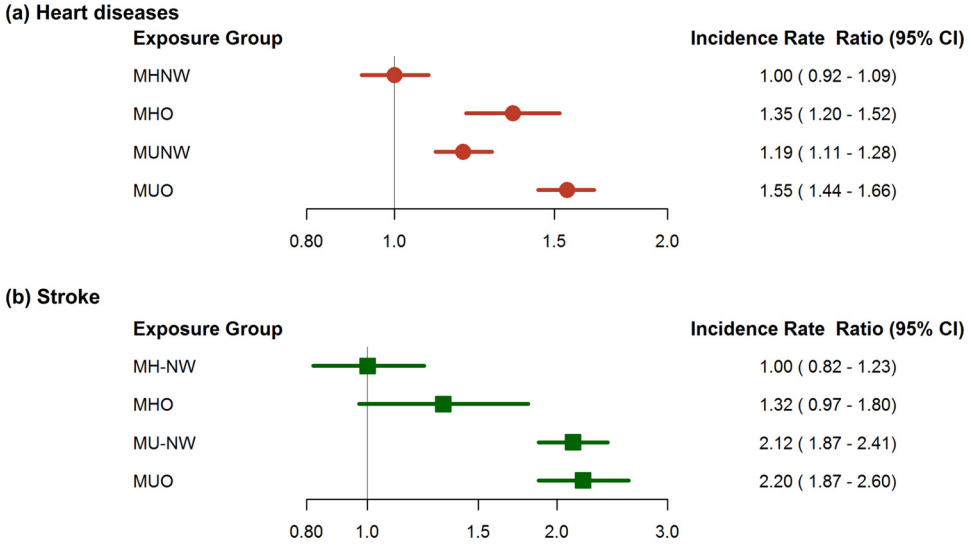

Fig. 2. Incidence Risk Ratio for Heart Diseases (including heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems) and Stroke Analyzed Separately Rather Than a Composite CVD Outcome Associated with BMI-Metabolic Status.

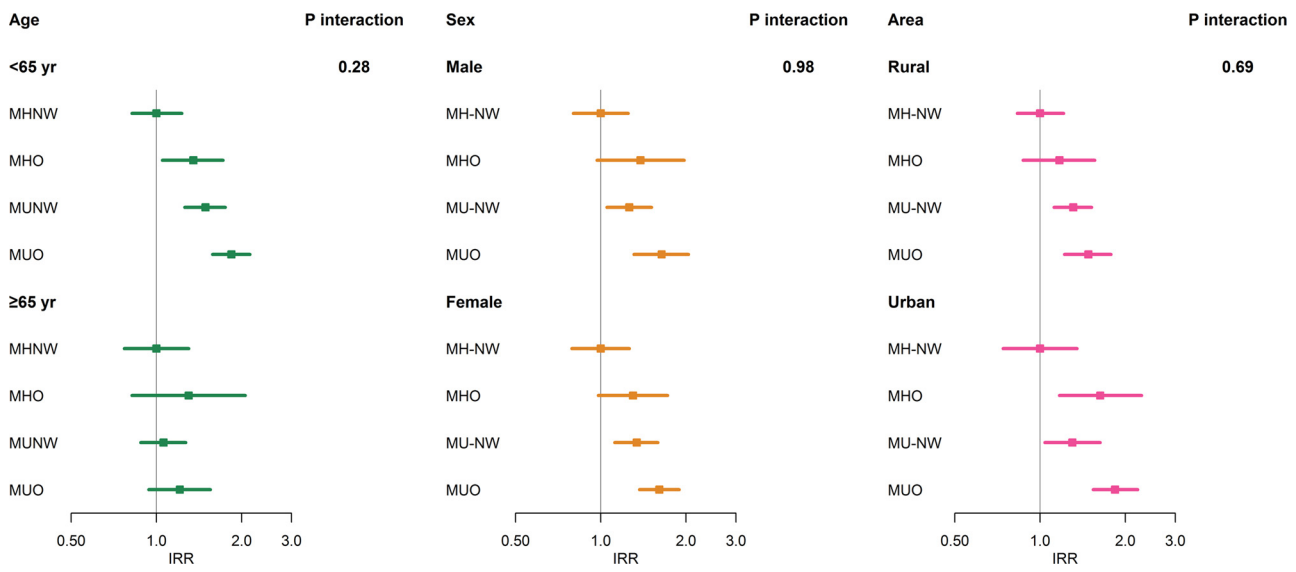

Fig. 3. Stratified Analysis of BMI-Metabolic Status for Risk of CVD According to Age, Sex and Area.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.archger.2019.01.004.

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