JCI insight

Overweight and obesity could not predicate all-cause mortality in metabolically healthy individuals

Qiuyue Tian, … , Shouling Wu, Youxin Wang

JCI Insight. 2020. https://doi.org/10.1172/jci.insight.136982.

Clinical Medicine In-Press Preview Metabolism

BACKGROUND. Metabolically healthy obesity (MHO) and metabolically healthy overweight (MH-OW) have been suggested to be an important and emerging phenotype with an increased risk of cardiovascular disease (CVD). However, whether MHO and MH-OW are associated with all-cause mortality remains inconsistent.

METHODS. The association of MHO and MH-OW and all-cause mortality was determined in China community-based prospective cohort study (Kailuan Study) including 93,272 adults at baseline. Data were analyzed from 2006 to 2017. Participants were categorized into six mutually exclusive groups according to the body mass index (BMI) and metabolic syndrome (MetS) status. The primary outcome is all-cause death, whereas accidental deaths were excluded.

RESULTS. During a median follow-up of 11.04 years (interquartile range: 10.74-11.22 years), 8,977 deaths occurred. Compared to healthy participants with normal BMI (MH-NW), MH-OW had lowest risk of all-cause mortality (multivariate-adjusted hazard ratio [aHR]: 0.926; 95% confidence interval [CI]: 0.861 to 0.997), whereas there was no increased or decreased risk for MHO (aHR: 1.009; 95% CI: 0.886 to 1.148). Stratified analyses and sensitivity analyses further validated that nonsignificant association between MHO and all-cause mortality.

CONCLUSIONS. Overweight and obesity do not predicate increased risk of all-cause mortality in […]

Overweight and obesity could not predicate all-cause mortality in metabolically healthy individuals

Qiuyue Tian[1,#], Anxin Wang[2,3,#], Yingting Zuo[1], Shuohua Chen[4], Haifeng Hou[5], Wei Wang[5,6], Shouling Wu[4], Youxin Wang[1]

[1]Beijing Key Laboratory of Clinical Epidemiology, School of Public Health, Capital Medical University, Beijing 100069, China

[2]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

[3]Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing, China.

[4]Department of Cardiology, Kailuan General Hospital, North China University of Science and Technology, Tangshan, China.

[5]School of Public Health, Shandong First Medical University & Shandong Academy of Medical Sciences, Tai'an 271000, China

[6]School of Medical and Health Sciences, Edith Cowan University, Perth WA 6027, Australia

Corresponding to:

Youxin Wang, PhD, Professor

School of Public Health, Capital Medical University

10 Youanmen Xitoutiao, Beijing 100069, China

Tel: 0086 10 83911779; Fax: 0086 10 83911508;

E-mail: wangy@ccmu.edu.cn

&

Shouling Wu, PhD, Professor

Department of Cardiology, Kailuan General Hospital

57 Xinhua East Road, Tangshan 063000, China

Tel: +86 315 3025655; Fax: + 86 315 3025655;

E-mail: drwusl@163.com

# Contributed equally.

Abstract

Background: Metabolically healthy obesity (MHO) and metabolically healthy overweight (MH-OW) have been suggested to be an important and emerging phenotype with an increased risk of cardiovascular disease (CVD). However, whether MHO and MH-OW are associated with all-cause mortality remains inconsistent.

Methods: The association of MHO and MH-OW and all-cause mortality was determined in China community-based prospective cohort study (Kailuan Study) including 93,272 adults at baseline. Data were analyzed from 2006 to 2017. Participants were categorized into six mutually exclusive groups according to the body mass index (BMI) and metabolic syndrome (MetS) status. The primary outcome is all-cause death, whereas accidental deaths were excluded.

Results: During a median follow-up of 11.04 years (interquartile range: 10.74-11.22 years), 8,977 deaths occurred. Compared to healthy participants with normal BMI (MH-NW), MH-OW had lowest risk of all-cause mortality (multivariate-adjusted hazard ratio [aHR]: 0.926; 95% confidence interval [CI]: 0.861 to 0.997), whereas there was no increased or decreased risk for MHO (aHR: 1.009; 95% CI: 0.886 to 1.148). Stratified analyses and sensitivity analyses further validated that nonsignificant association between MHO and all-cause mortality.

Conclusions: Overweight and obesity do not predicate increased risk of all-cause mortality in metabolic healthy Chinese individuals.

Introduction

Overweight and obesity have become serious public health issue, in both developed and developing countries (1, 2). Studies have shown that overweight and obesity are independent risk factors for cardiovascular diseases, including coronary disease, myocardial infarction (MI), ischemic heart disease and malignant tumors (3-9). Two systematic review and meta-analyses including at least 230 prospective studies showed that overweight and obesity were associated with increased risk of all-cause mortality (10, 11), which were consistent with study among 1.46 million white adults (12). Moreover, linear Mendelian randomization analyses have indicated that an increase of 1 unit in genetically predicted body mass index (BMI) gave rise to a 5-9% increased mortality risk in overweight and obese participants (13). However, a recent 22-year cohort study found that overweight had no effect on all-cause mortality, particularly it was protective effect in male or 30-39 years people (14). A large population-based cohort study found that BMI had a J-shaped association with all-cause mortality and lowest risk occurred in the range 21-25 kg/m^2 (15). A meta-analysis including 20 prospective cohort studies indicated that overweight and obesity were inversely associated with all-cause mortality with acute myocardial infarction history (16). Several large population meta-analyses findings including at least 50 prospective studies also produced the same results (17, 18). Therefore, the "obesity paradox" has been commonly identified in observational studies.

There is heterogeneity among overweight or obese individuals. Some have worse metabolic profiles and increased health risks as well as others have healthier

metabolic profiles and decreased health risks. The combination of BMI and metabolic profiles are categorized individuals into 6 groups: metabolically healthy and normal weight (MH-NW), metabolically healthy and overweight (MH-OW), metabolically healthy and obesity (MHO), metabolically unhealthy and normal weight (MU-NW), metabolically unhealthy and overweight (MU-OW), and metabolically unhealthy and obesity (MUO) (19-22). Thus, all obesity statuses are not equal.

In a previous study, we found that obesity was associated with myocardial infarction in a Chinese population, regardless of whether measurable metabolic abnormalities were present (21). This finding was consistent with several reports that aimed to identify a healthy obesity phenotype related to cardiovascular diseases (23-25). The studies about association of MH-OW or MHO phenotype with all-cause mortality risk were reported, but the results were inconsistent (26-28). Several studies have shown that MH-OW and MHO were not significantly associated with an increased risk of all-cause mortality (MH-NW as the reference) (27, 29, 30). In contrast, another study demonstrated that MHO and MH-OW were not benign conditions (28). Moreover, the association of MHO or MH-OW with all-cause mortality has not been investigated in a Chinese population. In this study, we aimed to explore the association between MHO or MH-OW and all-cause mortality in the Kailuan study, a longitudinal study including 101,510 participants and more than 10 years of follow-up.

Results

Participants were excluded with missing data (*n*=6539) or if their BMI was less than 18.5 kg/m^2 (*n*=1,699). Yet some individuals met more than one exclusion criterion. A total of 93,272 eligible participants were finally included in the analyses (Figure 1).

Among the 93,272 eligible participants, 80,569 (86.38%) were metabolically healthy. The results of MH-OW and MHO statuses were represented for 36.17% (*n*=33,736) and 14.22% (*n*=13,266) of the total samples, respectively. The demographic and biochemical characteristics of the participants were presented in Table 1. Compared with MH-NW individuals, the MH-OW and MHO individuals had a history of disease and a higher proportion of older individuals, men, and drinker. The levels of HDL-C and education in the MH-OW and MHO groups were significantly lower than those in the MH-NW groups. Besides, higher levels of blood pressure, TG, WC, LDL, and salt intake were also found in the MH-OW and MHO groups (Table 1). In addition, the MH-OW and MHO individuals had a higher proportion of abnormal index, including LDL-C, FBG, TG, and HDL-C, compared with MH-NW (*P*<0.001) (Table 1).

After a median follow-up period of 11.04 years (interquartile range: 10.74-11.22 years), 8,977 deaths occurred. The incidences of all-cause death per 1,000 person-years were 9.84 in MH-NW group, 9.31 in MH-OW group, 9.94 in MHO group, 13.95 in MUH-NW group, 11.59 in MUH-OW group, and 11.65 in MUO group. Figure 2 also showed that all-cause mortality was the highest in MUH-NW

group and the lowest in MH-OW group. In the crude Cox model, compared with MH-NW group, participants were at a 5.5% lower risk (HR: 0.945; 95% CI: 0.899-0.993) in MH-OW group, at no risk (HR: 1.009; 95% CI: 0.945-1.076) in MHO group, at a 42.7% higher risk (HR:1.427; 95% CI: 1.269-1.605) in MUH-NW group, at a 17.8% higher risk (HR: 1.178; 95% CI: 1.084-1.281) in MUH-OW group, and at a 18.5% higher risk (HR: 1.185; 95% CI: 1.078-1.302) in MUO group for all-cause mortality (Figure 3). After adjustment for sex, age, waist circumference, history of disease, socioeconomic status, lifestyle factors, and dyslipidemia, the HRs for all-cause mortality were 0.926 (95% CI: 0.861-0.997) in MH-OW group, 1.009 (95% CI: 0.886-1.148) in MHO group, 1.311 (95% CI: 1.162 -1.479) in MUH-NW group, 1.135 (95% CI: 1.023-1.260) in MUH-OW group, and 1.252 (95% CI: 1.075 -1.458) in MUO group compared with MH-NW group (Figure 3).

In the sensitivity analyses, we first carried out the main analysis among participants with no smoking habit at baseline, and similar results were obtained (Figure 4). The adjusted HRs were 0.895 (95% CI: 0.819-0.978) in MH-OW group, 0.969 (95% CI: 0.828-1.133) in MHO group, and 1.310 (95% CI: 1.136-1.510) in MUH-NW compared with MH-NW group (Figure 4A). The sensitivity analyses also showed similar results after the exclusion of participants who died during the first two years of follow-up (Figure 4B). Furthermore, we redefined obesity and MetS as well as obtained similar results. Compared to MH-NO individuals, MHO individuals had a no significantly increased risk of all-cause mortality (HR: 0.921, 95% CI: 0.742-1.144), whereas MU-NO and MUO individuals had a significantly increased

risk of all-cause mortality (MU-NO, HR: 1.207, 95% CI 1.128-1.291; MUO, HR: 1.393, 95% CI 1.146-1.692, respectively) after controlling for all confounding factors (Figure 4C). Also, the results showed that, for participants from 50 to 85 years, the adjusted HRs were 0.937 (95% CI: 0.866-1.014) in MH-OW group, 0.993 (95% CI: 0.863-1.142) in MHO group, and 1.257 (95% CI: 1.105-1.430) in MUH-NW compared with MH-NW group (Figure 4D).

In the stratified analyses, compared to MH-NW, MH-OW was associated with significantly decreased risk of all-cause mortality in women (HR: 0.732, 95% CI: 0.544-0.986), but there was no increased or decreased risk in men (HR: 0.938, 95% CI: 0.869-1.012); the association was significant in participants with a baseline age < 65 years (HR: 0.895, 95% CI: 0.807-0.993), but not in those with baseline age ≥ 65 years (HR: 0.951, 95% CI: 0.857-1.055) (Table 2). Similarly, MHO was not significantly associated with an increased risk of mortality in each stratum, and MUH remained the highest risk phenotype for all-cause mortality. There were significant interactions of age (<65 years old, ≥ 65 years old), sex and BMI-MetS phenotypes with all-cause mortality (*P*-interaction <0.01 for both), but no interactions were found for smoking status, drinking status, or physical activity (*P*-interaction >0.05 for all) (Table 2).

Discussion

In the prospective cohort study with a median follow-up of 11 years, we found that MH-OW participants had the lowest risk of all-cause mortality (HR: 0.926, 95% CI:

0.861-0.997) and participants MHO participants did not have an increased risk of all-cause mortality (HR: 1.009, 95% CI: 0.886-1.148), while MUH-NW participants had the highest risk of all-cause mortality (HR: 1.311, 95% CI: 1.162-1.479) compared to MH-NW participants, after adjusting for sex, age, waist circumference, history of disease, socioeconomic status, lifestyle factors, and dyslipidemia. The sensitivity and stratification analyses further validated these findings. To our knowledge, this is the first large population study to demonstrate that overweight and obesity do not predict an increased risk of all-cause mortality in a metabolically healthy Chinese population.

The association between MHO and all-cause mortality has been widely investigated, but the findings remain inconsistent. A systemic review and meta-analysis including 11 prospective studies from Europe, North America, and Asia (published from 1950 to June 5th 2013) indicated that MHO was not significantly associated with all-cause mortality and/or cardiovascular events (relative risk (RR): 1.07, 95% CI: 0.92-1.25) but was significantly when only studies with at least 10 years of follow-up were included (RR: 1.24, 95% CI: 1.02-1.55) (31). Another systematic review and meta-analysis (published through September 30th 2015) demonstrated that MHO was not associated with increased all-cause mortality risk (HR: 1.07; 95% CI: 0.92-1.25) (19). Recently, most studies have not favored the association between the MHO phenotype and an increased risk of all-cause mortality. A cohort study (54,089 participants, 12.8 years of follow-up) combining 5 cohort studies (Aerobics Center Longitudinal study (ACLS), Coronary Artery Risk Development in Young Adults

(CARDIA), Multi-Ethnic Study of Atherosclerosis (MESA), National Health and Nutrition Examination Survey (NHANES III) and Continuous) showed that obesity without other metabolic risk factors was not associated with an increased risk of all-cause mortality compared to lean healthy individuals (HR 1.10, 95% CI 0.8-1.6) (32). The English Longitudinal Study of Ageing (5427 participants, 8 years of follow-up) also indicated that there was no significant association between MHO and all-cause mortality (HR 1.14, 95% CI 0.83-1.52) (33). Another cohort study carried out in the United Kingdom (22,203 participants, follow-up 7 years) also revealed that the MHO phenotype (HRs: 0.91; 95% CI: 0.64-1.29) did not increase all-cause mortality risk compared with metabolically healthy individuals without obesity (27). A prospective cohort study in Finland (2,185men, 26 years of follow-up) demonstrated that metabolically healthy overweight/obese men were not at increased risk of sudden cardiac death (HR: 0.95; 95% CI: 0.40-2.24) compared with the MH-NW group (34). Consistent with these recent studies, the present study (93,272 participants, 11 years of follow-up) first verified no significant association between MHO and all-cause mortality in a Chinese population, suggesting that baseline obesity without metabolic syndrome does not have adverse effects to all-cause mortality.

Contrary to the approximately well-defined association between MHO and all-cause mortality, the association between MH-OW and all-cause mortality is more complex. Previously described systemic review and meta-analysis has indicated that MH-OW was not significantly associated with all-cause mortality and/or cardiovascular

events, in all studies (RR: 1.10, 95% CI: 0.90-1.24) or only in studies with at least 10 years of follow-up (RR: 1.21, 95% CI: 0.91-1.61) (31). Additionally, the cohort study (54,089 participants, 12.8 years of follow-up) combining 5 cohort studies (ACLS, CARDIA, MESA, National NHANES III, and Continuous) showed that overweight without other metabolic risk factors was not associated with an increased risk of all-cause mortality compared to lean healthy individuals (HR 0.95, 95% CI 0.7-1.2) (32). Most studies of the association between MH-OW and all-cause mortality demonstrated a negative relationship. The Reasons for Geographic and Racial Dereferences in Stroke (REGARDS) cohort study (22,514 participants, 6.5 years of follow-up) demonstrated that the MH-OW phenotype (HRs: 0.79; 95% CI: 0.63-0.98) was associated with a decreased risk of cancer mortality (35). Inconsistent with these studies, we first demonstrated that the MH-OW phenotype was associated with a decreased risk of all-cause mortality (HRs: 0.926; 95% CI: 0.861-0.997), suggesting that the MH-OW phenotype might be an independent protective factor for all-cause mortality.

An unusual, but understandable finding was that participants with MUH-NW phenotype were at the highest risk for all-cause mortality among six metabolic phenotypes (HR: 1.311, 95% CI: 1.162-1.479) in the present study. Consistent with our findings, several studies have shown that MUH-NW individuals were at increased risk for future cardiometabolic disease, including atrial fibrillation (26), hypertension (36), kidney disease (37), and death (27) compared with MH-NW individuals. Similarly, in a pooled analysis of 8 studies, the MUH-NW group (RR:

3.14; 95% CI: 2.36-3.93) had the highest risk for all-cause mortality compared to individuals with the other 5 metabolic phenotypes (19). Consistent with these findings, we observed that there was a highest risk of all-cause mortality in participants with the MUH-NW phenotype than in those with other phenotypes (HR: 1.311, 95% CI: 1.162-1.479). This counter-intuitive and perhaps unexpected result might be explained by that MUH-NW phenotype represents the most severe subtype along the phenotypic spectrum of individuals genetically predisposed to cardiovascular events or death (19). Genetic analyses supported the notion that metabolically unhealthy phenotypes might be associated with body-fat distribution patterns that favor visceral and ectopic fat accumulation over fat deposition in the periphery (38, 39). Furthermore, MUH-NW is most strongly characterized by a low percentage of gluteofemoral and leg fat mass (40). On the other hand, MUH-NW participants might have other undefined abnormalities (19, 41-43) or metabolic abnormalities resulting in fat distribution changes (44, 45), which might contribute to this adverse phenotype. In addition, the finding is supported by the observation that MUH-NW groups had high percentage of history of diabetes compared with other group (Table 1). Consequently, substantial attention should be given to individuals with metabolically unhealthy status despite normal weight.

MH-OW was found to be the healthiest metabolic phenotype, which is the most important strength of the present study. This large-scale prospective study, including approximately 100,000 participants who were followed-up for more than 10 years, might have resulted in the robust findings. Second, we first verified that MHO or

MH-OW did not increase the risk for all-cause mortality in a Chinese population. At this point, the present study supported the concept that “all obesity is not created equally”. However, considering our previous finding that obesity was associated with a higher risk of MI even without measurable metabolic abnormalities (21), whether participants with MHO or MH-OW should reduce their body weight which needs further consideration.

Apart from its strengths, several limitations should be addressed. First, there is no universally accepted definition of metabolic health, such as, 0 or 1 cardiometabolic abnormalities, fewer than two signs of metabolic components or limiting more serious criteria (46-48). Many previous studies used the IDF criteria to define the metabolic health as having less than two metabolic syndrome components (21, 26, 49). Therefore, we also adopted the above criteria to define metabolic health. Second, metabolic health status might change over time, specifically among individuals with obesity (50, 51); therefore, the baseline status did not represent actual exposure in a longitudinal study. Third, although a range of potential confounding factors was adjusted in the multivariate analysis, the bias resulting from unmeasured and residual confounding factors could not be completely avoided. Finally, the unbalanced sex ratio might restrict the generalization of the present findings. However, the consistencies among sensitivity and stratified analyses might minimize the limitation.

In brief, the present study shows that overweight and obesity do not predicate increased risk of all-cause mortality in metabolic healthy Chinese individuals.

Metabolic healthy overweight is the healthiest phenotype when only all-cause mortality was taken into account.

Methods

Study population

The Kailuan study is an ongoing prospective cohort study in Tangshan, China. This study was designed to investigate risk factors for chronic diseases (such as stroke, myocardial infarction, cancer, etc.). From June 2006 to October 2007, a total of 101,510 adults (81,110 men and 20,400 women) aged 18-98 years were enrolled to participate in a routine medical examinations which included physical examination, routine blood, urine, and biochemical tests every two years at 11 hospitals affiliated with the Kailuan community (52-54). This study was approved by the ethics committee of the Kailuan General Hospital and Beijing Tiantan Hospital, Capital Medical University. Written informed consent forms were obtained from all participants. In this analysis, we included all participants in the Kailuan Study, and excluded participants with missing data for biochemical parameters, socio-demographic characteristics, history of disease or current use of medication (hypertension, diabetes, stroke and myocardial infarction), and if their BMI was less than 18.5 kg/m^2 at baseline.

Exposure factors

BMI was calculated as weight in kilograms divided by height in meters squared, and participants were categorized into normal (18.50 $kg/m^2 \leq$ BMI $<$ 24.00 kg/m^2), overweight (24.00 $kg/m^2 \leq$ BMI $<$ 28.00 kg/m^2), or obesity (BMI $\geq$ 28.00 kg/m^2) groups according to Chinese-specific criteria (55). Based on the modified International Diabetes Federation criteria for the Asian population, metabolic syndrome (MetS) was defined as the presence of three or more abnormal components (WC$\geq$ 80 cm in women and $\geq$ 90 cm in men; triglyceride (TG) $\geq$1.70 mmol/L or current use of lipid-lowering agents; diastolic blood pressure $\geq$ 85 mmHg, systolic blood pressure $\geq$ 130mmHg, or self-reported history of hypertension or current use of blood pressure medication; fasting blood glucose level (FBG) $\geq$ 5.60 mmol/L, current use of glucose-lowering agents or self-reported history of diabetes; and high-density lipoprotein cholesterol (HDL-C)$<$ 1.03 mmol/L for men and $<$1.30 mmol/L for women or current use of lipid-lowering agents) (56). Metabolically healthy (MH) was defined as the presence of two or less abnormal components, while metabolically unhealthy (MUH) was defined as the presence of three or more abnormal components. Combined with BMI category (normal weight, overweight, and obesity), metabolic healthy participants were divided into 3 phenotypes: MH-NW, MH-OW and MHO, whereas metabolic unhealthy participants were divided into MUH-NW, MUH-OW and MUO (21, 46).

Covariables

Face-to-face questionnaire interviews and clinical examinations were conducted by well-trained medical staff following a standard protocol to collect information on socio-demographic characteristics, lifestyle factors, and medical history (57). Smoking status or drinking status was divided into 3 categories: “never,” “former,” and “current” (21, 52). Physical activity was evaluated regarding the frequency of physical activity, including “inactive,” “moderately active, 1-2 times/week,” and “vigorously active, ≥ 3 times/week and ≥ 30 minutes” (53). In addition, the levels of FBG, TG, and HDL-C were measured using an auto-analyzer (Hitachi 747; Hitachi, Tokyo, Japan) at the central laboratory of Kailuan General Hospital (58).

Follow-up and Outcome

All participants were followed up by face-to-face interviews at every two-year routine medical examination until December 31, 2017 or appeared the event of death. The follow-ups were performed by hospital physicians, research physicians, and research nurses who were blinded to the baseline data. For the participants without face-to-face follow-up, the follow-up information was collected by referring to death certificates from provincial vital statistics offices, discharge summaries from the 11 hospitals, or medical records from medical insurance (59).

We used all-cause death as the primary outcome. Considering unnatural death, we excluded the accidental deaths, which were transport-related accidents, violence, falling, natural hazard, medical malpractice, and food poisoning. Deaths were

assessed using family report, death certificates from provincial vital statistics offices, and medical records from medical insurance or hospitals (52).

Statistical analysis

The baseline characteristics of participants are presented as mean ± standard deviation or median with interquartile range for continuous variables, and percentage for categorical variables. Chi-square tests were used for the comparisons of categorical variables. The analysis of variance or Kruskal-Wallis tests were used for continuous variables. Person-years were calculated from the date of baseline examination to the date of death or the end of follow-up (December 31, 2017), whichever came first. The cumulative mortality among six phenotype groups was estimated using the Kaplan-Meier method and compared by log-rank tests. The Sidak method was used to adjust *P* values in the multiple-comparisons (21).

Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between the six BMI-MetS groups and all-cause mortality risk. The proportional hazards assumption was tested by the Schoenfeld residuals (21), and no violation was found. We fitted three Cox proportional hazard models. Model 1 was a crude model without adjusted covariates. Model 2 was adjusted for age and sex. Model 3 was further adjusted for smoking status, drinking status, educational level, family per-member monthly income, physical activity, salt intake, dyslipidemia, and history of disease.

To test the robustness of the main results, we conducted four sensitivity analyses in model 1 and model 3. We excluded participants who were current smokers at baseline or died during the first 2 years of follow-up. Also, we defined obesity using WC instead of BMI and defined MetS as having 2 or more of four metabolic components (excluding WC criteria). Participants were classified into the following four groups: no obesity (WC <80cm in women and < 90cm in men) without MetS (MH-NO) or with MetS (MU-NO), MHO (obesity defined as WC ≥ 80cm in women and ≥ 90cm in men), and MUO. We retained participants who were 50-85 years for avoiding differences in mortality for this reason of age. Likelihood ratio test was conducted to examine statistical interactions among BMI-MetS groups, sex, age (< 65 years, ≥65 years), smoking status, drinking status, and physical activity in association with all-cause mortality by comparing -2 log likelihood χ^2 between nested models with or without the multiplication interaction terms.

All statistical analyses were conducted using SAS, version 9.4(SAS Institute Inc). Two-sided P<0.05 was considered statistically significant.

Author contributions

Youxin Wang and Wei Wang conceived the study. Anxin Wang, Shuohua Chen, and Shouling Wu contributed population data resources. Qiuyue Tian, Anxin Wang, and Yingting Zuo analyzed data. Qiuyue Tian wrote the original draft; Youxin Wang reviewed and edited manuscript.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (NSFC) (81673247, 81872682 and 81773527), the Joint Project of the NSFC and the Australian National Health & Medical Research Council (NHMRC) (NSFC 81561128020-NHMRC APP1112767).

Reference

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF *et al*. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2014; 384(9945):766-781.

2. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet.* 2016; 387(10026):1377-1396.

3. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation.* 1983; 67(5):968-977.

4. Rabkin SW, Mathewson FA, Hsu PH. Relation of body weight to development of ischemic heart disease in a cohort of young North American men after a 26 year observation period: the Manitoba Study. *Am J Cardiol.* 1977; 39(3):452-458.

5. O'Brien EC, Fosbol EL, Peng SA, Alexander KP, Roe MT, Peterson ED. Association of body mass index and long-term outcomes in older patients with non-ST-segment-elevation myocardial infarction: results from the CRUSADE Registry. *Circ Cardiovasc Qual Outcomes.* 2014; 7(1):102-109.

6. Yatsuya H, Li Y, Hilawe EH, Ota A, Wang C, Chiang C, Zhang Y, Uemura M, Osako A, Ozaki Y *et al*. Global trend in overweight and obesity and its

association with cardiovascular disease incidence. *Circ J.* 2014; 78(12):2807-2818.

7. Riaz H, Khan MS, Siddiqi TJ, Usman MS, Shah N, Goyal A, Khan SS, Mookadam F, Krasuski RA, Ahmed H. Association Between Obesity and Cardiovascular Outcomes: A Systematic Review and Meta-analysis of Mendelian Randomization Studies. *JAMA Netw Open.* 2018; 1(7):e183788.

8. Arem H, Park Y, Pelser C, Ballard-Barbash R, Irwin ML, Hollenbeck A, Gierach GL, Brinton LA, Pfeiffer RM, Matthews CE. Prediagnosis body mass index, physical activity, and mortality in endometrial cancer patients. *J Natl Cancer Inst.* 2013; 105(5):342-349.

9. Ma J, Li H, Giovannucci E, Mucci L, Qiu W, Nguyen PL, Gaziano JM, Pollak M, Stampfer MJ. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *Lancet Oncol.* 2008; 9(11):1039-1047.

10. Aune D, Sen A, Prasad M, Norat T, Janszky I, Tonstad S, Romundstad P, Vatten LJ. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. *BMJ (Clinical research ed).* 2016; 353:i2156.

11. Global BMIMC, Di Angelantonio E, Bhupathiraju S, Wormser D, Gao P, Kaptoge S, Berrington de Gonzalez A, Cairns B, Huxley R, Jackson C *et al.* Body-mass index and all-cause mortality: individual-participant-data

meta-analysis of 239 prospective studies in four continents. *Lancet (London, England).* 2016; 388(10046):776-786.

12. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, Moore SC, Tobias GS, Anton-Culver H, Freeman LB *et al*. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med.* 2010; 363(23):2211-2219.

13. Sun YQ, Burgess S, Staley JR, Wood AM, Bell S, Kaptoge SK, Guo Q, Bolton TR, Mason AM, Butterworth AS *et al*. Body mass index and all cause mortality in HUNT and UK Biobank studies: linear and non-linear mendelian randomisation analyses. *BMJ.* 2019; 364:l1042.

14. Chen Y, Yang Y, Jiang H, Liang X, Wang Y, Lu W. Associations of BMI and Waist Circumference with All-Cause Mortality: A 22-Year Cohort Study. *Obesity (Silver Spring).* 2019; 27(4):662-669.

15. Bhaskaran K, Dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3 6 million adults in the UK. *Lancet Diabetes Endocrinol.* 2018; 6(12):944-953.

16. Wang L, Liu W, He X, Chen Y, Lu J, Liu K, Cao K, Yin P. Association of overweight and obesity with patient mortality after acute myocardial infarction: a meta-analysis of prospective studies. *Int J Obes (Lond).* 2016; 40(2):220-228.

17. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality

with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA.* 2013; 309(1):71-82.

18. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet (London, England).* 2009; 373(9669):1083-1096.

19. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. *Ann Intern Med.* 2013; 159(11):758-769.

20. Roberson LL, Aneni EC, Maziak W, Agatston A, Feldman T, Rouseff M, Tran T, Blaha MJ, Santos RD, Sposito A *et al*. Beyond BMI: The "Metabolically healthy obese" phenotype & its association with clinical/subclinical cardiovascular disease and all-cause mortality -- a systematic review. *BMC Public Health.* 2014; 14:14.

21. Xu Y, Li H, Wang A, Su Z, Yang G, Luo Y, Tao L, Chen S, Wu S, Wang Y *et al.* Association between the metabolically healthy obese phenotype and the risk of myocardial infarction: results from the Kailuan study. *Eur J Endocrinol.* 2018; 179(6):343-352.

22. Wei Y, Wang J, Han X, Yu C, Wang F, Yuan J, Miao X, Yao P, Wei S, Wang Y *et al*. Metabolically healthy obesity increased diabetes incidence in a middle-aged and elderly Chinese population. *Diabetes Metab Res Rev.* 2019:e3202.

23. Yeh TL, Chen HH, Tsai SY, Lin CY, Liu SJ, Chien KL. The Relationship between Metabolically Healthy Obesity and the Risk of Cardiovascular Disease: A Systematic Review and Meta-Analysis. *J Clin Med.* 2019; 8(8).

24. Xu R, Gao X, Wan Y, Fan Z. Association of Metabolically Healthy Overweight Phenotype With Abnormalities of Glucose Levels and Blood Pressure Among Chinese Adults. *JAMA Netw Open.* 2019; 2(10):e1914025.

25. Kouvari M, Panagiotakos DB, Yannakoulia M, Georgousopoulou E, Critselis E, Chrysohoou C, Tousoulis D, Pitsavos C. Transition from metabolically benign to metabolically unhealthy obesity and 10-year cardiovascular disease incidence: The ATTICA cohort study. *Metabolism.* 2019; 93:18-24.

26. Feng T, Vegard M, Strand LB, Laugsand LE, Morkedal B, Aune D, Vatten L, Ellekjaer H, Loennechen JP, Mukamal K *et al*. Metabolically Healthy Obesity and Risk for Atrial Fibrillation: The HUNT Study. *Obesity (Silver Spring).* 2019; 27(2):332-338.

27. Hamer M, Stamatakis E. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. *J Clin Endocrinol Metab.* 2012; 97(7):2482-2488.

28. Arnlov J, Ingelsson E, Sundstrom J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation.* 2010; 121(2):230-236.

29. Appleton SL, Seaborn CJ, Visvanathan R, Hill CL, Gill TK, Taylor AW, Adams

RJ. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. *Diabetes Care.* 2013; 36(8):2388-2394.

30. Sung KC, Ryu S, Cheong ES, Kim BS, Kim BJ, Kim YB, Chung PW, Wild SH, Byrne CD. All-Cause and Cardiovascular Mortality Among Koreans: Effects of Obesity and Metabolic Health. *Am J Prev Med.* 2015; 49(1):62-71.

31. Zheng R, Zhou D, Zhu Y. The long-term prognosis of cardiovascular disease and all-cause mortality for metabolically healthy obesity: a systematic review and meta-analysis. *J Epidemiol Community Health.* 2016; 70(10):1024-1031.

32. Kuk JL, Rotondi M, Sui X, Blair SN, Ardern CI. Individuals with obesity but no other metabolic risk factors are not at significantly elevated all-cause mortality risk in men and women. *Clin Obes.* 2018; 8(5):305-312.

33. Hamer M, Johnson W, Bell JA. Improving risk estimates for metabolically healthy obesity and mortality using a refined healthy reference group. *Eur J Endocrinol.* 2017; 177(2):169-174.

34. Jae SY, Kurl S, Fernhall B, Kunutsor SK, Franklin BA, Laukkanen JA. Are Metabolically Healthy Overweight/Obese Men at Increased Risk of Sudden Cardiac Death? *Mayo Clin Proc.* 2018; 93(9):1266-1270.

35. Akinyemiju T, Moore JX, Pisu M, Judd SE, Goodman M, Shikany JM, Howard VJ, Safford M, Gilchrist SC. A Prospective Study of Obesity, Metabolic Health, and Cancer Mortality. *Obesity (Silver Spring).* 2018; 26(1):193-201.

36. Tian S, Xu Y, Dong H. The effect of metabolic health and obesity phenotypes on

509 risk of hypertension: A nationwide population-based study using 5 representative
510 definitions of metabolic health. *Medicine (Baltimore).* 2018; 97(38):e12425.
511 37. Chang AR, Surapaneni A, Kirchner HL, Young A, Kramer HJ, Carey DJ, Appel
512 LJ, Grams ME. Metabolically Healthy Obesity and Risk of Kidney Function
513 Decline. *Obesity (Silver Spring).* 2018; 26(4):762-768.
514 38. Lotta LA, Gulati P, Day FR, Payne F, Ongen H, van de Bunt M, Gaulton KJ,
515 Eicher JD, Sharp SJ, Luan J *et al*. Integrative genomic analysis implicates
516 limited peripheral adipose storage capacity in the pathogenesis of human insulin
517 resistance. *Nat Genet.* 2017; 49(1):17-26.
518 39. Schulze MB. Metabolic health in normal-weight and obese individuals.
519 *Diabetologia.* 2019; 62(4):558-566.
520 40. Stefan N, Schick F, Haring HU. Causes, Characteristics, and Consequences of
521 Metabolically Unhealthy Normal Weight in Humans. *Cell Metab.* 2017;
522 26(2):292-300.
523 41. Kwon BJ, Kim DW, Her SH, Kim DB, Jang SW, Cho EJ, Ihm SH, Kim HY,
524 Youn HJ, Seung KB *et al*. Metabolically obese status with normal weight is
525 associated with both the prevalence and severity of angiographic coronary artery
526 disease. *Metabolism.* 2013; 62(7):952-960.
527 42. Pajunen P, Kotronen A, Korpi-Hyovalti E, Keinanen-Kiukaanniemi S, Oksa H,
528 Niskanen L, Saaristo T, Saltevo JT, Sundvall J, Vanhala M *et al*. Metabolically
529 healthy and unhealthy obesity phenotypes in the general population: the

FIN-D2D Survey. *BMC Public Health.* 2011; 11:754.

43. Hamer M, O'Donovan G, Stensel D, Stamatakis E. Normal-Weight Central Obesity and Risk for Mortality. *Ann Intern Med.* 2017; 166(12):917-918.

44. Aung K, Lorenzo C, Hinojosa MA, Haffner SM. Risk of developing diabetes and cardiovascular disease in metabolically unhealthy normal-weight and metabolically healthy obese individuals. *J Clin Endocrinol Metab.* 2014; 99(2):462-468.

45. Eckel N, Muhlenbruch K, Meidtner K, Boeing H, Stefan N, Schulze MB. Characterization of metabolically unhealthy normal-weight individuals: Risk factors and their associations with type 2 diabetes. *Metabolism.* 2015; 64(8):862-871.

46. Stefan N, Haring HU, Schulze MB. Metabolically healthy obesity: the low-hanging fruit in obesity treatment? *Lancet Diabetes Endocrinol.* 2018; 6(3):249-258.

47. Stefan N, Haring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. *Lancet Diabetes Endocrinol.* 2013; 1(2):152-162.

48. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, Sowers MR. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004).

Arch Intern Med. 2008; 168(15):1617-1624.

49. Suliga E, Ciesla E, Rebak D, Koziel D, Gluszek S. Relationship Between Sitting Time, Physical Activity, and Metabolic Syndrome Among Adults Depending on Body Mass Index (BMI). *Med Sci Monit.* 2018; 24:7633-7645.

50. Espinosa De Ycaza AE, Donegan D, Jensen MD. Long-term metabolic risk for the metabolically healthy overweight/obese phenotype. *Int J Obes (Lond).* 2018; 42(3):302-309.

51. Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. *Lancet Diabetes Endocrinol.* 2018; 6(9):714-724.

52. Wang A, Wu J, Zhou Y, Guo X, Luo Y, Wu S, Zhao X. Measures of adiposity and risk of stroke in China: a result from the Kailuan study. *PLoS One.* 2013; 8(4):e61665.

53. Wang A, Zhang Y, Li J, Zhao Q, Cao Y, Li J, Zhang R, Chen S, Gao J, Wu S. High SBP trajectories are associated with risk of all-cause death in general Chinese population. *J Hypertens.* 2018; 36(6):1299-1305.

54. Wu S, Huang Z, Yang X, Zhou Y, Wang A, Chen L, Zhao H, Ruan C, Wu Y, Xin A *et al*. Prevalence of ideal cardiovascular health and its relationship with the 4-year cardiovascular events in a northern Chinese industrial city. *Circ*

572 *Cardiovasc Qual Outcomes.* 2012; 5(4):487-493.
573 55. Chen C, Lu FC, Department of Disease Control Ministry of Health PRC. The
574 guidelines for prevention and control of overweight and obesity in Chinese
575 adults. *Biomed Environ Sci.* 2004; 17 Suppl:1-36.
576 56. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA,
577 Fruchart JC, James WP, Loria CM, Smith SC, Jr. Harmonizing the metabolic
578 syndrome: a joint interim statement of the International Diabetes Federation Task
579 Force on Epidemiology and Prevention; National Heart, Lung, and Blood
580 Institute; American Heart Association; World Heart Federation; International
581 Atherosclerosis Society; and International Association for the Study of Obesity.
582 *Circulation.* 2009; 120(16):1640-1645.
583 57. Wang A, Sun Y, Liu X, Su Z, Li J, Luo Y, Chen S, Wang J, Li X, Zhao Z *et al*.
584 Changes in proteinuria and the risk of myocardial infarction in people with
585 diabetes or pre-diabetes: a prospective cohort study. *Cardiovasc Diabetol.* 2017;
586 16(1):104.
587 58. Wang A, Liu X, Su Z, Chen S, Zhang N, Wu S, Wang Y, Wang Y. Two-Year
588 Changes in Proteinuria and the Risk of Stroke in the Chinese Population: A
589 Prospective Cohort Study. *J Am Heart Assoc.* 2017; 6(7).
590 59. Wang A, Chen S, Wang C, Zhou Y, Wu Y, Xing A, Luo Y, Huang Z, Liu X, Guo
591 X *et al*. Resting heart rate and risk of cardiovascular diseases and all-cause death:
592 the Kailuan study. *PLoS One.* 2014; 9(10):e110985.
593

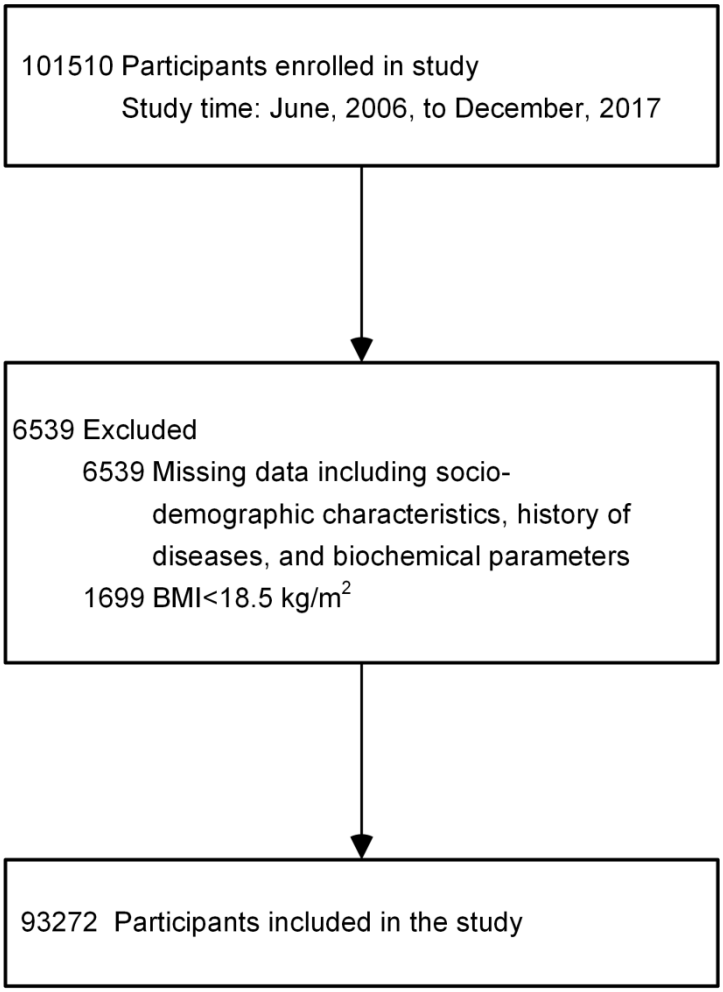

Figure 1 The flow diagram of study participants

Abbreviations: BMI, body mass index.

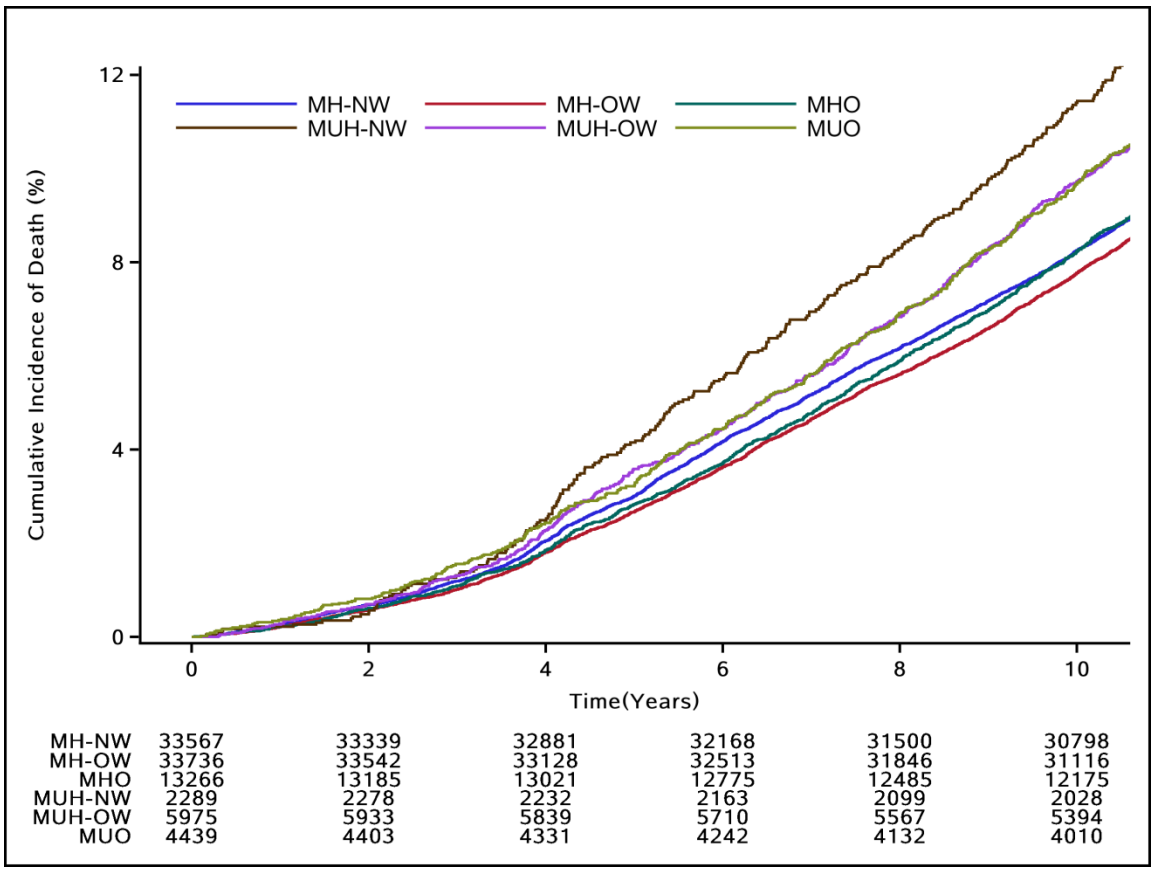

Figure 2 The cumulative incidence of death according to the BMI-MetS phenotypes

Abbreviations: BMI, body mass index; MetS, metabolic syndrome; MH-NW, metabolically healthy normal weight; MUH-NW, metabolically unhealthy normal weight; MH-OW, metabolically healthy overweight; MUH-OW, metabolically unhealthy overweight; MHO, metabolically healthy obesity; MUO, metabolically healthy obesity.

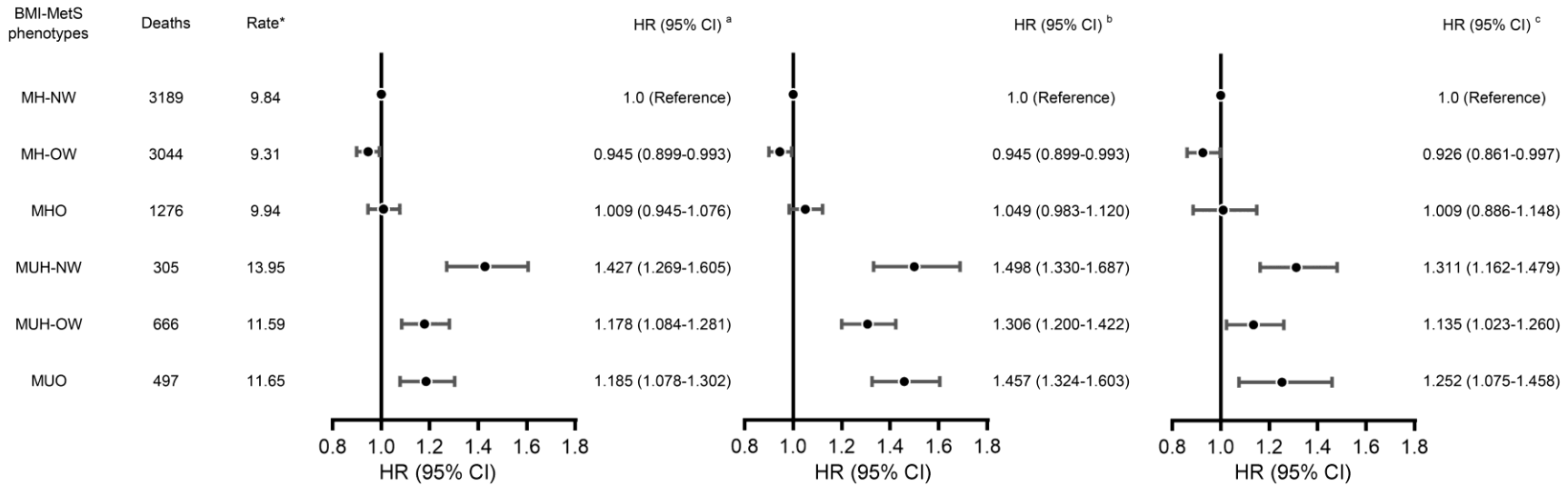

Figure 3 Association of BMI-MetS phenotypes with all-cause mortality risk

Multivariate cox regression analysis was used to evaluate the association of all-cause mortality risk with BMI-MetS phenotypes, adjusting for potential confounding factors (N=93272). [a] HR calculated by univariate cox regression. [b] HR calculated by cox regression adjusting for age and sex. [c] HR calculated by cox regression further adjusted for smoking, drinking, education, BMI index, income, exercise, salt intake, and history of disease (hyperlipidemia, hypertension, diabetes, myocardial infarction, and stroke). *Per 1,000 person-years.

Abbreviations: HR, hazard ratio; CI, confidence interval; MH-NW, metabolically healthy normal weight; MUH-NW, metabolically unhealthy normal weight; MH-OW, metabolically healthy overweight; MUH-OW, metabolically unhealthy overweight; MHO, metabolically healthy obesity; MUO, metabolically healthy obesity; BMI, body mass index; MetS, metabolic syndrome.

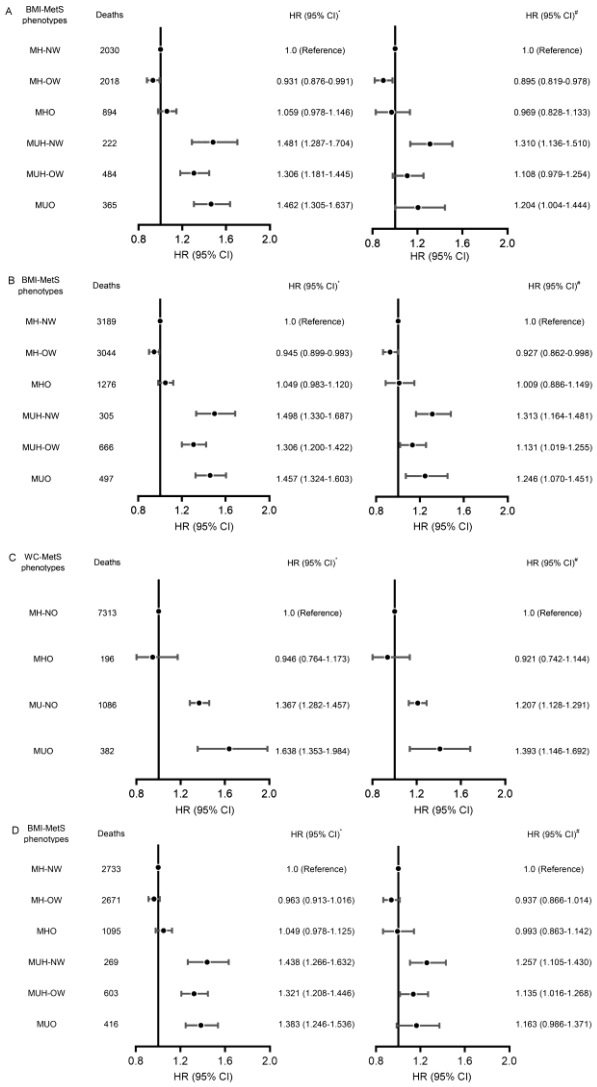

Figure 4 The sensitivity analyses of the association of all-cause mortality risk with BMI-MetS phenotypes

The association of all-cause mortality risk with BMI-MetS phenotypes excluding current smokers (A), excluding dead participants during the first two years (B), using WC instead of BMI and modifying the definition of MetS (≥ 2 among the 4 components excluding the WC criteria) (C), retaining 50-85 years participants (D). *n* (A) = 61002, *n* (B) = 93272, *n* (C) = 93272, *n* (D) = 52776.

Multivariate cox regression analysis was used to evaluate the association of all-cause mortality risk with BMI-MetS phenotypes, adjusting for potential confounding factors. *HR calculated by cox regression adjusting for age and sex. #HR calculated by cox regression further adjusting for smoking, drinking, education,

BMI index, income, exercise, salt intake, dyslipidemia, and history of disease (hypertension, hyperlipidemia, diabetes, myocardial infarction, and stroke).

Abbreviations: HR, hazard ratio; CI, confidence interval; MH-NW, metabolically healthy normal weight; MUH-NW, metabolically unhealthy normal weight; MH-OW, metabolically healthy overweight; MUH-OW, metabolically unhealthy overweight; MHO, metabolically healthy obesity; MUO, metabolically healthy obesity; MH-NO, metabolically healthy normal waist circumference; MU-NO, metabolically unhealthy normal waist circumference; BMI, body mass index; MetS, metabolic syndrome; WC, waist circumference.

635

Table 1 Baseline characteristics of participants according to BMI-MetS phenotypes

Characteristic	MH-NW (n=33567)	MH-OW (n=33736)	MHO (n=13266)	MUH-NW (n=2289)	MUH-OW (n=5975)	MUO (n=4439)	P^a	P^b
Age, years	50.77 (16.16)	51.63 (14.77)	51.22 (16.00)	54.77 (13.99)	54.21 (12.08)	53.56 (12.22)	<0.001	0.007
Men, No. (%)	26153 (77.91)	29368 (87.05)	11770 (88.72)	1196 (52.25)	3488 (58.38)	2580 (58.12)	<0.001	<0.001
BMI, kg/m^2	22.10 (2.26)	25.73 (1.91)	29.41 (2.28)	22.79 (1.73)	26.08 (1.94)	29.97 (2.68)	<0.001	<0.001
WC, cm	80 (10)	88 (9)	96 (11)	84 (9)	89 (9)	97 (11)	<0.001	<0.001
LDL-C, mmol/L	2.27 (1.01)	2.40 (0.95)	2.40 (0.97)	2.30 (1.04)	2.40 (1.10)	2.43 (1.08)	<0.001	<0.001
FBG, mmol/L	4.99 (0.87)	5.10 (0.89)	5.10 (0.88)	6.01 (1.51)	6.10 (1.63)	6.11 (1.65)	<0.001	<0.001
TG, mmol/L	1.02 (0.66)	1.27 (0.84)	1.45 (1.04)	2.20 (1.48)	2.31 (1.50)	2.37 (1.53)	<0.001	<0.001
HDL-C, mmol/L	1.56 (0.49)	1.49 (0.45)	1.45 (1.04)	1.49 (0.59)	1.48 (0.52)	1.44 (0.51)	<0.001	<0.001
LDL-C, No. (%)c								
≤ 2.03 mmol/L	12685 (37.81)	10316 (30.61)	3928 (29.64)	833 (36.50)	1876 (31.57)	1320 (29.90)	<0.001	<0.001
2.03-2.66 mmol/L	10979 (32.73)	11795 (35.00)	4545 (34.30)	710 (31.11)	1820 (30.62)	1394 (31.58)		
> 2.66 mmol/L	9885 (29.46)	11589 (34.39)	4778 (36.06)	739 (32.38)	2247 (37.81)	1700 (38.51)		
FBG, No. (%) c								
≤ 4.83 mmol/L	13846 (41.25)	11757 (34.85)	4364 (32.90)	291 (12.71)	593 (9.92)	424 (9.55)	<0.001	<0.001
4.83-5.49 mmol/L	11956 (35.62)	12545 (37.19)	4984 (37.57)	231 (10.09)	572 (9.57)	429 .66)		
> 5.49 mmol/L	7765 (23.13)	9434 (27.96)	3918 (29.53)	1767 (77.20)	4810 (80.50)	3586 (80.78)		
TG, No. (%) c								
≤ 1.02 mmol/L	16858 (50.22)	10533 (31.22)	2825 (21.30)	185 (8.08)	298 (4.99)	169 (3.81)	<0.001	<0.001
1.02-1.65 mmol/L	11351 (33.82)	13409 (39.75)	5304 (39.98)	223 (9.74)	519 (8.69)	418 (9.42)		
> 1.65 mmol/L	5358 (15.96)	9794 (29.03)	5137 (38.72)	1881 (82.18)	5158 (86.33)	3852 (86.78)		
HDL-C, No. (%) c								

≤ 1.35 mmol/L	9399 (28.00)	11416 (33.84)	5083 (38.32)	853 (37.27)	2232 (37.36)	1812 (40.82)	<0.001	<0.001
1.35-1.66 mmol/L	11169 (33.27)	11848 (35.12)	4560 (34.37)	615 (26.87)	1831 (30.64)	1322 (29.78)		
> 1.66 mmol/L	12999 (38.73)	10472 (31.04)	3623 (27.31)	821 (35.87)	1912 (32.00)	1305 (29.40)		
SBP, mmHg	120 (25)	129.30 (21.40)	130.70 (30)	140 (20)	140 (26)	142 (29.30)	<0.001	<0.001
DBP, mmHg	80 (14.30)	80.70 (10.70)	85 (15)	88 (11.30)	90 (16.70)	90 (18.70)	<0.001	<0.001
Current smoking, No. (%)	12076 (35.98)	12316 (36.51)	4690 (35.35)	543 (23.72)	1546 (25.87)	1099 (24.76)	0.152	0.206
Current drinking, No. (%)	12627 (37.62)	13483 (39.97)	5237 (39.48)	595 (25.99)	1712 (28.65)	1248 (28.11)	<0.001	<0.001
University or college or above, No. (%)	2731 (8.14)	2194 (6.50)	878 (6.62)	87 (3.80)	259 (4.33)	200 (4.51)	<0.001	<0.001
Family per-member income ≥ 800Yuan/month, No. (%)	4747 (14.14)	4858 (14.40)	1936 (14.59)	305 (13.32)	920 (15.40)	658 (14.82)	0.338	0.208
Physical activity, ≥ 3times /week, No. (%)	5064 (15.09)	5257 (15.58)	2058 (15.51)	415 (18.13)	1093 (18.29)	812 (18.29)	0.074	0.246
Salt intake >12 g/day, No. (%)	3302 (9.84)	3768 (11.18)	1674 (12.63)	187 (8.18)	639 (10.71)	569 (12.84)	<0.001	<0.001
History of hypertension, No. (%)	2306 (6.87)	4122 (12.22)	2336 (17.61)	495 (21.63)	1702 (28.49)	1577 (35.53)	<0.001	<0.001
History of diabetes, No. (%)	545 (1.62)	800 (2.37)	307 (2.31)	274 (11.97)	703 (11.77)	506 (11.40)	<0.001	<0.001
History of hyperlipidemia, No. (%)	1060 (3.16)	1959 (5.81)	1143 (8.62)	263 (11.49)	865 (14.48)	769 (17.32)	<0.001	<0.001
History of myocardial infarction, No. (%)	278 (0.83)	465 (1.38)	230 (1.73)	44 (1.92)	124 (2.08)	108 (2.43)	<0.001	<0.001
History of stroke, No. (%)	679 (2.03)	886 (2.63)	383 (2.89)	76 (3.32)	224 (3.75)	191 (4.30)	<0.001	<0.001

Note. Data represent median (interquartile range 25%-75%) or percentage. MH-NW, metabolically healthy normal weight; MUH-NW, metabolically unhealthy normal weight; MH-OW, metabolically healthy overweight; MUH-OW, metabolically unhealthy overweight; MHO, metabolically healthy obesity; MUO, metabolically healthy obesity; BMI, body mass index; WC, waist circumference; FBG, fasting blood glucose; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure. P^{a} values between metabolically healthy normal weight and metabolically healthy overweight groups; P^{b} values between metabolically healthy normal weight and metabolically healthy obese groups. ^{c}, data were grouped by tertiles.

Table 2 The association between BMI-MetS phenotypes and all-cause mortality in the whole and stratified subgroups

	MH-NW	MH-OW	MHO	MUH-NW	MUH-OW	MUO	*P* for Heterogeneity
Overall	1.000 (ref)	0.926 (0.861-0.997)	1.009 (0.886-1.148)	1.311 (1.162-1.479)	1.135 (1.023-1.260)	1.252 (1.075-1.458)	—
Sex							
men	1.000（ref）	0.938 (0.869-1.012)	1.026 (0.896-1.175)	1.235 (1.072-1.012)	1.102 (0.982-1.236)	1.198 (1.015-1.413)	0.007
women	1.000（ref）	0.732 (0.544-0.986)	0.803(0.485-1.329)	1.535 (1.183-1.991)	1.211 (0.913-1.607)	1.354 (0.866-2.117)	
Age							
<65 years	1.000（ref）	0.895 (0.807-0.993)	0.882 (0.734-1.060)	1.538 (1.298-1.823)	1.121 (0.970-1.296)	1.155 (0.935-1.426)	<0.001
≥65 years	1.000（ref）	0.951 (0.857-1.055)	1.127 (0.937-1.355)	1.133 (0.950-1.345)	1.108 (0.953-1.288)	1.217 (0.972-1.524)	
Smoking status							
No/former	1.000（ref）	0.895 (0.819-0.978)	0.969 (0.828-1.133)	1.310 (1.136-1.510)	1.108 (0.979-1.254)	1.204 (1.004-1.444)	0.957
Current	1.000（ref）	0.990 (0.871-1.127)	1.097 (0.870-1.384)	1.292 (1.029-1.622)	1.147 (0.947-1.389)	1.324 (1.000-1.754)	
Drinking status							
No/former	1.000（ref）	0.928 (0.850-1.012)	0.966 (0.828-1.128)	1.322 (1.147-1.522)	1.137 (1.007-1.285)	1.217 (1.017-1.455)	0.283
Current	1.000（ref）	0.935 (0.817-1.069)	1.132 (0.891-1.438)	1.297 (1.029-1.635)	1.098 (0.899-1.069)	1.320 (0.986-1.767)	
Physical activity							
< 3 times/week	1.000（ref）	0.910 (0.838-0.988)	0.971 (0.839-1.124)	1.335 (1.165-1.531)	1.099 (0.977-1.236)	1.279 (1.077-1.518)	0.137
≥3 times/week	1.000（ref）	0.994 (0.849-1.164)	1.162 (0.877-1.539)	1.260 (0.974-1.629)	1.261 (1.007-1.579)	1.127 (0.808-1.571)	

Note. Data represent hazard ratio (95% CI). Model was adjusted for age, sex, smoking, drinking, education, BMI index, income, exercise, salt intake, hyperlipidemia, and history of diseases (hypertension, diabetes, myocardial infarction, and stroke). Ref, reference; MH-NW, metabolically healthy normal weight; MUH-NW, metabolically unhealthy normal weight; MH-OW, metabolically healthy overweight; MUH-OW, metabolically unhealthy overweight; MHO, metabolically healthy obesity; MUO, metabolically healthy obesity. *P* for heterogeneity was attained from the likelihood ratio test.