All-cause mortality in metabolically healthy individuals was not predicted by overweight and obesity

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BACKGROUND. Metabolically healthy obesity (MHO) and metabolically healthy overweight (MH-OW) have been suggested to be important and emerging phenotypes 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 a Chinese community-based prospective cohort study (the Kailuan study), including 93,272 adults at baseline. Data were analyzed from 2006 to 2017. Participants were categorized into 6 mutually exclusive groups, according to BMI and metabolic syndrome (MetS) status. The primary outcome was all-cause death, and accidental deaths were excluded.

RESULTS. During a median follow-up of 11.04 years (interquartile range, 10.74–11.22 years), 8977 deaths occurred. Compared with healthy participants with normal BMI (MH-NW), MH-OW participants had the lowest risk of all-cause mortality (multivariate-adjusted HR [aHR], 0.926; 95% CI, 0.861–0.997), whereas there was no increased or decreased risk for MHO (aHR, 1.009; 95% CI, 0.886–1.148). Stratified analyses and sensitivity analyses further validated that there was a nonsignificant association between MHO and all-cause mortality.

CONCLUSIONS. Overweight and obesity do not predict increased risk of all-cause mortality in metabolic healthy Chinese individuals.

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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, ischemic heart disease, and malignant tumors (3–9). Two systematic reviews 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); these findings were consistent with a study of 1.46 million White adults (12). Moreover, linear Mendelian randomization analyses have indicated that an increase of 1 unit in genetically predicted 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 being overweight had no effect on all-cause mortality; in particular, it was protective effect in men or people aged 30–39 years (14). A large population-based cohort study found that BMI had a J-shaped association with all-cause mortality, and the 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; others have healthier metabolic profiles and decreased health risks. Combined BMI and metabolic profiles in individuals have been categorized into 6 groups: metabolically healthy normal weight (MH-NW), metabolically healthy overweight (MH-OW), metabolically healthy obesity (MHO), metabolically unhealthy normal weight (MUH-NW), metabolically unhealthy overweight (MUH-OW), and metabolically unhealthy 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 those in 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 control) (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 with 101,510 participants and more than 10 years of follow-up.

Results

Participants with missing data (n = 6539) or BMIs of less than 18.5 kg/m^2 (n = 1699) were excluded. Some individuals met more than 1 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. MH-OW and MHO statuses represented 36.17% (n = 33,736) and 14.22% (n = 13,266) of the total samples, respectively. The demographic and biochemical characteristics of the participants are presented in Table 1. Compared with MH-NW individuals, MH-OW and MHO individuals had a history of disease and a higher proportion of older individuals, men, and drinkers. The levels of HDL cholesterol (HDL-C) and education in the MH-OW and MHO groups were significantly lower than those in the MH-NW groups. In addition, higher blood pressure, triglyceride (TG), waist circumference (WC), LDL, and salt intake levels were also found in the MH-OW and MHO groups (Table 1). In addition, MH-OW and MHO individuals had a higher proportion of abnormal measures in other indices of disease, including LDL cholesterol (LDL-C), fasting blood glucose (FBG), TG, and HDL-C, compared with those in MH-NW individuals (P < 0.001) (Table 1).

After a median follow-up period of 11.04 years (interquartile range, 10.74–11.22 years), 8977 deaths occurred. The incidences of all-cause death per 1000 person-years were 9.84 in the MH-NW group, 9.31 in the MH-OW group, 9.94 in the MHO group, 13.95 in the MUH-NW group, 11.59 in the MUH-OW group, and 11.65 in the MUO group. As shown in Figure 2, all-cause mortality was highest in the MUH-NW group and the lowest in the MH-OW group. In the crude Cox model, compared with participants in the MH-NW group, participants were at a 5.5% lower risk (HR, 0.945; 95% CI, 0.899–0.993) in the MH-OW group, at no risk (HR, 1.009; 95% CI, 0.945–1.076) in the MHO group, at a 42.7% higher risk (HR, 1.427; 95% CI, 1.269–1.605) in the MUH-NW group, at a 17.8% higher risk (HR, 1.178; 95% CI, 1.084–1.281) in the MUH-OW group, and at a 18.5% higher risk (HR, 1.185; 95% CI, 1.078–1.302) in the MUO group for all-cause mortality (Figure 3). After adjustment for sex, age, WC, 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 the MH-OW group, 1.009 (95% CI, 0.886–1.148) in the MHO group, 1.311 (95% CI, 1.162–1.479) in the MUH-NW group, 1.135 (95% CI, 1.023–1.260) in the MUH-OW group, and 1.252 (95% CI, 1.075–1.458) in the MUO group, compared with the 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 the MH-OW group, 0.969 (95% CI, 0.828–1.133) in the MHO group, and 1.310 (95% CI, 1.136–1.510) in the MUH-NW, compared with the MH-NW group (Figure 4A). The sensitivity analyses also showed similar results after the exclusion of participants who died during the first 2 years of follow-up

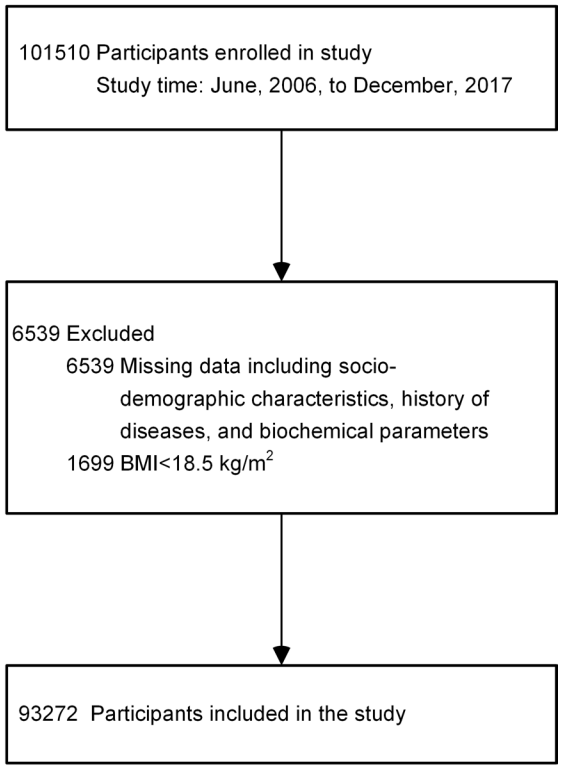

Figure 1. The flow diagram of study participants.

(Figure 4B). Furthermore, we redefined obesity and metabolic syndrome (MetS) and obtained similar results. Compared with MH-NO individuals, MHO individuals had 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). In addition, the results showed that, for participants aged 50–85 years, adjusted HRs were 0.937 (95% CI, 0.866–1.014) in the MH-OW group, 0.993 (95% CI, 0.863–1.142) in the MHO group, and 1.257 (95% CI, 1.105–1.430) in the MUH-NW, compared with the MH-NW group (Figure 4D).

In the stratified analyses, compared with that in the MH-NW group, 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) and sex in relationship 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 a 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 with the MH-NW participants, after adjusting for sex, age, WC, 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.

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, yr, median (IQR)	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/m2, median (IQR)	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, median (IQR)	80 (10)	88 (9)	96 (11)	84 (9)	89 (9)	97 (11)	<0.001	<0.001
LDL-C, mmol/L, median (IQR)	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, median (IQR)	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, median (IQR)	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, median (IQR)	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)		
2.03–2.66 mmol/L	10979 (32.73)	11795 (35.00)	4545 (34.30)	710 (31.11)	1820 (30.62)	1394 (31.58)	<0.001	<0.001
>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)		
4.83–5.49 mmol/L	11956 (35.62)	12545 (37.19)	4984 (37.57)	231 (10.09)	572 (9.57)	.66)	<0.001	<0.001
>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)		
1.02–1.65 mmol/L	11351 (33.82)	13409 (39.75)	5304 (39.98)	223 (9.74)	519 (8.69)	418 (9.42)	<0.001	<0.001
>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)		
1.35–1.66 mmol/L	11169 (33.27)	11848 (35.12)	4560 (34.37)	615 (26.87)	1831 (30.64)	1322 (29.78)	<0.001	<0.001
>1.66 mmol/L	12999 (38.73)	10472 (31.04)	3623 (27.31)	821 (35.87)	1912 (32.00)	1305 (29.40)		
SBP, mmHg, median (IQR)	120 (25)	129.30 (21.40)	130.70 (30)	140 (20)	140 (26)	142 (29.30)	<0.001	<0.001
DBP, mmHg, median (IQR)	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/mo., 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/d, 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

Data represent median (interquartile range [IQR] 25%–75%) or number and 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; WC, waist circumference; FBG, fasting blood glucose; TG, triglycerides; TC, total cholesterol; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure. [A]*P* values between metabolically healthy normal weight and metabolically healthy overweight groups. [B]*P* values between metabolically healthy normal weight and metabolically healthy obese groups. [C]Data were grouped by tertiles.

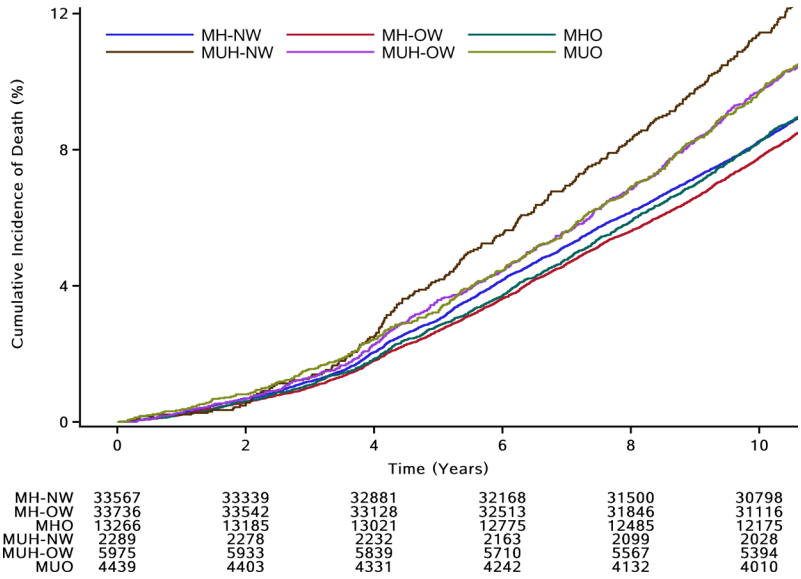

Figure 2. The cumulative incidence of death according to the BMI-MetS phenotypes. MetS, metabolic syndrome; MH-NW, metabolically healthy normal weight; MUH-NW, metabolically unhealthy normal weight; MH-OW, metabolically healthy overweight; MUH-OW, metabolically unhealthy overweight; MHO, metabolically healthy obesity; MUO, metabolically healthy obesity.

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 5, 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 associated 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 up until September 30, 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 National Health and Nutrition Examination Survey Continuous [NHANES Continuous]) showed that obesity without other metabolic risk factors was not associated with an increased risk of all-cause mortality compared with 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 (HR, 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 (2185 men, 26 years of follow-up) demonstrated that MH-OW/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) verified no significant association between MHO and all-cause mortality in a Chinese population, suggesting that baseline obesity without MetS 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, NHANES, and NHANES Continuous) showed that overweight without other metabolic risk factors was not associated with an increased risk of all-cause mortality compared with lean healthy individuals (HR, 0.95, 95% CI 0.7–1.2) (32). Most studies of

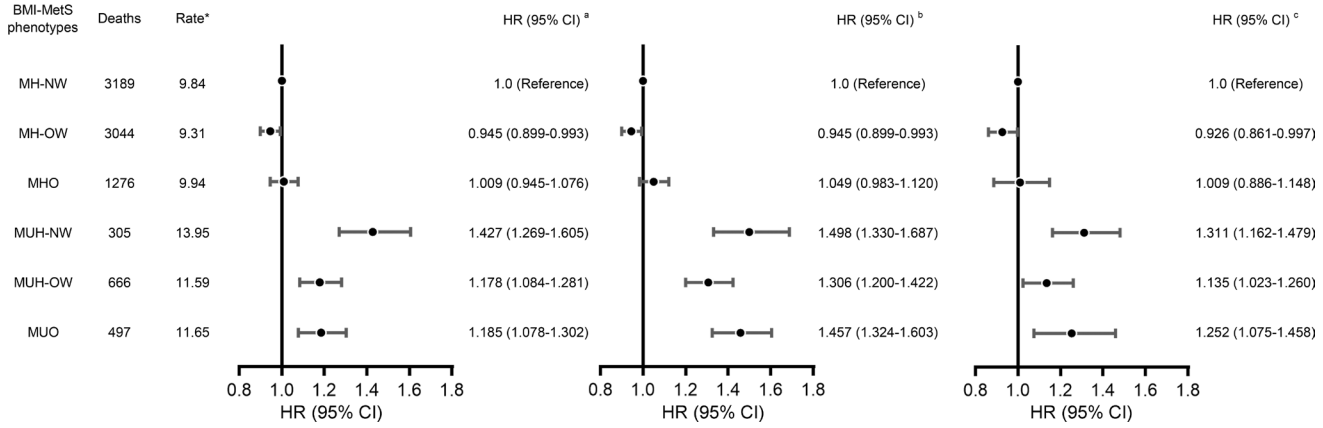

Figure 3. Association of BMI-MetS phenotypes with all-cause mortality risk. Multivariate cox regression analysis was used to evaluate the association of all-cause mortality risk with BMI-MetS phenotypes, adjusting for potential confounding factors (n = 93,272). HR calculated by univariate cox regression (left), HR calculated by cox regression adjusting for age and sex (middle), and 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) (right) are shown. *Per 1,000 person-years. 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; MetS, metabolic syndrome.

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 (HR, 0.79; 95% CI, 0.63–0.98) was associated with a decreased risk of cancer mortality (35). In contrast to these studies, we demonstrated that the MH-OW phenotype was associated with a decreased risk of all-cause mortality (HR, 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 the MUH-NW phenotype were at the highest risk for all-cause mortality among 6 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 the 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 with 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 counterintuitive and perhaps unexpected result might be explained by the fact that the 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 finding 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 myocardial infarction, even without measurable metabolic abnormalities (21), whether participants with the MHO or MH-OW phenotype should reduce their body weight needs further consideration.

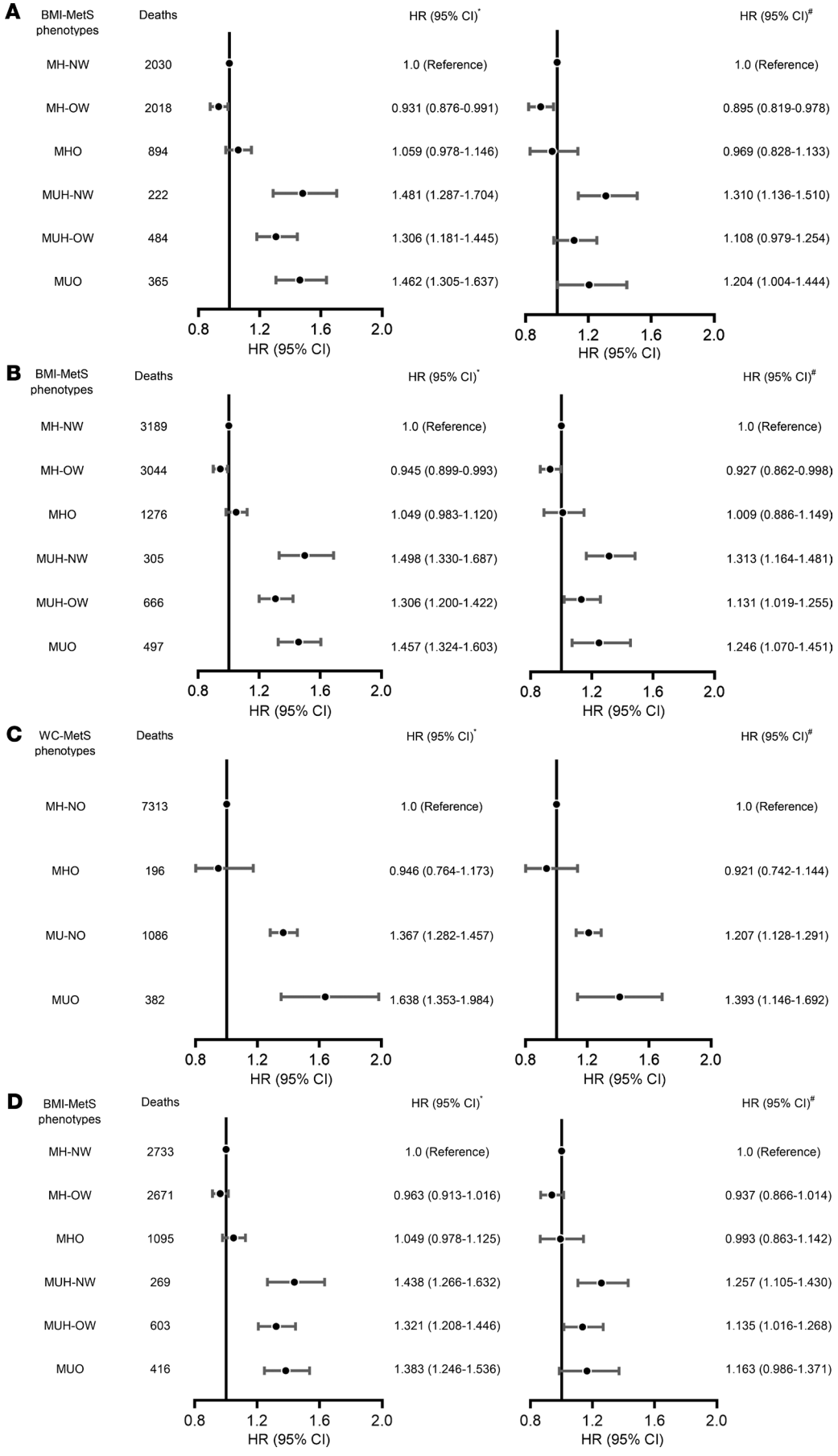

Figure 4. The sensitivity analyses of the association of all-cause mortality risk with BMI-MetS phenotypes. The association of all-cause mortality risk with BMI-MetS phenotypes excluding current smokers (**A**), excluding dead participants during the first 2 years (**B**), using WC instead of BMI and modifying the definition of MetS (≥2 among the 4 components excluding the WC criteria) (**C**), retaining participants aged 50–85 years (**D**). *n* = 61,002 (**A**); *n* = 93,272 (**B**); *n* = 93,272 (**C**); *n* = 52,776 (**D**). Multivariate cox regression analysis was used to evaluate the association of all-cause mortality risk with BMI-MetS phenotypes, adjusting for potential confounding factors. The asterisk indicates HR calculated by cox regression adjusting for age and sex, and the pound sign indicates 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). 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; MetS, metabolic syndrome; WC, waist circumference.

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

	MH-NW (reference group)	MH-OW	MHO	MUH-NW	MUH-OW	MUO	P for Heterogeneity
Overall	1.000	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							
Male	1.000	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
Female	1.000	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	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	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	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	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	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	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	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	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)	

Data represent HR (95% CI). MH-NW was used as a reference group. 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). 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.

Apart from its strengths, several limitations should be addressed. First, there is no universally accepted definition for metabolic health, such as, 0 or 1 cardiometabolic abnormalities, fewer than 2 signs of metabolic components, or other criteria (46–48). Many previous studies have used the International Diabetes Federation criteria to define metabolic health as the presence of less than 2 MetS 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 (Table 1) 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 predict 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 2 years at 11 hospitals affiliated with the Kailuan

community (52–54). In this analysis, we included participants from the Kailuan study, excluding participants with missing data for biochemical parameters, sociodemographic 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 ≤ BMI < 24.00 kg/m^2), overweight (24.00 kg/m^2 ≤ BMI < 28.00 kg/m^2), or obese (BMI ≥ 28.00 kg/m^2) groups according to Chinese-specific criteria (55). Based on the modified International Diabetes Federation criteria for the Asian population, MetS was defined as the presence of 3 or more abnormal components (WC ≥80 cm in women and ≥90 cm in men; TG ≥1.70 mmol/L or current use of lipid-lowering agents; diastolic blood pressure ≥85 mmHg, systolic blood pressure ≥130 mmHg, or self-reported history of hypertension or current use of blood pressure medication; FGB level ≥5.60 mmol/L, current use of glucose-lowering agents or self-reported history of diabetes; and 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 2 or less abnormal components, while metabolically unhealthy (MUH) was defined as the presence of 3 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, and metabolic unhealthy participants were divided as well, 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 sociodemographic characteristics, lifestyle factors, and medical history (57). Smoking and drinking status were divided into 3 categories: never, former, and current (21, 52). Physical activity was evaluated with regard to 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, levels of FBG, TG, and HDL-C were measured using an autoanalyzer (Hitachi 747) at the central laboratory of Kailuan General Hospital (58).

Follow-up and outcome. All participants were followed by face-to-face interviews at every 2-year routine medical examination until December 31, 2017, or until 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).

Statistics. The baseline characteristics of participants are presented as mean ± standard deviation or median with interquartile range for continuous variables and percentage for categorical variables. χ^2 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 6 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 HRs and 95% CIs for the association between the 6 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 3 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 4 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. In addition, we defined obesity using WC instead of BMI and defined MetS as having 2 or more of 4 metabolic components (excluding WC criteria). Participants were classified into the following 4 groups: no obesity (WC <80 cm in women and <90 cm in men) without MetS (MH-NO) or with MetS (MU-NO), MHO (obesity defined as WC ≥80 cm in women and ≥90 cm 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.

Study approval. This study was approved by the ethics committees of Kailuan General Hospital and Beijing Tiantan Hospital, Capital Medical University. Written informed consent form was obtained from all participants.

Author contributions

YW, WW, and HH conceived the study. AW, SC, and SW contributed population data resources. QT, AW, and YZ analyzed data. QT wrote the original draft. YW reviewed and edited manuscript.

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