Association between the metabolically healthy obese phenotype and the risk of myocardial infarction: results from the Kailuan study

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Abstract

Objective: This study aimed to determine if the metabolically healthy obese (MHO) is associated with an increased risk of myocardial infarction (MI) in Chinese population.

Design: The Kailuan study is a community-based prospective cohort study.

Methods: BMI and metabolic syndrome (MetS) were assessed in 91 866 participants without a history of MI or stroke. Participants were categorised into six mutually exclusive groups according to the BMI-MetS status: normal weight (BMI: ≤ 18.5 to < 24.0 kg/m²) without MetS (MH-NW), normal weight with MetS (MUH-NW), overweight (BMI: ≤ 24.0 to < 28.0 kg/m²) without MetS (MH-OW), overweight with MetS (MUH-OW), obese (BMI ≥ 28.0 kg/m²) without MetS (MHO) and obese with MetS (MUO). The hazard ratio (HR) with 95% CI was calculated for the incidence of MI using a multivariable Cox model.

Results: A total of 6745 (7.34%) individuals were classified as MHO. During a median 8-year follow-up, 1167 (1.27%) participants developed MI. The MHO group had an increased risk of MI (HR: 1.76, 95% CI: 1.37–2.25) in comparison with the MH-NW group after adjusting for potential confounding variables. After a similar adjustment, the risk of MI was significantly elevated in the MUH-NW (HR: 1.62, 95% CI: 1.28–2.05), MUH-OW (HR: 1.98, 95% CI: 1.67–2.35) and MUO group (HR: 2.06, 95% CI: 1.70–2.49).

Conclusions: MHO subjects showed a substantially higher risk of MI in comparison with MH-NW subjects. That said, even without measurable metabolic abnormalities, obesity was associated with a higher risk of MI.

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Introduction

As most epidemiological studies have recognised, obesity, measured either by BMI or several other measures of adiposity, is one of the most important modifiable and causal risk factors of myocardial infarction (MI), stroke,

cardiovascular diseases (CVDs) and all-cause mortality (1, 2, 3). Metabolic syndrome (MetS) is characterised by a cluster of conditions, including dyslipidaemia, hyperglycaemia and hypertension (4). Previous meta-

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analyses (5, 6) and cohort studies (7, 8, 9) have shown that MetS significantly increases the risk of CVDs and all-cause mortality. However, a fraction of obese individuals who do not have MetS is considered as metabolically healthy obese (MHO) (10). Correspondingly, a subset of lean individuals who have MetS is referred to as metabolically unhealthy normal weight (MUH-NW).

Previous prospective cohort studies have demonstrated that MHO individuals are at an increased risk of CVDs and all-cause mortality compared with metabolically healthy normal weight (MH-NW) individuals (7, 9, 11, 12, 13, 14, 15). For example, a recent large-scale study investigating a 30-year follow-up period in 90 257 women found that the MHO group had an increased 1.44-fold risk of MI, 1.37-fold risk of stroke and 1.39-fold risk of CVDs (15). On the other hand, some observational studies had reported that the MHO phenotype was not significantly associated with increased risk of CVDs (16, 17). The reason for their findings may partially be due to the small sample size in each study and the relatively small fraction of CVD cases over a short-term follow-up. In addition, studies on the association between MHO and risk of MI have mostly been conducted in the Western population (8, 9). Because the pattern and prevalence of obesity and CVDs risk in the Chinese population are different from those in the Western population, it is necessary to perform a large prospective cohort study to further elucidate the impact of MHO phenotype on the risk of MI.

The Kailuan study is a large and ongoing prospective community-based study. Baseline data for BMI, MetS and assessment of MI were collected prospectively to identify the association between the MHO phenotype and risk of MI in the Chinese population. Therefore, the present study aimed to investigate the association between MetS and the risk of MI across BMI categories. We hypothesised that the MHO group had a greater risk of MI than that of the MH-NW group.

Methods

Study population

The Kailuan study is a prospective cohort study comprising 101 510 participants aged between 18 and 98 years, located in Tangshan, Hebei, China (18). Details regarding the design and methods of the study have been previously published (18). Briefly, beginning in 2006–2007, both questionnaire information and clinical/laboratory examinations were performed every 2 years.

In the current analysis, we initially excluded 3330 participants with a history of MI or stroke at baseline, and 3801 participants lacking a fasting blood sample. Furthermore, we excluded 834 participants who did not have weight, height or waist circumference measurements as well as 1679 individuals who were underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$). Therefore, the final sample consisted of 91 866 respondents (Supplementary Fig. 1, see section on [supplementary data](#) given at the end of this article). The Ethics Committees of both Kailuan General Hospital and Beijing Tian Tan Hospital approved this study, and all participants gave their written informed consent.

Data collection and baseline measurements

Standardised questionnaires were used to collect sociodemographic and clinical characteristics, including age, sex, educational level (less than high school, high school or above), income ($< \text{¥}800/\text{month}$, $\geq \text{¥}800/\text{month}$), lifestyle, history of diabetes and hypertension, and current antihypertensive, antidiabetic or blood lipid-lowering agents. Lifestyle information included smoking status (never, former/current smoker), drinking status (never, former/current drinker), physical activity levels (< 3 times/week, ≥ 3 times/week) and sodium intake ($< 10 \text{ g/day}$, $\geq 10 \text{ g/day}$). Trained doctors and nurses measured the participants' height, weight, waist circumference (WC) and blood pressure (BP). Height was measured using a fixed stadiometer with a vertical backboard, and weight was measured on a digital scale. BMI was calculated by dividing weight in kg by height in square metres (kg/m^2). WC was measured to the nearest 2.5 cm above the umbilicus. BP was measured using a mercury sphygmomanometer, and the average of three BP measurements was calculated for systolic and diastolic BP, respectively.

Fasting blood samples were collected in the morning and analysed using an auto-analyser (Hitachi 747; Hitachi). Fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoproteins cholesterol (LDL-C), high-sensitivity C-reactive protein (hs-CRP) and serum creatinine were measured using a standardised method (19). Moreover, the estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (20).

Definition of BMI-MetS groups

Obesity was defined according to the Working Group on Obesity in China (21) as $\text{BMI} \geq 28.0 \text{ kg/m}^2$, overweight

as $24.0 \leq \text{BMI} < 28.0 \text{ kg/m}^2$ and normal weight as $18.5 \leq \text{BMI} < 24.0 \text{ kg/m}^2$. MetS was defined as having ≥ 3 metabolic abnormalities according to the harmonized International Diabetes Federation criteria (4) published in 2009 (Table 1). Participants were divided into six mutually exclusive groups based on their BMI categories (normal weight, overweight and obesity) and the presence or absence of MetS: (1) metabolically healthy normal weight (MH-NW), (2) metabolically healthy overweight (MH-OW), (3) metabolically healthy obese (MHO), (4) metabolically unhealthy normal weight (MUH-NW), (5) metabolically unhealthy overweight (MUH-OW) and (6) metabolically unhealthy obese (MUO) (Table 1).

Assessment of MI

After the baseline examination, participants were followed up for the first occurrence of MI, including nonfatal and fatal MI. The occurrence of MI was identified from the medical records of all 11 Kailuan hospitals and the Municipal Social Insurance Institution from the baseline examination date until 31 December 2015. Death due to

MI was verified from death certificates from the provincial vital statistic offices. The diagnostic criteria of MI were consistent across all 11 hospitals collectively based on chest pain symptoms, electrocardiographic changes and cardiac enzyme levels.

Statistical analysis

All statistical analyses were performed using the SAS software version 9.4 (SAS Institute Inc), and a two-sided P value of <0.05 was considered statistically significant. Characteristics of participants were summarised according to the BMI-MetS categories. Continuous variables are expressed as mean $\pm$ standard deviation and categorical variables are presented as frequencies and percentages. Trend association was assessed by assigning a median BMI value to each categories of BMI in both the metabolically healthy and metabolically unhealthy groups and tested using linear regression or logistic regression, as appropriate.

Person-years were calculated from the baseline examination date until the date of MI diagnosis, death, lost follow-up or the end of follow-up (31 December 2015), whichever occurred first. The time to occurrence of MI was first estimated using the Kaplan–Meier method, and the BMI-MetS group differences were tested using the log-rank test. The Šidák method was applied to obtain a multiple-comparison adjustment of P values for the paired comparison. Hazard ratio (HR) and corresponding 95% CI were estimated using Cox proportional hazards models. The proportional hazards assumption was checked by plotting the Schoenfeld residuals (22) and no violation was found. Four Cox models were applied: model 1 was unadjusted; model 2 was adjusted for age and sex; model 3 was adjusted for age, sex, educational level, income, smoking, drinking, physical activity and sodium intake and model 4 was adjusted for covariates in model 3 plus LDL-C, hs-CRP and eGFR. We chose these sociodemographic factors and traditional CVDs risk factors as adjusted covariates, which were proved to be associated with CVDs in previous report of the Kailuan study (18, 19).

Multivariable adjusted model was stratified by the following potential effect modifiers: sex (male or female), age (<65 or ≥ 65 years), smoking status (never or former/current smoker), drinking status (never or former/current drinker) and physical activity (yes or no). The multiplicative interaction terms between these subgroups and BMI-MetS status were added to the fully adjusted model, and model with and without multiplicative interaction terms were compared using

Table 1 Definition of obesity, metabolic syndrome and metabolically healthy obesity.

- BMI categories were based on the Working Group on Obesity in China:
 1. Normal weight: $\text{BMI} \leq 18.5$ to $<24.0 \text{ kg/m}^2$;
 2. Overweight: $\text{BMI} \leq 24.0$ to $<28.0 \text{ kg/m}^2$;
 3. Obesity: $\text{BMI} \geq 28.0 \text{ kg/m}^2$;
- Metabolic syndrome (MetS) was defined as ≥ 3 of following components based on the harmonized International Diabetes Federation criteria:
 1. Systolic blood pressure ≥ 130 and/or diastolic blood pressure $\geq 85 \text{ mmHg}$ and/or use of antihypertensive medication and/or self-reported history of hypertension;
 2. Fasting blood glucose $\geq 5.6 \text{ mmol/L}$ (100 mg/dL) and/or current use of antidiabetic medication and/or self-reported history of diabetes;
 3. Triglycerides $\geq 1.7 \text{ mmol/L}$ (150 mg/dL) or current use of lipid-lowering medication;
 4. High-density lipoprotein cholesterol $<1.0 \text{ mmol/L}$ (40 mg/dL) for men and $<1.3 \text{ mmol/L}$ (50 mg/dL) for women;
 5. Waist circumference $\geq 85 \text{ cm}$ for man and $\geq 80 \text{ cm}$ for women;
- BMI-MetS groups:
 1. Metabolically healthy normal weight (MH-NW): normal weight without MetS;
 2. Metabolically healthy overweight (MH-OW): overweight without MetS;
 3. Metabolically healthy obese (MHO): obese without MetS;
 4. Metabolically unhealthy normal weight (MUH-NW): normal weight with MetS;
 5. Metabolically unhealthy overweight (MUH-OW): overweight with MetS;
 6. Metabolically unhealthy obese (MUO): obese with MetS;

Table 2 Baseline characteristics of the study participants according to BMI-MetS. Values were (%) for categorical variables and mean $\pm$ s.d. for continuous variables.

	Metabolically healthy (n = 58 579)			Metabolically unhealthy (n = 33 287)		
	Normal weight (n = 29 279)	Overweight (n = 22 555)	Obese (n = 6745)	Normal weight (n = 6161)	Overweight (n = 16 568)	Obese (n = 10 558)
Age, years	49.79 $\pm$ 13.15	50.21 $\pm$ 11.88	49.04 $\pm$ 12.63	55.67 $\pm$ 11.46	54.16 $\pm$ 10.77	52.44 $\pm$ 11.33
Male, %	76.09	82.13	80.15	76.82	83.08	81.31
High school or above, %	22.59	19.86	20.47	13.78	16.04	17.50
Average income $\geq$ ¥800/month, %	14.12	14.16	13.98	11.25	13.77	14.25
Current smoker, %	34.96	33.52	31.33	30.86	34.56	32.59
Current drinker, %	37.02	37.06	35.32	31.96	38.20	36.88
Physical activity $\geq$ 3 times/week, %	14.10	13.49	12.87	16.75	17.15	16.94
Salt intake $\geq$ 10 g/day, %	9.56	10.05	10.87	8.85	11.43	13.00
hs-CRP, mg/L	2.01 $\pm$ 5.84	2.18 $\pm$ 6.40	2.81 $\pm$ 6.89	2.71 $\pm$ 7.58	2.60 $\pm$ 5.72	3.02 $\pm$ 7.79
eGFR, mL/min/1.73m ²	85.00 $\pm$ 24.97	82.49 $\pm$ 26.05	81.43 $\pm$ 20.64	81.82 $\pm$ 31.63	79.92 $\pm$ 26.45	79.17 $\pm$ 24.05
BMI, kg/m ²	21.84 $\pm$ 1.42	25.71 $\pm$ 1.47	30.08 $\pm$ 2.20	22.45 $\pm$ 1.26	26.03 $\pm$ 1.44	30.38 $\pm$ 2.30
LDL-C, mmol/L	2.25 $\pm$ 0.85	2.33 $\pm$ 0.82	2.34 $\pm$ 0.80	2.38 $\pm$ 1.11	2.50 $\pm$ 1.03	2.47 $\pm$ 0.99
Total cholesterol, mmol/L	4.80 $\pm$ 1.02	4.87 $\pm$ 0.97	4.86 $\pm$ 0.93	5.10 $\pm$ 1.40	5.18 $\pm$ 1.38	5.18 $\pm$ 1.29
History of diabetes, %	3.13	2.86	1.85	19.77	20.37	20.32
History of hypertension, %	25.25	32.22	38.59	63.53	68.42	74.82
Waist circumference, cm	79.95 $\pm$ 8.06	87.08 $\pm$ 7.72	93.86 $\pm$ 9.26	86.90 $\pm$ 7.84	90.96 $\pm$ 6.79	97.42 $\pm$ 8.38
Systolic BP, mmHg	122.70 $\pm$ 18.59	126.75 $\pm$ 19.18	129.73 $\pm$ 19.78	138.90 $\pm$ 19.52	140.76 $\pm$ 19.61	143.59 $\pm$ 19.69
Diastolic BP, mmHg	78.94 $\pm$ 10.46	81.78 $\pm$ 10.70	83.95 $\pm$ 11.15	86.38 $\pm$ 10.95	88.57 $\pm$ 11.11	91.17 $\pm$ 11.80
Fasting glucose, mmol/L	5.08 $\pm$ 1.21	5.08 $\pm$ 1.04	5.01 $\pm$ 0.83	6.26 $\pm$ 2.44	6.20 $\pm$ 2.17	6.16 $\pm$ 2.02
Triglycerides, mmol/L	1.20 $\pm$ 0.90	1.39 $\pm$ 0.98	1.48 $\pm$ 0.97	2.09 $\pm$ 1.67	2.36 $\pm$ 1.75	2.52 $\pm$ 1.72
HDL-C, mmol/L	1.61 $\pm$ 0.39	1.56 $\pm$ 0.35	1.53 $\pm$ 0.33	1.51 $\pm$ 0.50	1.49 $\pm$ 0.44	1.47 $\pm$ 0.42

BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoproteins cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoproteins cholesterol; MetS, metabolic syndrome.

the likelihood ratio test. In addition, several sensitivity analyses were performed to confirm the robustness of our findings, including (1) considering non-MI death as a competing risk event rather than a censoring event, where Fine-Gray competing risk model was applied to address this issue (23); (2) modifying the definition of MetS defined as ≥ 2 among the four components (Table 1, excludes the WC criterion) (13) and (3) using the World Health Organization criteria (24) to define normal weight ($18.5 \leq \text{BMI} < 25.0 \text{ kg/m}^2$), overweight ($25.0 \leq \text{BMI} < 30.0 \text{ kg/m}^2$) and obese ($\text{BMI} \geq 30.0 \text{ kg/m}^2$).

Results

Table 2 shows the baseline characteristics of the participants according to BMI-MetS categories. In total, 33 287 (33.26%) participants were classified as metabolically unhealthy and 58 579 (63.77%) as metabolically healthy. Overall, 18.83% of participants ($n=17\ 303$) were obese. The MHO phenotype represented 7.34% ($n=6745$) of the total analytic sample and 38.98% of the obese population. TG, LDL-C, FBG, WC and BP were higher in the metabolically unhealthy group. There was no difference in the proportions of physically active individuals in the MH-NW, MH-OW and MHO groups.

Over a median of 8.09 years (interquartile range: 7.82–8.24 years) of follow-up, 1167 (1.27%) incident MI cases were documented. The crude incidence rate per 1000 person-years of MI was 1.12 in the MH-NW group, 1.09 in the MH-OW group, 1.71 in the MHO group, 2.11 in the MUH-NW group, 2.46 in the MUH-OW group and 2.42 in the MUO group. Figure 1 shows the cumulative hazard for MI stratified by the BMI-MetS group (log-rank test, $P < 0.001$). These curves significantly differed from each other except for MH-NW vs MH-OW ($P=0.780$), MHO vs MUH-NW ($P=0.973$), MUH-NW vs MUO ($P=0.197$) and MUH-OW vs MUO ($P=0.098$).

Figure 1

Cumulative incidences of myocardial infarction (MI) according to the combined BMI category (normal weight, overweight, obese) and metabolic syndrome (absence or presence). A full colour version of this figure is available at <https://doi.org/10.1530/EJE-18-0356>.

Table 3 shows the association between the BMI-MetS group and risk of MI. Overall, the adjusted HR (model 4 in Table 3) for the incidence of MI in MHO individuals (MH-NW group as the reference) was 1.76 (95% CI: 1.37–2.25). The adjusted HR for the incidence of MI in the MUH-NW (HR: 1.62, 95% CI: 1.28–2.05) and MUO (HR: 2.06, 95% CI: 1.70–2.49) group was also significantly higher than that in the MH-NW group.

Associations between the BMI-MetS group and risk of MI did not significantly differ by sex, age group, smoking status, drinking status or physical activity (all $P > 0.05$ for heterogeneity, Table 4), and sensitivity analyses showed similar results (Supplementary Table 1). The association between MHO and risk of MI was mildly attenuated after adjusting for competing risk of non-MI death (HR:

Table 3 Association of BMI-MetS at baseline and risk of myocardial infarction. Data was reported as hazard ratio and 95% confidence intervals.

	MI, n	Incidence rate ^a	Model 1 [†]	Model 2 [‡]	Model 3 [§]	Model 4
Metabolically healthy normal weight	246	1.05	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Metabolically healthy overweight	197	1.09	1.06 (0.88–1.28)	1.10 (0.91–1.33)	1.09 (0.90–1.32)	1.08 (0.89–1.31)
Metabolically healthy obese	92	1.71	1.71 (1.35–2.18)	1.86 (1.37–2.16)	1.79 (1.40–2.29)	1.76 (1.37–2.25)
Metabolically unhealthy normal weight	104	2.11	2.04 (1.62–2.56)	1.72 (1.37–2.16)	1.62 (1.28–2.06)	1.62 (1.28–2.05)
Metabolically unhealthy overweight	325	2.46	2.32 (1.97–2.75)	2.08 (1.76–2.46)	2.03 (1.71–2.40)	1.98 (1.67–2.35)
Metabolically unhealthy obese	204	2.42	2.19 (1.82–2.64)	2.17 (1.80–2.62)	2.13 (1.76–2.58)	2.06 (1.70–2.49)

^aPer 1000 person-years. [†]Model 1 was unadjusted. [‡]Model 2 was adjusted for age and sex. [§]Model 3 was adjusted for age, sex, educational level, income, smoking, drinking, physical activity and sodium intake. ^{||}Model 4 was adjusted for in Model 3 plus LDL cholesterol, high-sensitive C-reactive protein and glomerular filtration rate (eGFR). MI, myocardial infarction

1.67, 95% CI: 1.30–2.14). Excluding the WC criterion from the definition of MetS demonstrated a somewhat stronger association between the MHO group and MI (HR: 1.84, 95% CI: 1.42–2.38). Finally, when obesity was defined as $\text{BMI} \geq 30 \text{ kg/m}^2$, the HR for MI was somewhat stronger in all of BMI-MetS group except the MUH-NW group. The MHO group was associated with a 2.19-fold (95% CI: 1.58–3.03) risk of MI compared with that of the MH-NW group.

Discussion

In this prospective cohort study, we examined the combined effects of BMI-MetS on the risk of MI over an 8-year follow-up. The main finding of this study was that MHO subjects had roughly a 1.8-fold higher risk of incidence of MI in comparison with their nonobese counterparts (MH-NW).

BMI, a measure of general adiposity, is an established causal risk factor for CVDs and type 2 diabetes (7, 25). Based on the Kailuan study, our previous studies demonstrated that BMI, WC, waist-to-hip ratio and waist-to-height ratio were also associated with MI, ischaemic stroke and diabetes (18, 19). The current study further elucidated that obesity had a strong positive association with the risk of MI regardless of having MetS, suggesting that the management of excess weight seemed to be necessary for all individuals. Findings from the community-based Uppsala Longitudinal Study of Adult Men also supported our results (7).

There remains considerable debate regarding the criteria for the definition of the MHO phenotype (26). Proposed by Wildman (27), Aguilar-Salinas (28), Meigs (29, 30), Karelis (31) and the National Cholesterol Education Program-Adult Treatment Panel III (ATP-III) (32), these criteria were commonly used to assess metabolic status. Thus, the prevalence of the MHO phenotype may vary widely due to the different definitions and diversified study population characteristics (33, 34). Using the International Diabetes Federation consensus definition, the prevalence of the MHO phenotype in the present study was 7.34% in Chinese adults. Our results were consistent with those of a recent meta-analysis, reporting a the prevalence rate of 7.27% (95% CI: 5.93–8.90%) for MHO (33). The prevalence of MHO in the Chinese population was reported to range from 4 to 20% (35, 36, 37, 38). However, some studies had relatively small sample sizes ($n < 5000$) (35, 36). Notably, the prevalence of the MHO phenotype was related to metabolically healthy criteria, sample size and study population characteristics (33).

Therefore, it is necessary to formulate a comprehensive definition of ‘metabolically healthy’ and identify high-risk groups in order to prevent CVDs.

Numerous prospective cohort studies have previously investigated the association between MHO phenotype and CVDs risk as a composite outcome (7, 9, 11, 12, 13, 14, 15, 16, 25, 34, 39, 40), whereas specific outcomes, such as MI were limited. Our results were also consistent with those of recent meta-analyses showing that MHO individuals were at increased risk for cardiovascular events over a long-term follow-up (41). Similar to our findings, the Copenhagen General Population Study of 71 527 individuals identified MHO as being associated with a higher risk of MI (HR: 1.80, 95% CI: 1.34–2.63) compared with MH-NW subjects (9). In the San Antonio Heart Study, MUH-NW and MHO individuals were associated with an increased risk of incident CVDs (HR: 2.9, 95% CI: 1.3–6.4 and HR: 3.9, 95% CI: 1.9–7.8, respectively) (25). Interestingly, in the Nord-Trøndelag Health Study, where 61 299 participants were followed up with a median of 12.2 years, Morkedal *et al.* found that MHO individuals did not have an increased risk of MI in comparison with MH-NW subjects (HR: 1.10, 95% CI: 0.90–1.40) (8). We considered such inconsistencies between findings of the former study and our study may be due to differences in the definition of obesity and the population characteristics. There are different BMI cut-off values for obesity. The estimated association of MHO and MI may vary according to the different BMI cut-off values for obesity in the Nord-Trøndelag Health Study. In our sensitivity analysis, when using $\text{BMI} \geq 30 \text{ kg/m}^2$ for obesity, the effect estimate of MI was significantly larger than that estimated in the Nord-Trøndelag Health Study (HR: 2.19 vs 1.10). In fact, Asians have a higher amount of visceral fat at the same level of BMI compared to Caucasians (42). Abdominal obesity has been linked to increased risks of MetS and type 2 diabetes (18, 19); therefore, Chinese individuals may have a higher risk for CVDs at the same level of obesity. This may explain why the current study population was at higher risk of MI as compared that in Nord-Trøndelag Health Study.

The association between MHO and cardiovascular outcomes in the elderly remain controversial (16, 43). In the subpopulation aged ≥ 65 years, we did not find a high risk of MI in MHO individuals compared with the NM-NW group (HR: 1.04, 95% CI: 0.60–1.80). Our findings were consistent with the finding those of the Rotterdam Study (16), which study also reported that MHO did not confer a higher cardiovascular risk in 5314 individuals aged ≥ 55 years (16). The different impacts of MHO on cardiovascular risk may be due to the differences

Table 4 Association of BMI-MetS at baseline and risk of myocardial infarction stratified by potential risk factors. Data was reported as hazard ratio and 95% confidence intervals estimated from Model 4 expect for adjusted for subgroups variables.

	Metabolically healthy normal weight	Metabolically healthy overweight	Metabolically healthy obese	Metabolically unhealthy normal weight	Metabolically unhealthy overweight	Metabolically unhealthy obese	P for Heterogeneity†
Overall	1.00 (Reference)	1.08 (0.89–1.31)	1.76 (1.37–2.25)	1.62 (1.28–2.05)	1.98 (1.67–2.35)	2.06 (1.70–2.49)	0.304
Male (n = 73 291)							
MI, n	231	185	88	93	292	181	
HR (95% CI)	1.00 (Reference)	1.06 (0.87–1.30)	1.80 (1.39–2.32)	1.58 (1.23–2.02)	1.90 (1.60–2.27)	2.00 (1.59–2.39)	
Female (n = 18 575)							
MI, n	15	12	4	11	33	23	
HR (95% CI)	1.00 (Reference)	1.19 (0.55–2.57)	1.08 (0.35–3.28)	1.79 (0.80–4.00)	2.51 (1.32–4.78)	2.66 (1.34–5.26)	0.646
<65 years of age (n = 79 412)							
MI, n	160	148	75	65	213	152	
HR (95% CI)	1.00 (Reference)	1.06 (0.85–1.34)	1.87 (1.41–2.47)	1.87 (1.39–2.52)	2.06 (1.67–2.54)	2.06 (1.64–2.60)	
≥65 years of age (n = 12 454)							
MI, n	86	49	17	39	112	52	
HR (95% CI)	1.00 (Reference)	0.95 (0.66–1.36)	1.04 (0.60–1.80)	1.44 (0.97–2.14)	1.91 (1.42–2.56)	1.77 (1.24–2.54)	0.102
Never smoker (n = 60 888)							
MI, n	146	115	58	76	222	751	
HR (95% CI)	1.00 (Reference)	1.00 (0.78–1.28)	1.63 (1.18–2.23)	1.84 (1.38–2.46)	2.15 (1.73–2.67)	2.06 (1.62–2.63)	
Former/Current smoker (n = 30 978)							
MI, n	100	82	34	28	103	70	
HR (95% CI)	1.00 (Reference)	1.27 (0.95–1.72)	2.06 (1.39–3.06)	1.17 (0.77–1.79)	1.72 (1.30–2.28)	2.16 (1.57–2.95)	0.141
Never drinker (n = 58 096)							
MI, n	154	139	70	85	238	136	
HR (95% CI)	1.00 (Reference)	1.16 (0.92–1.47)	1.95 (1.45–2.61)	1.95 (1.48–2.57)	2.23 (1.81–2.75)	2.13 (1.68–2.71)	
Former/Current drinker (n = 33 770)							
MI, n	92	58	22	19	87	68	
HR (95% CI)	1.00 (Reference)	0.96 (0.69–1.36)	1.41 (0.88–2.26)	0.95 (0.58–1.56)	1.54 (1.14–2.08)	1.94 (1.41–2.68)	0.139
Physical inactivity <3 times/week (n = 78 165)							
MI, n	189	156	82	86	270	162	
HR (95% CI)	1.00 (Reference)	1.06 (0.85–1.32)	1.93 (1.47–2.52)	1.75 (1.35–2.30)	2.15 (1.78–2.60)	2.13 (1.71–2.60)	
Physical activity ≥3 times/week (n = 13 701)							
MI, n	57	41	10	18	55	42	
HR (95% CI)	1.00 (Reference)	1.18 (0.79–1.78)	1.06 (0.54–2.09)	1.17 (0.68–2.00)	1.42 (0.97–2.08)	1.77 (1.17–2.68)	

†P for heterogeneity was attained from the likelihood ratio test.

in body weight, body composition and health behaviour between the young and the elderly (44). The interaction term was not statistically significant, either. In addition, we did not find any potential effect modifiers, such as sex, smoking status or physical activity. However, caution should be taken when interpreting the results of the subgroup analysis due to the small numbers of MI events in certain subgroups.

Our study has several limitations. First, MHO is an unstable state (14), and we did not assess the impact of the transition from MHO to MUO on MI prospectively. The recent Multi-Ethnic Study of Atherosclerosis Study found that almost half of MHO subjects developed MUO (45). Notably, subjects with unstable MHO had a higher risk of CVDs than that of subjects with stable MHO or healthy normal weight (45). Second, although we cautiously adjusted for potential confounders, we could not adjust for some residual or unmeasured confounding factors, e.g., social deprivation and depressive symptoms, as previous study reported an increased odds of depressive symptoms in the MHO group (46). Third, participants in the present study were recruited from the Kailuan community located in the city of Tangshan, Hebei Province, China. This study cohort was not nationally representative, and the association between MHO and risk of MI in this population may not be directly generalised to other populations. Our study also has several strengths, including the prospective cohort design, large sample size in a fixed functional community in China and a standardised evaluation of directly measured metabolic markers and body sizes. Moreover, we affirmed the combined effect of obesity and MetS on the risk of MI. Our findings suggest that MHO is not a low-risk state. In addition, our future work will focus on the association between the transition from metabolically healthy to unhealthy phenotypes and the risk of CVDs in this population.

Conclusions

In conclusion, our study showed that MHO individuals had a substantially increased risk of incident MI in comparison with MH-NW individuals in a large Chinese community, indicating that all obese individuals, even those without MetS should be encouraged to lower their weight to reduce the risk of MI.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-18-0356>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Authors contribution statement

H L and Y X applied data and wrote the manuscript. A W contributed to introduction and discussion. Z S, Y W, L T, S C contributed to the discussion. S W, Y X and X G contributed to the discussion and reviewed and edited the manuscript. All authors read and approved the final manuscript.

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