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All-cause mortality risk with different metabolic abdominal obesity phenotypes: the Rural Chinese Cohort Study

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Abstract

We aimed to investigate the association of metabolic obesity phenotypes with all-cause mortality risk in a rural Chinese population. This prospective cohort study enrolled 15 704 Chinese adults (38·86 % men) with a median age of 51·00 (interquartile range: 41·00–60·00) at baseline (2007–2008) and followed up during 2013–2014. Obesity was defined by waist circumference (WC: ≥ 90 cm for men and ≥ 80 cm for women) or waist-to-height ratio (WHtR: ≥ 0·5). The hazard ratio (HR) and 95 % CI for the risk of all-cause mortality related to metabolic obesity phenotypes were calculated using the Cox hazards regression model. During a median follow-up of 6·01 years, 864 deaths were identified. When obesity was defined by WC, the prevalence of participants with metabolically healthy non-obesity (MHNO), metabolically healthy obesity (MHO), metabolically unhealthy non-obesity (MUNO) and metabolically unhealthy obesity (MUO) at baseline was 12·12 %, 2·80 %, 41·93 % and 43·15 %, respectively. After adjusting for age, sex, alcohol drinking, smoking, physical activity and education, the risk of all-cause mortality was higher with both MUNO (HR = 1·20, 95 % CI 1·14, 1·26) and MUO (HR = 1·20, 95 % CI 1·13, 1·27) *v.* MHNO, but the risk was not statistically significant with MHO (HR = 0·99, 95 % CI 0·89, 1·10). This result remained consistent when stratified by sex. Defining obesity by WHtR gave similar results. MHO does not suggest a greater risk of all-cause mortality compared to MHNO, but participants with metabolic abnormality, with or without obesity, have a higher risk of all-cause mortality. These results should be cautiously interpreted as the representation of MHO is small.

Key words: **Obesity: Metabolism: All-cause mortality: Prospective cohort study**

Over the past few decades, the prevalence of obesity has continued to increase such that it has become a serious public health issue worldwide[1]. Obesity is associated with death[2] and various chronic conditions such as hypertension[3], cancer[4] and CVD[5]. There is, however, heterogeneity among people with obesity which can be divided into two phenotypes: metabolically healthy and metabolically unhealthy[6–8]. People who were obese with favourable blood pressure, lipid profile, inflammation levels and insulin sensitivity are considered to have metabolically healthy obesity (MHO)[6–8]. Other metabolic obesity phenotypes include metabolically healthy non-obesity (MHNO), metabolically unhealthy non-obesity (MUNO) and metabolically unhealthy obesity (MUO)[9–11]. In population-based research, the association between different

Abbreviations: MHNO, metabolically healthy non-obesity; MHO, metabolically healthy obesity; MUNO, metabolically unhealthy non-obesity; MUO, metabolically unhealthy obesity; WC, waist circumference; WHtR, waist-to-height ratio.

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metabolic obesity phenotypes and death has received increasing attention. The association between these metabolic obesity phenotypes and the risk of mortality is inconsistent[10–16]. Moreover, so far as we know, only two research examined the relation in the Chinese population[17,18]. These, however, were based on data from physical examination and hospital visit populations in older men, suggesting some bias and limited generalisability to the general population. Data on the relationship of metabolic obesity phenotypes with mortality in rural natural China in areas of relatively low-socioeconomic status are still lacking.

Most of the current studies linking mortality to metabolic obesity phenotypes were based on Western populations and used BMI to define obesity[14,15,19]. Previous studies have shown that Asians are more inclined to abdominal obesity than Western populations[20], and that increased waist circumference (WC) or waist-to-height ratio (WHtR) are better indicators of all-cause mortality risk independent of BMI[21–23]. Nevertheless, no study has investigated the association between metabolic obesity phenotypes and death with abdominal obesity as the focus rather than general obesity, which is defined by BMI in the rural Chinese population.

This study therefore prospectively explored the relationship of different metabolic obesity phenotypes with all-cause mortality risk by using WC and WHtR to define obesity on the basis of the Rural Chinese Cohort Study.

Materials and methods

Study participants

The Rural Chinese Cohort Study recruited 20 194 Chinese adults aged over 18 residing in a rural area in the middle of China from July to August 2007 and July to August 2008 at baseline examination[24]. Two towns, Tiemen and Cijian in Xin'an County, were selected as representatives of the area's geographical and rural economic status. The study participants were randomly recruited by a cluster sampling procedure, with villages as the sampling unit from the two towns. Details of the eligibility requirements for study participants have been previously described[25]. The first follow-up survey was conducted from July to August 2013 and July to October 2014, with 17 265 individuals successfully followed up (response rate 85·5 %). For the current study, we excluded participants who had missing data for defining metabolic status (*n* 84), those with missing data for defining obesity (height or WC) (*n* 6), those who were underweight (BMI < 18·5 kg/m^2) (*n* 562) and those with CVD and/or cancer (*n* 909) at baseline. Ultimately, a total of 15 704 participants were included in the final analysis (Fig. 1). This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Medical Ethics Committee of Shenzhen University. All the participants gave written informed consent.

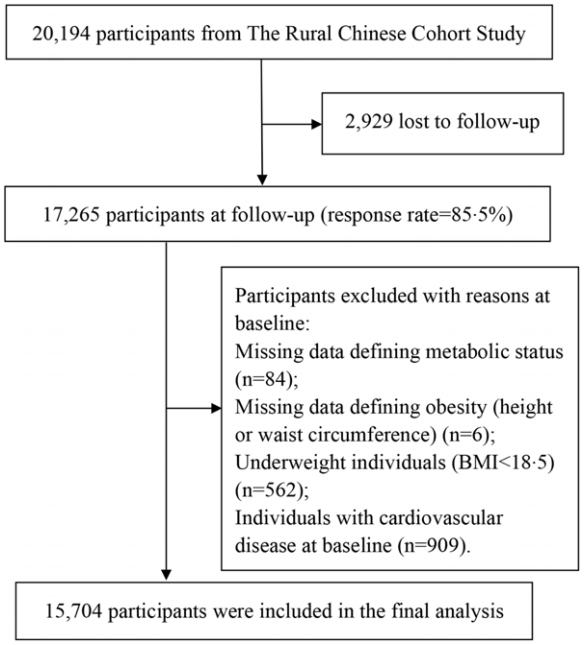

Fig. 1. Flow chart of the selection of participants.

Data collection

We conducted face-to-face interviews, physical examinations and blood sample collection using the same procedures during the baseline and follow-up surveys. Detailed information on demographic characteristics and lifestyles was collected by interview with standardised questionnaires. Education level was dichotomised as high school or above and low education level. Smoking was defined as currently smoking and/or having smoked at least 100 cigarettes in a lifetime[26]. Alcohol drinking was defined as having consumed alcohol twelve or more times during the last year[27]. Physical activity level was classified as low or moderate/high physical activity level according to the International Physical Activity Questionnaire[28]. With participants wearing light clothing, body weight was measured to the nearest 0·5 kg on a vertical weight scale. Height was measured to the nearest 0·1 cm with participants standing erect in bare feet. With participants gently breathing, WC was measured at the mid-point between the lowest rib and the iliac crest to the nearest 0·1 cm. WC, height and body weight were measured twice according to standard methods[29], with the average used in the analysis. WHtR was calculated as WC (metres)/height (metres). BMI was calculated as weight (kilograms) divided by the square of height (metres). In accordance with the standardised protocol of the American Heart Association, blood pressure was assessed three times on the right arm at 30-s intervals using an electronic sphygmomanometer (HEM-770A Fuzzy), with the mean of the three measurements used in the analysis. Fasting blood samples for biochemical analysis were collected after an overnight fast of at least 8 h. TAG, HDL-cholesterol and fasting plasma glucose were measured using a HITACHI automatic clinical analyzer (Model 7060, Tokyo). Detailed information about storage and measurement methods has been previously described[25]. The same measurements as for the baseline examination were taken during the follow-up examination.

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Definition of metabolic obesity phenotypes

Metabolically healthy individuals were defined as having zero metabolic risk factors among the following harmonised criteria by the Joint Interim Statement: (1) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or antihypertensive drug treatment; (2) TAG level ≥ 1·7 mmol/l or drug treatment; (3) HDL-cholesterol level < 40 mg/dl (1·034 mmol/l) for men or < 50 mg/dl (1·293 mmol/l) for women or drug treatment and (4) fasting plasma glucose level ≥ 5·6 mmol/l or drug treatment[30,31]. Participants with one or more of the four metabolic risk factors were defined as metabolically unhealthy. Obesity was defined by WC (≥ 90 cm for men and ≥ 80 cm for women[32]) or WHtR (≥ 0·5[33]). Participants were divided into four metabolic obesity phenotypes: MHNO, MHO, MUNO and MUO.

Follow-up of mortality

Death information was collected through face-to-face interviews with participants' family members, the village doctor or other health care providers during the follow-up survey. The information on death was further checked with the local Centers for Disease Control and Prevention. For conflicting data, we verified the information with relatives or local village doctors[34].

Statistical analyses

For baseline characteristics, continuous variables with skewed distribution are presented as median (interquartile range) and were compared using the Kruskal–Wallis test. Categorical variables are presented as number (percentage), with chi-square test used for comparison. The proportional hazard assumption was met and tested by the Kaplan–Meier Curve and Schoenfeld residuals. Cox proportional-hazards regression model was thus used to calculate the hazard ratio and 95 % CI for the risk of all-cause mortality associated with different metabolic obesity phenotypes. We chose MHNO as the reference group and adjusted for several potential confounders, including sex, age, alcohol drinking, smoking, physical activity level and education, in the final analyses. To examine the potential effects of known confounding factors, we conducted subgroup analyses stratified by sex (men or women) and age (< 60 or ≥ 60 years). To assess the robustness of the results, we performed sensitivity analyses that involved excluding participants with diabetes, those who were smokers at baseline, and those who died within the first year.

All statistical analyses were conducted with SAS v9.4 (SAS Inst.). Statistical significance was established as two-sided $P < 0·05$.

Results

Baseline characteristics

A total of 15 704 participants were eligible for inclusion, with a median age of 51·00 (interquartile range: 41·00–60·00). When obesity was defined by WC, the prevalence of participants with MHNO, MHO, MUNO and MUO at baseline was 12·12 %, 2·80 %, 41·93 % and 43·15 %, respectively (Table 1). The baseline characteristics including age, sex, education, smoking, alcohol drinking, physical activity, BMI, WC, WHtR, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, TAG and HDL-cholesterol levels significantly differed by metabolism and obesity status as defined by WC (all $P < 0·05$) (Table 1). Metabolically unhealthy individuals are older compared to metabolically healthy individuals, with a median age of 45·00 (39·00–53·00) and 53·00 (44·00–60·00) for individuals with MHO and MUO, respectively. Individuals who are obese, especially MUO, are more likely to be women, have lower levels of education, be non-smokers, non-drinkers and be physically inactive. These individuals also have higher levels of BMI, WC, WHtR, systolic blood pressure, diastolic blood pressure, fasting plasma glucose and TG, but lower levels of HDL-cholesterol. When obesity was defined by WHtR, the prevalence was 10·23 %, 4·68 %, 28·24 % and 56·85 %, respectively. Individuals with different metabolic obesity phenotypes have similar characteristics to those defined as obese by WHtR.

Metabolic obesity phenotypes at baseline and risk of all-cause mortality

During the follow-up of 92 805·61 person-years (average follow-up of 6·01 years), we identified 864 deaths (all-cause mortality 9·31/1000 person-years).

When obesity was defined by WC, the all-cause mortality was 5·40, 4·48, 11·38 and 8·77/1000 person-years with MHNO, MHO, MUNO and MUO, respectively (Table 2). After adjusting for age, sex, alcohol drinking, smoking, physical activity level and education, the risk of all-cause mortality was higher with MUNO (adjusted hazard ratio (aHR) = 1·20, 95 % CI 1·14, 1·26) and MUO (aHR = 1·20, 95 % CI 1·13, 1·27) *v.* MHNO (Table 2), but the association was not statistically significant for MHO (aHR = 0·99, 95 % CI 0·89, 1·10) (Table 2).

When obesity was defined by WHtR, all-cause mortality was 4·45, 6·98, 10·85 and 9·66/1000 person-years with MHNO, MHO, MUNO and MUO, respectively (Table 2). After adjusting for age, sex, smoking, physical activity level and education confounding factors, the risk of all-cause mortality was higher with both MUNO (aHR = 1·18, 95 % CI 1·12, 1·26) and MUO (aHR = 1·21, 95 % CI 1·14, 1·28) *v.* MHNO, but the association was not statistically significant for MHO (aHR = 1·00, 95 % CI 0·91, 1·09) (Table 2).

The results of the sensitivity analyses were all similar to the main analysis (online Supplementary Table 2). When obesity was defined by WC, the aHR (95 % CI) for all-cause mortality with MHO, MUNO, and MUO *v.* MHNO was 0·99 (0·89, 1·10), 1·20 (1·14, 1·26) and 1·20 (1·13, 1·27) after excluding participants who died within 1 year; the aHR (95 % CI) was 0·99 (0·89, 1·10), 1·19 (1·13, 1·25) and 1·18 (1·11, 1·24) after excluding participants with diabetes at baseline; the aHR (95 % CI) was 0·96 (0·85, 1·09), 1·18 (1·10, 1·26) and 1·16 (1·09, 1·24) after excluding participants who smoke. When obesity was defined by WHtR, the results were equally robust (online Supplementary Table 2).

Subgroup analyses

All subgroup analyses stratified by sex and age gave similar results for MHO, MUNO and MUO with obesity defined using

Table 1. Baseline characteristics of study participants by metabolic obesity phenotypes

	Obesity defined by WC								
	MHNO		MHO		MUNO		MUO		
Baseline characteristics	*n*	%	*n*	%	*n*	%	*n*	%	*P* value
No. of participants (%)	1903	12·12	439	2·80	6585	41·93	6777	43·15	< 0·0001
Age (years)									
Median	45·00		45·00		51·00		53·00		< 0·0001
IQR	36·00–55·00		39·00–53·00		41·00–61·00		44·00–60·00		
Men (%)	1132	59·49	107	24·37	3370	51·18	1493	22·03	< 0·0001
High school or above (%)	265	13·93	43	9·79	775	11·77	535	7·89	< 0·0001
Smoking (%)	812	42·67	72	16·40	2328	35·35	1001	14·77	< 0·0001
Alcohol drinking (%)	364	19·13	49	11·16	854	12·97	551	8·13	< 0·0001
Low physical activity level (%)	428	22·49	132	30·07	1920	29·16	2410	35·56	< 0·0001
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
BMI (kg/m^2)	21·49	20·24–23·01	25·98	24·44–27·56	22·35	20·89–23·91	26·83	25·09–28·81	< 0·0001
WC (cm)	74·00	70·30–78·50	86·90	83·00–92·60	76·65	72·25–80·25	90·55	85·00–95·75	< 0·0001
WHtR	0·46	0·44–0·49	0·55	0·53–0·58	0·48	0·46–0·51	0·57	0·55–0·61	< 0·0001
SBP (mmHg)	112·33	105·33–119·33	115·67	107·33–121·33	121·67	110·33–136·00	129·33	116·67–144·33	< 0·0001
DBP (mmHg)	70·67	66·00–75·33	73·33	68·67–78·33	76·33	69·67–84·00	81·67	74·67–89·67	< 0·0001
FPG (mmol/l)	5·03	4·75–5·28	5·13	4·86–5·33	5·34	4·98–5·74	5·54	5·16–6·06	< 0·0001
TG (mmol/l)	0·93	0·71–1·21	1·04	0·81–1·31	1·28	0·93–1·81	1·73	1·23–2·52	< 0·0001
HDL-C (mmol/l)	1·36	1·19–1·50	1·39	1·31–1·52	1·11	0·96–1·27	1·09	0·95–1·24	< 0·0001
	Obesity defined by WHtR								
	MHNO		MHO		MUNO		MUO		
Baseline characteristics	*n*	%	*n*	%	*n*	%	*n*	%	*P* value
No. of participants (%)	1607	10·23	735	4·68	4435	28·24	8927	56·85	< 0·0001
Age (years)									
Median	44·00		47·00		48·00		53·00		< 0·0001
IQR	35·00–54·00		40·00–56·00		39·00–59·00		44·00–61·00		
Men (%)	939	58·43	300	40·82	2137	48·18	2726	30·54	< 0·0001
High school or above (%)	234	14·56	74	10·07	527	11·88	783	8·77	< 0·0001
Smoking (%)	672	41·82	212	28·84	1517	34·21	1812	20·30	< 0·0001
Alcohol drinking (%)	296	18·42	117	15·92	530	11·95	875	9·80	< 0·0001
Low physical activity level (%)	355	22·09	205	27·89	1221	27·53	3109	34·83	< 0·0001
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
BMI (kg/m^2)	21·12	20·05–22·38	24·97	23·65–26·64	21·51	20·37–22·78	26·03	24·33–28·11	< 0·0001
WC (cm)	73·00	69·90–76·50	84·60	81·10–89·75	74·05	70·75–77·70	88·05	83·10–93·75	< 0·0001
WHtR	0·46	0·43–0·48	0·53	0·51–0·56	0·47	0·44–0·48	0·56	0·53–0·59	< 0·0001
SBP (mmHg)	112·00	105·00–119·00	115·00	107·67–121·33	119·67	108·67–133·33	128·67	116·33–143·33	< 0·0001
DBP (mmHg)	70·33	65·67–75·00	73·00	68·33–77·33	75·00	68·67–82·67	81·00	74·00–89·00	< 0·0001
FPG (mmol/l)	5·03	4·75–5·28	5·10	4·80–5·30	5·30	4·95–5·68	5·51	5·14–6·02	< 0·0001
TG (mmol/l)	0·91	0·69–1·18	1·04	0·81–1·33	1·18	0·87–1·66	1·68	1·19–2·42	< 0·0001
HDL-C (mmol/l)	1·36	1·20–1·50	1·37	1·25–1·50	1·13	0·97–1·28	1·09	0·95–1·24	< 0·0001

Abbreviations: DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, HDL-cholesterol; IQR, interquartile range; MHNO, metabolically healthy non-obesity; MHO, metabolically healthy obesity; MUNO, metabolically unhealthy non-obesity; MUO, metabolically unhealthy obesity; SBP, systolic blood pressure; WC, waist circumference; WHtR, waist-to-height ratio.
Data are median (interquartile range) or number (percentage). The *P* value was generated by Kruskal–Wallis H test or chi-square test for continuous variables and categorical variables.

Table 2. Association of metabolic obesity phenotypes at baseline with risk of all-cause mortality

Metabolically healthy and obese status	No. of deaths	Person-years	Mortality*	HR	95 % CI†	*P* value†	HR	95 % CI‡	*P* value‡
Obesity defined by WC									
MHNO (*n* 1903)	63	11 657·21	5·40	1·00 (ref)		–	1·00 (ref)		–
MHO (*n* 439)	12	2677·71	4·48	1·06	0·96, 1·18	0·2545	0·99	0·89, 1·10	0·8527
MUNO (*n* 6585)	440	38 665·88	11·38	1·27	1·21, 1·34	< 0·0001	1·20	1·14, 1·26	< 0·0001
MUO (*n* 6777)	349	39 804·81	8·77	1·37	1·30, 1·44	< 0·0001	1·20	1·13, 1·27	< 0·0001
Obesity defined by WHtR									
MHNO (*n* 1607)	44	9892·26	4·45	1·00 (ref)		–	1·00 (ref)		–
MHO (*n* 735)	31	4442·66	6·98	1·08	0·99, 1·18	0·0799	1·00	0·91, 1·09	0·9988
MUNO (*n* 4435)	284	26 180·41	10·85	1·24	1·17, 1·32	< 0·0001	1·18	1·12, 1·26	< 0·0001
MUO (*n* 8927)	505	52 290·28	9·66	1·39	1·31, 1·47	< 0·0001	1·21	1·14, 1·28	< 0·0001

Abbreviations: HR, hazard ratio; MHNO, metabolically healthy non-obesity; MHO, metabolically healthy obesity; MUNO, metabolically unhealthy non-obesity; MUO, metabolically unhealthy obesity; WC, waist circumference; WHtR, waist-to-height ratio.
* Per 1000 person-years.
† Unadjusted model.
‡ Adjusted for sex, age, alcohol drinking, smoking, physical activity level and education.

WC or WHtR. In comparison with MHNO, MHO was not associated with the risk of all-cause mortality, while the risk with MUNO and MUO was higher by sex and age groups. Detailed results of subgroup analyses are shown in Fig. 2 and 3.

Discussion

In this large prospective cohort study, we included 15 704 adults with a median follow-up of 6·01 years to explore the association between different metabolic obesity phenotypes and the risk of all-cause mortality. Regardless of whether WC or WHtR was used to define obesity, after adjusting for potential confounding factors, the risk of all-cause mortality was higher with MUNO and MUO *v.* MHNO, with no significant association found for MHO. The results persisted in subgroup and sensitivity analyses.

The association between different metabolic obesity phenotypes and the risk of all-cause mortality remains controversial. Consistent with our results, some studies found that both MUNO and MUO were positively associated with the risk of all-cause mortality[11,14,15], with no association found for MHO[11,14,16,17,35] compared with MHNO. One systematic review and meta-analysis[36] that included eleven prospective studies (2705 deaths and 118 471 participants) did not find a positive association of MHO with all-cause mortality risk; however, other studies have questioned the benign health status of MHO[10,12,13]. A prospective cohort study that included 22 654 participants with an average follow-up time of 13·4 years found that[10], compared to MHNO, MHO defined by WC was associated with a higher risk of all-cause mortality, while another cohort study of 1758 individuals followed up for 30 years and with 788 deaths showed that MHO could increase the risk of all-cause mortality[37].

Follow-up duration may be one of the factors explaining the inconsistent results. Kramer et al. included eight studies systematically evaluating the association of MHO and all-cause mortality or risk of cardiovascular events. The results suggested that MHO represented a similar risk to that shown in our results (hazard ratio = 1·19, 95 % CI 0·98, 1·38), but when the review included only four studies with a follow-up of > 10 years, MHO increased the risk (hazard ratio = 1·24, 95 % CI 1·02, 1·55)[38]. This finding may suggest that a longer follow-up is warranted to identify any increased risk associated with MHO[38]. Reis et al. deeply explored the association between obesity duration and coronary artery calcification, finding that the risk was significant among participants with > 10 years' abdominal obesity defined by WC and > 20 years' general obesity defined by BMI[39]. Bell et al. studied the natural course of MHO over 20 years, finding that after a 5-year follow-up, 31·8 % of MHO individuals changed to metabolically unhealthy and after a 20-year follow-up, 51·5 % of MHO individuals changed to metabolically unhealthy[40]. This finding may also explain the importance of follow-up duration in the association between MHO and risk of all-cause mortality. Additionally, the inconsistent definition of MHO in different studies may lead to discrepant findings[11,14,17,35,41]. Some studies defined metabolic health by including one or two risk factors[11,35,42], while in the present study, we adopted a stricter definition (none of the metabolic abnormality indicators is defined as metabolic healthy), which can reduce the impact of metabolic abnormality factors on the outcome. However, using a strict definition resulted in a smaller sample size of metabolic health. Moreover, by using WC to define obesity, only 2·80 % of participants were classified as MHO, with relatively fewer deaths among them, resulting in a wide CI for risk estimates. Future research should therefore use a unified standard to define metabolic healthy when comparing the risk among different studies and populations.

Our study indicates that special attention should be paid to individuals with MUNO. Consistent with other studies[11,14,15], this group, similar to MUO, could be at increased risk of all-cause mortality. It's mortality rate is higher than that of the MUO group in our study. It may represent the most severe subtype in the phenotype spectrum[38]. Because people in the MUNO group are not obese, this population is easily overlooked by the usual preventive healthcare strategies. Regardless of obesity, metabolic abnormalities could increase the risk of all-cause mortality. Compared with obesity, therefore, metabolic abnormalities may be more strongly associated with all-cause mortality risk, suggesting that people should maintain a metabolically healthy status. Regular evaluation of metabolic levels of blood glucose, blood lipid and blood pressure for people with obesity is essential for preventing all-cause mortality.

Subgroup	Deaths	Person-years	Mortality[a]	HR (95% CI)[b]	HR (95% CI)[c]
Men					
MHNO	45	6,996·52	6·43	1·00 (ref)	1·00 (ref)
MHO	6	656·01	9·15	1·12 (0·91-1·37)	1·11 (0·90-1·36)
MUNO	317	19,656·12	16·13	1·32 (1·24-1·42)	1·26 (1·17-1·35)
MUO	99	8,770·21	11·29	1·38 (1·27-1·49)	1·32 (1·22-1·43)
Women					
MHNO	18	4,660·69	3·86	1·00 (ref)	1·00 (ref)
MHO	6	2,021·70	2·97	0·96 (0·84-1·10)	0·90 (0·79-1·03)
MUNO	123	19,009·76	6·47	1·18 (1·09-1·28)	1·12 (1·03-1·21)
MUO	250	31,034·60	8·06	1·24 (1·15-1·34)	1·10 (1·02-1·19)
Age<60 years					
MHNO	25	9,976·42	2·51	1·00 (ref)	1·00 (ref)
MHO	6	2,308·73	2·60	1·08 (0·97-1·22)	0·99 (0·88-1·11)
MUNO	138	28,312·58	4·87	1·25 (1·18-1·32)	1·19 (1·12-1·26)
MUO	111	29,345·13	3·78	1·39 (1·31-1·47)	1·19 (1·12-1·26)
Age≥60 years					
MHNO	38	1,680·79	22·61	1·00 (ref)	1·00 (ref)
MHO	6	368·98	16·26	0·92 (0·69-1·23)	0·88 (0·66-1·18)
MUNO	302	10,353·30	29·17	1·22 (1·07-1·39)	1·25 (1·09-1·43)
MUO	238	10,459·68	22·75	1·16 (1·01-1·32)	1·14 (0·99-1·31)

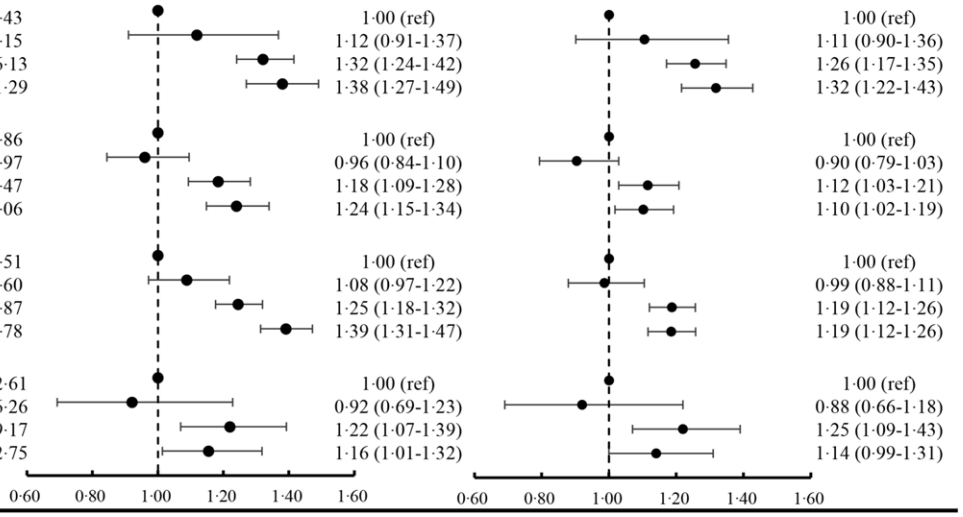

Fig. 2. Association of metabolic obesity phenotypes (by WC) at baseline with risk of all-cause mortality by sex and age. Abbreviations: HR, hazard ratio; MHNO, metabolically healthy non-obesity; MHO, metabolically healthy obesity; MUNO, metabolically unhealthy non-obesity; MUO, metabolically unhealthy obesity; WC, waist circumference. [a]Per 1000 person-years. [b]Unadjusted model. [c]Adjusted for sex, age, alcohol drinking, smoking, physical activity level and education. Each group adjusted for the other covariates except for itself.

Subgroup	Deaths	Person-years	Mortality[a]	HR (95% CI)[b]	HR (95% CI)[c]
Men					
MHNO	31	5,829·48	5·32	1·00 (ref)	1·00 (ref)
MHO	20	1,823·05	10·97	1·10 (0·96-1·25)	1·03 (0·90-1·17)
MUNO	202	12,528·88	16·12	1·29 (1·20-1·40)	1·24 (1·14-1·34)
MUO	214	15,897·45	13·46	1·41 (1·31-1·52)	1·30 (1·21-1·41)
Women					
MHNO	13	4,062·78	3·20	1·00 (ref)	1·00 (ref)
MHO	11	2,619·61	4·20	1·02 (0·90-1·15)	0·95 (0·84-1·07)
MUNO	82	13,651·53	6·01	1·16 (1·06-1·26)	1·12 (1·02-1·22)
MUO	291	36,392·83	8·00	1·28 (1·18-1·39)	1·12 (1·03-1·22)
Age<60 years					
MHNO	21	8,605·51	2·44	1·00 (ref)	1·00 (ref)
MHO	10	3,679·64	2·72	1·09 (0·99-1·20)	0·96 (0·89-1·09)
MUNO	91	20,194·77	4·51	1·21 (1·14-1·29)	1·17 (1·09-1·24)
MUO	158	37,462·94	4·22	1·40 (1·32-1·49)	1·20 (1·13-1·27)
Age≥60 years					
MHNO	23	1,286·75	17·87	1·00 (ref)	1·00 (ref)
MHO	21	763·02	27·52	0·98 (0·78-1·23)	0·99 (0·78-1·24)
MUNO	193	5,985·64	32·24	1·26 (1·08-1·47)	1·30 (1·11-1·52)
MUO	347	14,827·34	23·40	1·17 (1·01-1·36)	1·19 (1·02-1·38)

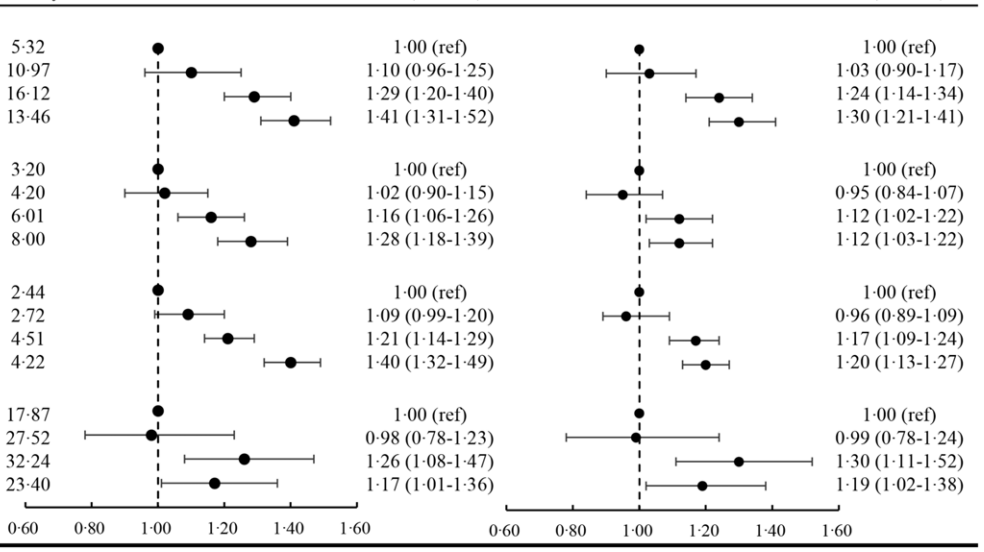

Fig. 3. Association of metabolic obesity phenotypes (by WHtR) at baseline with risk of all-cause mortality by sex and age. Abbreviations: HR, hazard ratio; MHNO, metabolically healthy non-obesity; MHO, metabolically healthy obesity; MUNO, metabolically unhealthy non-obesity; MUO, metabolically unhealthy obesity; WHtR, waist-to-height ratio. [a]Per 1000 person-years. [b]Unadjusted model. [c]Adjusted for sex, age, alcohol drinking, smoking, physical activity level and education. Each group adjusted for the other covariates except for itself.

Our study has several strengths. To our knowledge, it is the first to use abdominal obesity (WC and WHtR) to explore the association of metabolic obesity phenotypes with the risk of all-cause mortality in a rural Chinese adult population. In addition, we adjusted for confounding factors, including demographic characteristics and behavioural factors, in the statistical model to test whether the metabolic obesity phenotypes were independently related to the risk of all-cause mortality. We also conducted subgroup and sensitivity analyses to test the robustness of the current findings. Nevertheless, our study had several limitations. First, there may still be some unmeasured confounding factors, such as anxiety, depression or stress, that are associated with mortality[43,44]. Second, using a strict definition resulted in a smaller sample size for metabolic healthy, especially for the MHO, with relatively fewer deaths, resulting in a wide CI for risk estimates. In addition, we have had only one follow-up result so far; hence, we could not assess the association between dynamic changes in metabolic obesity phenotypes and

the risk of all-cause mortality. More research in this area is needed in the future. Finally, the participants in our study were from a rural Chinese population which may not be a representative sample of a multi-ethnic, multi-centre cohort of Chinese adults.

Conclusions

Compared with MHNO, MUNO and MUO were positively associated with the risk of all-cause mortality at 6·01 years of follow-up among rural Chinese people, while MHO did not relate to the risk. The short follow-up period and small sample size for the healthy metabolic group, especially for the MHO, may indicate the need to interpret results with caution. Larger studies with longer follow-up periods are therefore needed to provide more information in this field. Our findings indicate that people with MUNO should also be included in routine preventive care. Additionally, the combined assessment of both obesity and metabolic status should be considered to predict the risk of all-cause mortality.

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X. W., Y. Z., and D. H. substantially contributed to the design and drafting of the study and the analysis and interpretation of the data. X. W. and Y. Z. wrote the manuscript. Q. Z., M. H., R. Q., P. Q., Y. Z., Z. H., J. L., F. H., X. L., M. Z., Y. L., X. S., and D. H. revised it critically for important intellectual content. All authors were involved in the collection of data and approved the final manuscript.

The authors declare that they have no competing interests.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114523000673

References

1. Collaboration NCDRF (2017) Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet* **390**, 2627–2642.
2. Aune D, Sen A, Prasad M, *et al.* (2016) 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* **353**, i2156.
3. Seravalle G & Grassi G (2017) Obesity and hypertension. *Pharmacol Res* **122**, 1–7.
4. Deng T, Lyon CJ, Bergin S, *et al.* (2016) Obesity, inflammation, and cancer. *Annu Rev Pathol* **11**, 421–449.
5. Ortega FB, Lavie CJ & Blair SN (2016) Obesity and cardiovascular disease. *Circ Res* **118**, 1752–1770.
6. Phillips CM (2013) Metabolically healthy obesity: definitions, determinants and clinical implications. *Rev Endocr Metab Disord* **14**, 219–227.
7. Primeau V, Coderre L, Karelis AD, *et al.* (2011) Characterizing the profile of obese patients who are metabolically healthy. *Int J Obes* **35**, 971–981.
8. Karelis AD, Faraj M, Bastard JP, *et al.* (2005) The metabolically healthy but obese individual presents a favorable inflammation profile. *J Clin Endocrinol Metab* **90**, 4145–4150.
9. Zhao Y, Qin P, Sun H, *et al.* (2020) Metabolically healthy general and abdominal obesity are associated with increased risk of hypertension. *Br J Nutr* **123**, 583–591.
10. van der AD, Nooyens AC, van Duijnhoven FJ, *et al.* (2014) All-cause mortality risk of metabolically healthy abdominal obese individuals: the EPIC-MORGEN study. *Obesity* **22**, 557–564.
11. Doustmohamadian S, Serahati S, Barzin M, *et al.* (2017) Risk of all-cause mortality in abdominal obesity phenotypes: Tehran Lipid and Glucose Study. *Nutr Metab Cardiovasc Dis* **27**, 241–248.
12. Loprinzi PD & Frith E (2017) Cardiometabolic healthy obesity paradigm and all-cause mortality risk. *Eur J Intern Med* **43**, 42–45.
13. Hinnouho GM, Czernichow S, Dugravot A, *et al.* (2013) Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? *Diabetes Care* **36**, 2294–2300.
14. Al-Khalidi B, Kimball SM, Kuk JL, *et al.* (2019) Metabolically healthy obesity, vitamin D, and all-cause and cardiometabolic mortality risk in NHANES III. *Clin Nutr* **38**, 820–828.
15. Kuk JL, Rotondi M, Sui X, *et al.* (2018) Individuals with obesity but no other metabolic risk factors are not at significantly elevated all-cause mortality risk in men and women. *Clin Obes* **8**, 305–312.
16. Bo S, Musso G, Gambino R, *et al.* (2012) Prognostic implications for insulin-sensitive and insulin-resistant normal-weight and obese individuals from a population-based cohort. *Am J Clin Nutr* **96**, 962–969.
17. Zhang R, Dong SY, Wang WM, *et al.* (2018) Obesity, metabolic abnormalities, and mortality in older men. *J Geriatr Cardiol* **15**, 422–427.
18. Tian Q, Wang A, Zuo Y, *et al.* (2020) All-cause mortality in metabolically healthy individuals was not predicted by overweight and obesity. JCI Insight 5, e136982.
19. Guo F & Garvey WT (2016) Cardiometabolic disease risk in metabolically healthy and unhealthy obesity: stability of metabolic health status in adults. *Obesity* **24**, 516–525.
20. Nazare JA, Smith JD, Borel AL, *et al.* (2012) Ethnic influences on the relations between abdominal subcutaneous and visceral adiposity, liver fat, and cardiometabolic risk profile: the International Study of Prediction of Intra-Abdominal Adiposity and Its Relationship With Cardiometabolic Risk/Intra-Abdominal Adiposity. *Am J Clin Nutr* **96**, 714–726.
21. Leitzmann MF, Moore SC, Koster A, *et al.* (2011) Waist circumference as compared with body-mass index in predicting mortality from specific causes. *PloS One* **6**, e18582.
22. Bigaard J, Frederiksen K, Tjønneland A, *et al.* (2005) Waist circumference and body composition in relation to all-cause mortality in middle-aged men and women. *Int J Obes* **29**, 778–784.

23. Ashwell M, Mayhew L, Richardson J, *et al.* (2014) Waist-to-height ratio is more predictive of years of life lost than body mass index. *PloS One* **9**, e103483.
24. Zhou Q, Wu X, Zhang D, *et al.* (2020) Age and sex differences in the association between sleep duration and general and abdominal obesity at 6-year follow-up: the rural Chinese cohort study. *Sleep Med* **69**, 71–77.
25. Zhao Y, Zhang M, Luo X, *et al.* (2016) Association of obesity categories and high blood pressure in a rural adult Chinese population. *J Hum Hypertens* **30**, 613–618.
26. Bondy SJ, Victor JC & Diemert LM (2009) Origin and use of the 100 cigarette criterion in tobacco surveys. *Tobacco Contr* **18**, 317–323.
27. Han C, Liu Y, Sun X, *et al.* (2017) Prediction of a new body shape index and body adiposity estimator for development of type 2 diabetes mellitus: the Rural Chinese Cohort Study. *Br J Nutr* **118**, 771–776.
28. Craig CL, Marshall AL, Sjöström M, *et al.* (2003) International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sport Exerc* **35**, 1381–1395.
29. The WHO Monica Project (1988) Geographical variation in the major risk factors of coronary heart disease in men and women aged 35–64 years. *World Health Stat Q* **41**, 115–140.
30. Alberti KG, Eckel RH, Grundy SM, *et al.* (2009) Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* **120**, 1640–1645.
31. Scherer PE & Hill JA (2016) Obesity, diabetes, and cardiovascular diseases: a compendium. *Circ Res* **118**, 1703–1705.
32. Alberti KG, Zimmet P, Shaw J, *et al.* (2005) The metabolic syndrome–a new worldwide definition. *Lancet* **366**, 1059–1062.
33. Hsieh SD & Muto T (2005) The superiority of waist-to-height ratio as an anthropometric index to evaluate clustering of coronary risk factors among non-obese men and women. *Prev Med* **40**, 216–220.
34. Liu L, Chen X, Liu Y, *et al.* (2019) The association between fasting plasma glucose and all-cause and cause-specific mortality by gender: the rural Chinese cohort study. *Diabetes/Metab Res Rev* **35**, e3129.
35. Lee SH, Jeong MH, Kim JH, *et al.* (2018) Influence of obesity and metabolic syndrome on clinical outcomes of ST-segment elevation myocardial infarction in men undergoing primary percutaneous coronary intervention. *J Cardiol* **72**, 328–334.
36. Zheng R, Zhou D & Zhu Y (2016) 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* **70**, 1024–1031.
37. Arnlöv J, Ingelsson E, Sundström J, *et al.* (2010) Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation* **121**, 230–236.
38. Kramer CK, Zinman B & Retnakaran R (2013) Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. *Ann Intern Med* **159**, 758–769.
39. Reis JP, Loria CM, Lewis CE, *et al.* (2013) Association between duration of overall and abdominal obesity beginning in young adulthood and coronary artery calcification in middle age. *JAMA* **310**, 280–288.
40. Bell JA, Hamer M, Sabia S, *et al.* (2015) The natural course of healthy obesity over 20 years. *J Am Coll Cardiol* **65**, 101–102.
41. Caleyachetty R, Thomas GN, Toulis KA, *et al.* (2017) Metabolically healthy obese and incident cardiovascular disease events among 3·5 million men and women. *J Am Coll Cardiol* **70**, 1429–1437.
42. Cheng FW, Gao X, Mitchell DC, *et al.* (2016) Metabolic health status and the obesity paradox in older adults. *J Nutr Gerontol Geriatr* **35**, 161–176.
43. Russ TC, Stamatakis E, Hamer M, *et al.* (2012) Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies. *BMJ* **345**, e4933.
44. Batty GD, Russ TC, Stamatakis E, *et al.* (2017) Psychological distress in relation to site specific cancer mortality: pooling of unpublished data from 16 prospective cohort studies. *BMJ* **356**, j108.

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