*British Journal of Nutrition* (2020), 123, 583–591
doi:10.1017/S0007114519003143



# Metabolically healthy general and abdominal obesity are associated with increased risk of hypertension

Yang Zhao[1,2,3†], Pei Qin[1†], Haohang Sun[4], Yu Liu[2,3], Dechen Liu[1,2], Qionggui Zhou[1,2,3], Chunmei Guo[1,5], Quanman Li[1,5], Gang Tian[1,5], Xiaoyan Wu[1,2,3], Dongsheng Hu[1,2,3,5], Xizhuo Sun[2,3] and Ming Zhang[1,2,3]*

[1]*Department of Biostatistics and Epidemiology, School of Public Health, Shenzhen University Health Science Center, Shenzhen, Guangdong, People's Republic of China*

[2]*The Affiliated Luohu Hospital of Shenzhen University Health Science Center, Shenzhen, Guangdong, People's Republic of China*

[3]*Study Team of Shenzhen's Sanming Project, The Affiliated Luohu Hospital of Shenzhen University Health Science Center, Shenzhen, Guangdong, People's Republic of China*

[4]*Cardiovascular Department, Zhengzhou Yihe Hospital, Zhengzhou, Henan, People's Republic of China*

[5]*Department of Epidemiology and Health Statistics, College of Public Health, Zhengzhou University, Zhengzhou, Henan, People's Republic of China*

*(Submitted 19 August 2019 – Final revision received 11 November 2019 – Accepted 26 November 2019 – First published online 3 December 2019)*

## Abstract

Metabolically healthy obesity refers to a subset of obese people with a normal metabolic profile. We aimed to explore the association between metabolically healthy and obesity status and risk of hypertension among Chinese adults from The Rural Chinese Cohort Study. This prospective cohort study enrolled 9137 Chinese adults without hypertension, type 2 diabetes or treatment for lipid abnormality at baseline (2007–2008) and followed up during 2013–2014. Modified Poisson regression models were used to examine the risk of hypertension by different metabolically healthy and obesity status, estimating relative risks (RR) and 95 % CI. During 6 years of follow-up, we identified 1734 new hypertension cases (721 men). After adjusting for age, sex, smoking and other confounding factors, risk of hypertension was increased with metabolically healthy general obesity (MHGO) defined by BMI (RR 1·75, 95 % CI 1·02, 3·00) and metabolically healthy abdominal obesity (MHAO) defined by waist circumference (RR 1·51, 95 % CI 1·12, 2·04) as compared with metabolically healthy non-obesity. The associations between metabolically healthy and obesity status and hypertension outcome were consistent after stratifying by sex, age, smoking, alcohol drinking and physical activity. Both MHGO and MHAO were associated with increased risk of hypertension. Obesity control programmes should be implemented to prevent or delay the development of hypertension in rural China.

**Key words: Obesity: Hypertension: Epidemiology: Metabolism**



The substantially increased prevalence of obesity has become a major public health problem worldwide[1]. The health effects of obesity have been extensively assessed in various populations, confirming an association of obesity with CVD, cancer, diabetes, chronic kidney disease and even death[2–4]. However, a subset of obese people with a normal metabolic profile, called 'metabolically healthy obesity (MHO)', were proposed not to have increased risk of CVD and its related complications[5,6]. Whether MHO is a benign condition or associated with increased risk of CVD regardless of metabolic profile is still not fully understood.

Increased blood pressure (BP) is associated with the risk of developing CVD[7]. Hypertension is an identified predictor of CVD death[8]. Understanding the association of MHO and hypertension might be helpful to explain the underlying mechanism linking MHO and CVD morbidity and mortality. A recent meta-analysis reported MHO was associated with a 1·54-fold increased risk of hypertension as compared with metabolically healthy non-obesity[9]. However, previous studies were mainly based on Asian populations and focused on metabolically healthy general obesity (MHGO), defined by BMI, but overlooked metabolically healthy abdominal obesity (MHAO),

**Abbreviations:** BP, blood pressure; MHAO, metabolically healthy abdominal obesity; MHGO, metabolically healthy general obesity; MHO, metabolically healthy obesity; RR, relative risk; WC, waist circumference.

* **Corresponding author:** Ming Zhang, fax +86 0755 86671906, email zhangming@szu.edu.cn

† These authors contributed equally to this work.

defined by waist circumference (WC), which is also closely associated with hypertension[10,11]. Studies from Iran and Switzerland showed no significant association of MHO and hypertension[12,13]. Another major issue is that studies used different MHO definitions when estimating the associated hypertension risk, so comparing existing data is difficult[9]. Thus, researchers proposed a harmonised definition of MHO, which was recommended to be used in future epidemiological studies[14].

Nearly half of Chinese adults 35–75 years old had hypertension in 2017[15]. Clarifying the association of MHO and hypertension is urgently needed to develop effective strategies for preventing hypertension in Chinese adults. Only two cohort studies have examined the MHO–hypertension association in Chinese adults. However, the Taiwan Survey focused only on general obesity, and the China Health and Nutrition Survey failed to consider several major confounding factors, including socio-economic factors, family history of hypertension, diabetes status and lipid-lowering treatment[16,17].

Therefore, to better evaluate the MHO–hypertension association, we investigated rural Chinese adults without hypertension, type 2 diabetes or lipid-lowering treatment at baseline and used the harmonised definition of MHO to test whether MHGO and MHAO were both associated with increased risk of hypertension. We further analysed the effect of sex, age, smoking, alcohol drinking and physical activity on the association of MHO and hypertension.

## Materials and methods

### Study participants

The Rural Chinese Cohort Study was initiated during 2007–2008 with the enrollment of 20 194 Chinese adults aged ≥18 years living in a rural area in the middle of China. All study participants were randomly selected by using the cluster random sampling method. Detailed descriptions regarding inclusion criteria of eligible study participants were described elsewhere[18]. The first follow-up survey was conducted from 2013 to 2014, and the response rate was 85·5 %. All study participants gave their signed informed consent, and the present study was approved by the Ethics Committee of Zhengzhou University.

For the present study, we first excluded participants with hypertension (*n* 6299), type 2 diabetes (*n* 830) and type 1 diabetes (*n* 4) and those receiving lipid-lowering medication (*n* 671) or had missing data on anthropometric (*n* 6) or laboratory measurements (*n* 36) at baseline. Participants were further excluded if they died (*n* 394) or were lost to follow-up (*n* 2817). Thus, a total of 9137 eligible study participants were included in the final analysis.

### Data collection

We performed face-to-face interviews, physical examination and blood sample collection during baseline and follow-up surveys following the same procedures. Information on demographic characteristics, lifestyles and personal and family medical history were obtained with questionnaires. Marital status was classified as married *v.* unmarried/divorced/widowed; individual income >500 *v.* ≤500 Chinese Yuan per month; education level low *v.* high (high school or higher); smoking former/current *v.* never smokers if people smoked ≥100 cigarettes during the lifetime[19]; alcohol drinking yes *v.* no if people consumed alcohol ≥12 times in the last year[19] and physical activity low, moderate and high based on the International Physical Activity Questionnaire[20]. Family history of hypertension or type 2 diabetes was considered positive if study participants reported that their parents had these diseases.

Anthropometric variables were measured with participants wearing light clothing. Weight and height were measured twice to the nearest 0·5 kg and 0·1 cm, respectively. BMI, as an index of general obesity, was calculated as the ratio of weight (kg):height squared (m$^2$). WC, as an index of abdominal obesity, was measured at the midpoint between the lowest rib and the iliac crest to the nearest 0·1 cm with participants performing gentle breathing[19]. Fasting blood samples were collected in a vacuum tube containing sodium fluoride and were further used to assess fasting plasma glucose, total cholesterol, TAG and HDL-cholesterol levels. Detailed information about the storage and measurement methods were previously described[21]. Type 2 diabetes was defined as fasting plasma glucose ≥7·0 mmol/l or participants reporting the use of insulin or oral hypoglycaemic agents or history of type 2 diabetes[22].

### Assessment of hypertension

BP and resting heart rate were measured by using an electronic brachial sphygmomanometer (HEM-770AFuzzy). Smoking; alcohol, coffee and tea consumption and excessive exercise were prohibited 30 min before measuring BP, and participants were not allowed to talk during measurement. BP was measured three times on the upper arm with participants in a seated position after at least a 5-min rest and at intervals of 30 s[23]. The mean BP and resting heart rate for each participant were used for analysis. Hypertension was defined as currently taking antihypertensive medication or systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, which agreed with the diagnostic criteria for hypertension at baseline and follow-up surveys[24].

### Definition of metabolically healthy and obesity status

Study participants were considered metabolically healthy if they met none of the following harmonised criteria: (1) TAG level ≥1·7 mmol/l; (2) HDL-cholesterol level <1·0 mmol/l in men or <1·3 mmol/l in women; (3) systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg and (4) fasting plasma glucose ≥5·6 mmol/l[14,25]. Participants were classified as underweight (BMI < 18·5 kg/m$^2$), normal weight (BMI 18·5–24 kg/m$^2$), overweight (BMI 24–28 kg/m$^2$) and general obesity (BMI ≥ 28 kg/m$^2$) based on Chinese standards[26]. Abdominal obesity was defined as WC ≥90 cm for men and WC ≥80 cm for women[25]. People classified as both metabolically healthy and obese were considered MHO. Detailed definitions of metabolically healthy and obesity status are in Fig. 1.

### Statistical analysis

We grouped study participants into four categories based on metabolically healthy and obesity status. For baseline


British Journal of Nutrition

(a) Metabolically healthy and obesity status defined by BMI

| | Non-general obesity (BMI <28 kg/m$^2$) | General obesity† (BMI ≥28 kg/m$^2$) |
|---|---|---|
| Metabolically healthy<br>Meeting none of the MetS criteria*:<br>1. SBP ≥130 mmHg or DBP ≥85 mmHg<br>2. FPG ≥5·6 mmol/l<br>3. TAG ≥1·7 mmol/l<br>4. HDL-cholesterol <1·0 mmol/l in men and HDL-cholesterol <1·3 mmol/l in women | Metabolically healthy non-general obesity (MHNGO) | Metabolically healthy general obesity (MHGO) |
| Metabolically unhealthy<br>Meeting 1 – 4 of the MetS criteria* indicated above | Metabolically unhealthy non-general obesity (MUNGO) | Metabolically unhealthy general obesity (MUGO) |

(b) Metabolically healthy and obesity status defined by WC

| | Non-abdominal obesity (WC <90 cm in men and WC <80 cm in women) | Abdominal obesity‡ (WC ≥90 cm in men and WC ≥80 cm in women) |
|---|---|---|
| Metabolically healthy<br>Meeting none of the MetS criteria*:<br>1. SBP ≥130 mmHg or DBP ≥85 mmHg<br>2. FPG ≥5·6 mmol/l<br>3. TAG ≥1·7 mmol/l<br>4. HDL-cholesterol <1·0 mmol/l in men and HDL-cholesterol <1·3 mmol/l in women | Metabolically healthy non-abdominal obesity (MHNAO) | Metabolically healthy abdominal obesity (MHAO) |
| Metabolically unhealthy<br>Meeting 1–4 of the MetS criteria* indicated above | Metabolically unhealthy non-abdominal obesity (MUNAO) | Metabolically unhealthy abdominal obesity (MUAO) |

**Fig. 1.** Definitions of metabolically healthy and obesity status. * Based on metabolic syndrome (MetS) criteria[25]. † Based on Chinese BMI criteria[26]. ‡ Based on International Diabetes Federation criteria[25]. SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; WC, waist circumference.

characteristics, the median (interquartile range) for continuous data abnormally distributed and number (frequency) for categorical data were compared among groups by Kruskal–Wallis or $\chi^2$ test, as appropriate. Because we lacked time-to-event data for hypertension outcome, a modified Poisson approach was used to estimate the relative risks (RR) and 95 % CI for incident hypertension associated with different metabolically healthy and obesity phenotypes[27]. We chose people who were metabolically healthy and non-obese as the reference group and adjusted for several potential confounders including sex, age, marital status, income, education, smoking, alcohol drinking, physical activity, family history of hypertension, family history of type 2 diabetes, resting heart rate and follow-up months in the final analyses.

To examine the potential modification effects by known associated factors, we performed a series of subgroup analyses stratified by sex (men or women), age (<60 or ≥60), smoking (never or current/former), alcohol drinking (yes or no) and physical activity (low or moderate/high). Interactions were assessed by multiplicative interaction terms in the adjusted models. Because overweight was a risk factor of hypertension and the number of people with general obesity is small, we pooled overweight and general obesity together as a sensitivity analysis to evaluate whether excess adiposity was associated with increased risk of hypertension independent of the metabolic profile. We further defined abdominal obesity based on Chinese criteria (WC ≥85 cm in men and WC ≥80 cm in women) to test the robustness of our findings[26]. All statistical analyses involved using SAS version 9.1 (SAS Institute Inc.). Statistical significance was determined with two-sided $P < 0·05$.

## Results

Among the 9137 study participants, 9·5 % people had general obesity and 35·9 % abdominal obesity. The prevalence of MHGO was 9·3 % in people with general obesity (Table 1) and that of MHAO was 12·8 % in people with abdominal obesity (online Supplementary Table S1). The prevalence of metabolically unhealthy non-general obesity was 73·8 % in people with non-general obesity and that of metabolically unhealthy non-abdominal obesity was 68·8 % in people with non-abdominal obesity. The baseline characteristics, age, sex, marital status, smoking, alcohol drinking, physical activity, family history of type 2 diabetes, resting heart rate, systolic BP, diastolic BP, BMI, WC, fasting plasma glucose and total cholesterol, TAG and HDL-cholesterol levels significantly differed according to metabolically healthy and general obesity status (all $P < 0·05$).

British Journal of Nutrition

**Table 1.** Baseline characteristics of study participants by metabolically healthy and general obesity status
(Medians and interquartile ranges (IQR); numbers and percentages)

| Baseline characteristics | Non-general obesity | | | | General obesity | | | | *P* |
|---|---|---|---|---|---|---|---|---|---|
| | Metabolically healthy | | Metabolically unhealthy | | Metabolically healthy | | Metabolically unhealthy | | |
| | Median | IQR | Median | IQR | Median | IQR | Median | IQR | |
| *n* | 2163 | | 6090 | | 82 | | 802 | | |
| Age (years) | 46 | 37, 56 | 47 | 39, 57 | 45 | 40, 52 | 45 | 39, 54 | 0·0001 |
| Men | | | | | | | | | |
| *n* | 1131 | | 2278 | | 26 | | 237 | | |
| % | 52·3 | | 37·4 | | 31·7 | | 29·6 | | <0·0001 |
| Marital status | | | | | | | | | |
| Married | | | | | | | | | |
| *n* | 1999 | | 5637 | | 75 | | 770 | | |
| % | 92·4 | | 92·6 | | 91·5 | | 96·0 | | 0·0035 |
| Individual income | | | | | | | | | |
| >500 CNY per month | | | | | | | | | |
| *n* | 155 | | 402 | | 4 | 4 | 63 | | |
| % | 7·2 | | 6·6 | | 4·9 | | 7·9 | | 0·4400 |
| Education | | | | | | | | | |
| High school or higher | | | | | | | | | |
| *n* | 252 | | 672 | | 8 | | 86 | | |
| % | 11·7 | | 11·0 | | 9·8 | | 10·7 | | 0·8165 |
| Smoking | | | | | | | | | |
| *n* | 829 | | 1628 | | 16 | | 165 | | |
| % | 38·3 | | 26·7 | | 19·5 | | 20·6 | | <0·0001 |
| Alcohol drinking | | | | | | | | | |
| *n* | 371 | | 675 | | 8 | | 115 | | |
| % | 17·2 | | 11·1 | | 9·8 | | 14·3 | | <0·0001 |
| Physical activity | | | | | | | | | |
| Low | | | | | | | | | |
| *n* | 495 | | 1550 | | 25 | | 233 | | |
| % | 22·9 | | 25·5 | | 30·5 | | 29·1 | | 0·0031 |
| Family history of hypertension | | | | | | | | | |
| *n* | 619 | | 1801 | | 23 | | 270 | | |
| % | 28·6 | | 29·6 | | 28·0 | | 33·7 | | 0·0599 |
| Family history of type 2 diabetes | | | | | | | | | |
| *n* | 107 | | 333 | | 4 | | 69 | | |
| % | 4·9 | | 5·5 | | 4·9 | | 8·6 | | 0·0013 |
| Resting heart rate (beats/min) | 72 | 66, 79 | 74 | 68, 82 | 74 | 70, 79 | 75 | 70, 82 | <0·0001 |
| SBP (mmHg) | 112·3 | 105·3, 119·3 | 116·3 | 107·7, 125·7 | 117·3 | 110·0, 123·7 | 120·0 | 111·7, 127·7 | <0·0001 |
| DBP (mmHg) | 71·0 | 66·0, 75·7 | 74·0 | 68·7, 79·3 | 77·0 (0) | 71·7, 80· | 78·3 | 73·3, 83·0 | <0·0001 |
| BMI (kg/m$^2$) | 21·8 | 20·2, 23·8 | 23·4 | 21·4, 25·2 | 29·4 | 28·6, 30·1 | 29·5 | 28·7, 30·8 | <0·0001 |
| WC (cm) | 74·9 | 70·3, 81·1 | 79·6 | 73·8, 85·4 | 93·7 | 90·5, 98·6 | 95·5 | 90·7, 100·3 | <0·0001 |
| FPG (mmol/l) | 5·1 | 4·8, 5·3 | 5·3 | 5·0, 5·7 | 5·2 | 4·9, 5·4 | 5·5 | 5·2, 5·9 | <0·0001 |
| TC (mmol/l) | 4·2 | 3·8, 4·8 | 4·2 | 3·7, 4·9 | 4·6 | 4·0, 5·0 | 4·5 | 4·0, 5·1 | <0·0001 |
| TAG (mmol/l) | 1·0 | 0·7, 1·2 | 1·4 | 1·0, 1·9 | 1·1 | 0·9, 1·3 | 1·7 | 1·3, 2·4 | <0·0001 |
| HDL-cholesterol (mmol/l) | 1·4 | 1·2, 1·5 | 1·1 | 1·0, 1·2 | 1·4 | 1·3, 1·5 | 1·1 | 0·9, 1·2 | <0·0001 |

CNY, Chinese Yuan; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; FPG, fasting plasma glucose; TC, total cholesterol.

Similar results were found when the abdominal definition was used (online Supplementary Table S1).

During 6 years of follow-up (range 57–87 months), we identified 1734 new hypertension cases (721 men). The overall cumulative incidence of hypertension was 11·5, 17·1, 20·4 and 28·6 % in metabolically healthy non-general obesity, MHGO, metabolically unhealthy non-general obesity and metabolically unhealthy general obesity groups, respectively ($P_{\text{among groups}}<$ 0·0001) (Fig. 2). This trend did not change by abdominal status. When stratifying by sex, the cumulative incidence of hypertension was always higher in men than women among all metabolically healthy and obesity phenotypes, except MHGO. After adjusting for age, sex, smoking and other confounding factors, the risk of developing hypertension was increased for people with MHGO, metabolically unhealthy non-general obesity and metabolically unhealthy general obesity, by 75, 77 and 1·77 %, respectively, as compared with metabolically healthy non-general obesity (Table 2). The RR values for hypertension for MHAO, metabolically unhealthy non-abdominal obesity and metabolically unhealthy abdominal obesity were 1·51 (95 % CI 1·12, 2·04), 1·61 (95 % CI 1·36, 1·90) and 2·70 (95 % CI 2·28, 3·20), respectively, as compared with metabolically healthy non-abdominal obesity.

Risk of hypertension was increased with both metabolically unhealthy non-general obesity and metabolically unhealthy general obesity as compared with metabolically healthy non-general

British Journal of Nutrition

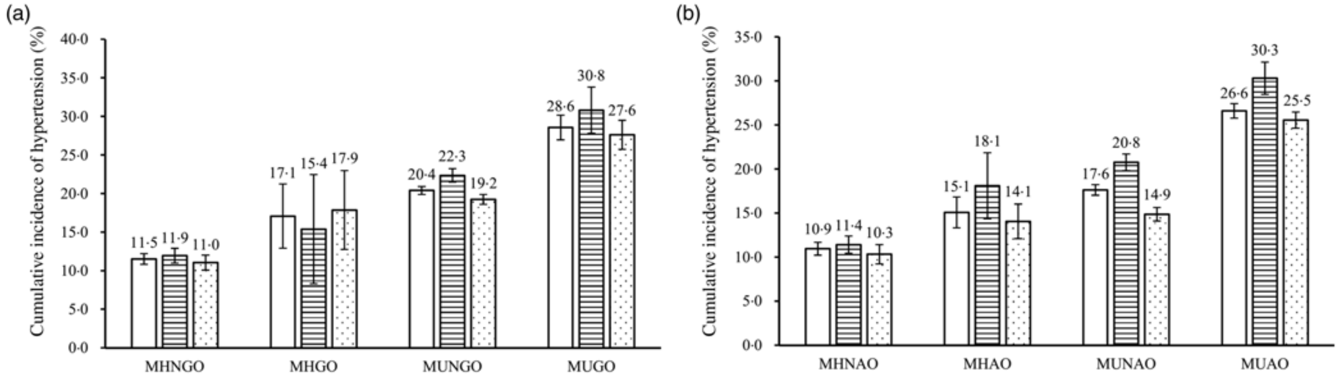


**Fig. 2.** Cumulative incidence of hypertension in different metabolically healthy and obesity status by sex. Data are incidence rates, with standard errors represented by vertical bars. (a) General obesity definition and (b) abdominal obesity definition. Comparisons among different groups were statistically significant overall ($P < 0·0001$ for both (a) and (b)) and for men ($P < 0·0001$ for both (a) and (b)) and women ($P < 0·0001$ for both (a) and (b)). MHNGO, metabolically healthy non-general obesity; MHGO, metabolically healthy general obesity; MUNGO, metabolically unhealthy non-general obesity; MUGO, metabolically unhealthy general obesity; MHNAO, metabolically healthy non-abdominal obesity; MHAO, metabolically healthy abdominal obesity; MUNAO, metabolically unhealthy non-abdominal obesity; MUAO, metabolically unhealthy abdominal obesity. □, Overall; ▤, men; ▨, women.

obesity in all subgroup analyses stratified by sex, age, smoking, alcohol drinking and physical activity status (Table 3). We observed similar results on subgroup analyses for the MHAO phenotype (Table 4). We did not find a significant interaction between potential factors and metabolically healthy and obesity status.

Similar results were found in the sensitivity analyses when pooling overweight and general obesity together or using Chinese abdominal obesity criteria. The prevalence of metabolically healthy overweight/general obesity was 14·5 % in people with overweight/general obesity (online Supplementary Table S2), and 13·7 % of abdominal obese people had the MHAO phenotype according to Chinese criteria. Risk of hypertension was associated with both metabolically healthy overweight/general obesity and MHAO. Detailed results of subgroup analyses are in online Supplementary Tables S3 and S4. We found no significant interaction between potential factors and metabolically healthy and obesity status in the sensitivity analyses.

## Discussion

In this large 6-year follow-up prospective cohort study, we first used the simple and harmonised definition of MHO and found MHO, as measured by BMI or WC, associated with increased risk of hypertension in Chinese adults. Similarly, risk of hypertension was high for metabolically unhealthy people regardless of obesity status. The associations between metabolically healthy and obesity status and hypertension outcome were consistent after stratifying by factors including sex, age, smoking, alcohol drinking and physical activity. Our results indicate that MHO might not be a benign condition and emphasise the importance of maintaining a healthy weight and waist size in terms of hypertension prevention.

Metabolically healthy definitions including the Adult Treatment Panel III[28,29], International Diabetes Federation[11,16], Wildman[10] and Karelis[10] definitions are inconsistent and controversial and are generally applied to identify metabolically unhealthy status with more than two or three criteria. These definitions

**Table 2.** Adjusted risks of incident hypertension in different metabolically healthy and obesity status groups
(Relative risks (RR) and 95 % confidence intervals)

| | | | Model 1* | | | Model 2† | | |
|---|---|---|---|---|---|---|---|---|
| Metabolically healthy and obesity status | Total | Hypertension cases | RR | 95 % CI | *P* | RR | 95 % CI | *P* |
| General obesity defined by BMI | | | | | | | | |
| Metabolically healthy non-general obesity | 2163 | 249 | 1·00 | | – | 1·00 | | – |
| Metabolically healthy general obesity | 82 | 14 | 1·59 | 0·98, 2·59 | 0·0625 | 1·75 | 1·02, 3·00 | 0·0425 |
| Metabolically unhealthy non-general obesity | 6090 | 1242 | 1·72 | 1·52, 1·95 | <0·0001 | 1·77 | 1·53, 2·05 | <0·0001 |
| Metabolically unhealthy general obesity | 802 | 229 | 2·59 | 2·21, 3·05 | <0·0001 | 2·77 | 2·31, 3·32 | <0·0001 |
| Abdominal obesity defined by WC | | | | | | | | |
| Metabolically healthy non-abdominal obesity | 1827 | 200 | 1·00 | | – | 1·00 | | – |
| Metabolically healthy abdominal obesity | 418 | 63 | 1·46 | 1·13, 1·90 | 0·0044 | 1·51 | 1·12, 2·04 | 0·0070 |
| Metabolically unhealthy non-abdominal obesity | 4034 | 711 | 1·59 | 1·37, 1·84 | <0·0001 | 1·61 | 1·36, 1·90 | <0·0001 |
| Metabolically unhealthy abdominal obesity | 2858 | 760 | 2·52 | 2·17, 2·92 | <0·0001 | 2·70 | 2·28, 3·20 | <0·0001 |

WC, waist circumference.
* Model 1 was adjusted for age and sex.
† Model 2 was adjusted for the variables in model 1, plus marital status, income, education, smoking, alcohol drinking, physical activity, family history of hypertension, family history of type 2 diabetes, resting heart rate and follow-up months.



British Journal of Nutrition

**Table 3.** Association of metabolically healthy and general obesity status and incident hypertension stratified by potential risk factors (Relative risks (RR) and 95 % confidence intervals)

| Potential risk factors | Metabolically healthy non-general obesity | Metabolically healthy general obesity | | Metabolically unhealthy non-general obesity | | Metabolically unhealthy general obesity | | $P_{interaction}$ |
|---|---|---|---|---|---|---|---|---|
| | | RR* | 95 % CI | RR* | 95 % CI | RR* | 95 % CI | |
| Sex | | | | | | | | |
| Men | 1·00 | 1·69 | 0·67, 4·26 | 1·82 | 1·49, 2·22 | 2·86 | 2·17, 3·77 | 0·7153 |
| Women | 1·00 | 1·70 | 0·87, 3·32 | 1·66 | 1·34, 2·06 | 2·57 | 2·00, 3·29 | |
| Age (years) | | | | | | | | |
| <60 | 1·00 | 1·84 | 1·01, 3·35 | 1·78 | 1·50, 2·12 | 2·97 | 2·42, 3·65 | 0·0868 |
| ≥60 | 1·00 | 1·23 | 0·35, 4·31 | 1·68 | 1·27, 2·21 | 2·00 | 1·34, 2·98 | |
| Smoking | | | | | | | | |
| Never | 1·00 | 1·74 | 0·96, 3·14 | 1·72 | 1·43, 2·07 | 2·63 | 2·12, 3·28 | 0·7275 |
| Current/former | 1·00 | 1·52 | 0·42, 5·47 | 1·85 | 1·46, 2·36 | 2·94 | 2·10, 4·12 | |
| Alcohol drinking | | | | | | | | |
| No | 1·00 | 1·94 | 1·13, 3·34 | 1·78 | 1·52, 2·09 | 2·67 | 2·18, 3·26 | 0·3534 |
| Yes | 1·00 | NA | | 1·67 | 1·17, 2·40 | 3·30 | 2·17, 5·02 | |
| Physical activity | | | | | | | | |
| Low | 1·00 | 4·01 | 1·65, 9·75 | 2·28 | 1·61, 3·23 | 3·62 | 2·42, 5·41 | 0·2555 |
| Moderate/high | 1·00 | 1·24 | 0·62, 2·49 | 1·66 | 1·41, 1·95 | 2·59 | 2·10, 3·18 | |

NA, not analysed.
* RR was adjusted for age, sex, marital status, income, education, smoking, alcohol drinking, physical activity, family history of hypertension, family history of type 2 diabetes, resting heart rate and follow-up months.

**Table 4.** Association of metabolically healthy and abdominal obesity status and incident hypertension stratified by potential risk factors (Relative risks (RR) and 95 % confidence intervals)

| Potential risk factors | Metabolically healthy non-abdominal obesity | Metabolically healthy abdominal obesity | | Metabolically unhealthy non-abdominal obesity | | Metabolically unhealthy abdominal obesity | | $P_{interaction}$ |
|---|---|---|---|---|---|---|---|---|
| | | RR* | 95 % CI | RR* | 95 % CI | RR* | 95 % CI | |
| Sex | | | | | | | | |
| Men | 1·00 | 1·44 | 0·85, 2·42 | 1·71 | 1·38, 2·11 | 2·77 | 2·20, 3·49 | 0·9301 |
| Women | 1·00 | 1·43 | 0·97, 2·11 | 1·44 | 1·09, 1·88 | 2·41 | 1·85, 3·13 | |
| Age (years) | | | | | | | | |
| <60 | 1·00 | 1·57 | 1·11, 2·21 | 1·57 | 1·28, 1·91 | 2·88 | 2·36, 3·51 | 0·0710 |
| ≥60 | 1·00 | 1·24 | 0·67, 2·29 | 1·65 | 1·21, 2·25 | 2·03 | 1·45, 2·84 | |
| Smoking | | | | | | | | |
| Never | 1·00 | 1·30 | 0·91, 1·86 | 1·46 | 1·18, 1·82 | 2·45 | 1·98, 3·03 | 0·8733 |
| Current/former | 1·00 | 2·18 | 1·25, 3·76 | 1·86 | 1·43, 2·42 | 2·88 | 2·17, 3·82 | |
| Alcohol drinking | | | | | | | | |
| No | 1·00 | 1·57 | 1·14, 2·16 | 1·63 | 1·36, 1·97 | 2·65 | 2·20, 3·20 | 0·3694 |
| Yes | 1·00 | 1·07 | 0·44, 2·62 | 1·42 | 0·94, 2·13 | 2·85 | 1·92, 4·24 | |
| Physical activity | | | | | | | | |
| Low | 1·00 | 2·11 | 1·09, 4·09 | 2·01 | 1·33, 3·05 | 3·75 | 2·47, 5·69 | 0·1632 |
| Moderate/high | 1·00 | 1·37 | 0·98, 1·92 | 1·53 | 1·27, 1·83 | 2·46 | 2·04, 2·97 | |

* RR was adjusted for age, sex, marital status, income, education, smoking, alcohol drinking, physical activity, family history of hypertension, family history of type 2 diabetes, resting heart rate and follow-up months.

were criticised for considering people with one or two metabolically unhealthy criteria as metabolically healthy. Recently, a harmonised definition of MHO, taking advantage of previous consensus efforts by major international organisations and large collaborative projects, aimed to provide a logical and reasonable standardised definition for clinical and public health settings[14]. The definition is useful and feasible for routine health check-ups because the markers are relatively simple, inexpensive and quickly measured. This definition is more reasonable because people with no abnormal metabolic criteria would be considered metabolically healthy. The prevalence of MHO ranges from 1·1 to 28·5 % in different populations[30]. The prevalence of MHO we reported in our rural Chinese adults was obviously lower than that in previous studies because of the strictness of the metabolically healthy definition[16,31]. By contrast, the proportions of metabolically unhealthy individuals with or without obesity were relatively higher, which indicates the need for making interventional strategies to ensure that people are metabolically healthy in rural China.

A meta-analysis of eight Asian prospective cohort studies reported a significant positive association of MHO and risk of hypertension (pooled effect size: 1·54, 95 % CI 1·48, 1·55)[9].



https://doi.org/10.1017/S0007114519003143 Published online by Cambridge University Press

Except for the Iran study, results from Chinese, Korean and Japanese studies were consistent. However, the sample size of the Iran study was small (*n* 591) and the study might not have enough statistical power to test the significant difference[12]. The Taiwan study reported each 1 kg/m$^2$ gain of BMI associated with an 18 % increase in risk of hypertension in 1547 men and women (age range 18–59 years) who were free of the metabolic syndrome components except for WC criteria[17]. However, the study did not provide detailed results specifically for MHO people. The China Health and Nutrition Survey study considered overweight and general obesity as obesity and reported the prevalence of metabolically healthy as 70·1 % in adults (age range 18–65 years) with overweight/obesity[16]. It also found risk of hypertension increased with metabolically healthy overweight/obesity (1·78-fold increase, 95 % CI 1·39, 2·27), which agrees with our findings. However, it failed to control for important confounding factors of hypertension (e.g. family history of hypertension), which may have biased the results. People with diabetes and dyslipidaemia are known to be at high risk of hypertension, and treatment of these diseases might influence the occurrence of hypertension[32,33]. Therefore, our study excluded people with diabetes or receiving lipid-lowering treatment at baseline and still demonstrated MHO as harmful for hypertension in a Chinese rural population, which may provide further evidence that MHO might increase the risk of CVD.

Although the mechanisms to explain the MHO and hypertension association were not clear, previous epidemiological studies proposed excess body weight as associated with adipose tissue dysfunction[34], subtle changes in left-ventricular structure and function[35], activation of the renin–angiotensin–aldosterone and sympathetic nervous systems[36], chronic vascular inflammation[37] and oxidative stress[38], which further lead to hypertension.

In 2017, the prevalence of hypertension was higher in rural than urban China, but the awareness, treatment and control rates were lower than that in urban China[15]. It is important to identify the risk factors of hypertension and develop prevention strategies focused on the rural Chinese population. Our study first reported MHO as associated with the risk of hypertension in a rural Chinese population. Thus, maintaining healthy weight and WC via lifestyle modifications (e.g. healthy diet or exercise) might be a cost-effective way to prevent hypertension in people with MHO. Moreover, we found a large proportion of metabolically unhealthy people among non-obese people. This phenotype was also associated with increased risk of developing hypertension, which was consistent with previous findings[10,16]. This result indicates that screening for hypertension should also be implemented among non-obese people who may be potentially at high risk of hypertension but who are easily ignored. Subgroup and sensitivity analyses confirmed the consistent results in people with different characteristics (age, sex, smoking, alcohol drinking or physical activity), which indicates that MHO is not a benign condition and obese people should not be considered 'healthy'.

Our study is the first to use the harmonised definition of MHO and demonstrate a positive association of obesity with risk of hypertension in a rural Chinese adult population. The large sample size of this cohort study allowed us to restrict study participants to people without diabetes or taking lipid medication at baseline to minimise the potential bias. Furthermore, we adjusted for confounding factors including social economic and behavioural factors and family history of diseases in the statistical models to test whether MHO was independently associated with the risk of hypertension. We also conducted subgroup analyses and sensitivity analyses to test the potential interactions with known risk factors and robustness of present findings. Our study still had several limitations. First, we focused on a rural Chinese population, and further studies of other ethnicities are needed. Second, obesity was defined by BMI or WC, which might not be good indexes of excess adiposity as compared with percentage body fat. Because assessing percentage body fat is time-consuming and expensive and our results indicate that both BMI and WC were able to identify people at high risk of hypertension, interventions and treatments aiming to maintain healthy BMI and WC are targeted from a clinical and public health viewpoint because they are simple and measurable estimates. Third, our study lacked time-to-event data, which precluded survival analysis.

In conclusion, general and abdominal obesity are risk factors for hypertension, regardless of metabolically healthy status. Therefore, with the huge burden of hypertension in China, obesity control programmes should be implemented to prevent or delay the development of hypertension.

### What is already known about this subject?

Metabolically healthy obesity (MHO) refers to a subset of obese people with a normal metabolic profile. However, the definitions of MHO were not consistent in previous studies. Whether MHO is a benign condition or associated with increased risk of CVD regardless of metabolic profile is still not fully understood. Hypertension is a major predictor of CVD, so understanding the association of MHO and hypertension might be helpful to explain the underlying mechanism linking MHO and CVD morbidity and mortality.

### What does our study add?

Our study used the proposed harmonised definition of the MHO phenotype and found both metabolically healthy general and abdominal obesity were positively associated with the risk of hypertension. The associations between metabolically healthy and obesity status and hypertension outcome were consistent after stratifying by sex, age, smoking, alcohol drinking and physical activity.

### How might this impact on clinical practice?

With the huge burden of hypertension in China, long-term obesity control programmes should be implemented to prevent or delay the development of hypertension. Screening for hypertension should also be stressed and implemented among metabolically unhealthy non-obese people who are potentially at high risk of hypertension but who are easily ignored.

## Acknowledgements

The authors thank all of the participants, coordinators and administrators for their support and help during the research.

This work was supported by the National Natural Science Foundation of China (grant nos. 81373074, 81402752 and 81673260); the Natural Science Foundation of Guangdong Province (grant no. 2017A030313452); the Medical Research Foundation of Guangdong Province (grant no. A2017181) and the Science and Technology Development Foundation of Shenzhen (grant nos. JCYJ20140418091413562, JCYJ20160307155707264, JCYJ20170302143855721 and JCYJ20170412110537191).

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

There are no conflicts of interest.

## Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114519003143

## References

1. NCD Risk Factor Collaboration (NCD-RisC) (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. Emerging Risk Factors Collaboration, Wormser D, Kaptoge S, *et al.* (2011) Separate and combined associations of body mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet* **377**, 1085–1095.
3. Renehan AG, Tyson M, Egger M, *et al.* (2008) Body mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* **371**, 569–578.
4. Flegal KM, Kit BK, Orpana H, *et al.* (2013) Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* **309**, 71–82.
5. Stefan N, Haring HU, Hu FB, *et al.* (2013) Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. *Lancet Diabetes Endocrinol* **1**, 152–162.
6. Hamer M & Stamatakis E (2012) Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. *J Clin Endocrinol Metab* **97**, 2482–2488.
7. Tzoulaki I, Elliott P, Kontis V, *et al.* (2016) Worldwide exposures to cardiovascular risk factors and associated health effects: current knowledge and data gaps. *Circulation* **133**, 2314–2333.
8. Yamagishi K, Sawachi S, Tamakoshi A, *et al.* (2019) Blood pressure levels and risk of cardiovascular disease mortality among Japanese men and women: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study). J Hypertens 37, 1366–1371.
9. Mirzababaei A, Mozaffari H, Shab-Bidar S, *et al.* (2019) Risk of hypertension among different metabolic phenotypes: a systematic review and meta-analysis of prospective cohort studies. *J Hum Hypertens* **33**, 365–377.
10. Kang YM, Jung CH, Jang JE, *et al.* (2016) The association of incident hypertension with metabolic health and obesity status: definition of metabolic health does not matter. *Clin Endocrinol* **85**, 207–215.
11. Kuwabara M, Kuwabara R, Hisatome I, *et al.* (2017) "Metabolically healthy" obesity and hyperuricemia increase risk for hypertension and diabetes: 5-year Japanese cohort study. *Obesity* **25**, 1997–2008.
12. Latifi SM, Karandish M, Shahbazian H, *et al.* (2017) Prevalence of metabolically healthy obesity (MHO) and its relation with incidence of metabolic syndrome, hypertension and type 2 diabetes amongst individuals aged over 20 years in Ahvaz: a 5 year cohort study (2009-2014). *Diabetes Metab Syndr* **11**, Suppl. 2, S1037–S1040.
13. Fingeret M, Marques-Vidal P & Vollenweider P (2018) Incidence of type 2 diabetes, hypertension, and dyslipidemia in metabolically healthy obese and non-obese. *Nutr Metab Cardiovasc Dis* **28**, 1036–1044.
14. Scherer PE & Hill JA (2016) Obesity, diabetes, and cardiovascular diseases: a compendium. *Circ Res* **118**, 1703–1705.
15. Lu J, Lu Y, Wang X, *et al.* (2017) Prevalence, awareness, treatment, and control of hypertension in China: data from 1.7 million adults in a population-based screening study (China PEACE Million Persons Project). *Lancet* **390**, 2549–2558.
16. Cao ZK, Huang Y, Yu HJ, *et al.* (2017) Association between obesity phenotypes and incident hypertension among Chinese adults: a prospective cohort study. *Public Health* **149**, 65–70.
17. Hwang LC, Bai CH, Sun CA, *et al.* (2012) Prevalence of metabolically healthy obesity and its impacts on incidences of hypertension, diabetes and the metabolic syndrome in Taiwan. *Asia Pac J Clin Nutr* **21**, 227–233.
18. 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.
19. Zhao Y, Zhang M, Luo X, *et al.* (2017) Association of 6-year waist circumference gain and incident hypertension. *Heart* **103**, 1347–1352.
20. Craig CL, Marshall AL, Sjostrom M, *et al.* (2003) International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* **35**, 1381–1395.
21. Zhao Y, Sun H, Wang B, *et al.* (2017) Impaired fasting glucose predicts the development of hypertension over 6 years in female adults: results from the rural Chinese cohort study. *J Diabetes Complications* **31**, 1090–1095.
22. Weng J, Ji L, Jia W, *et al.* (2016) Standards of care for type 2 diabetes in China. *Diabetes Metab Res Rev* **32**, 442–458.
23. Perloff D, Grim C, Flack J, *et al.* (1993) Human blood pressure determination by sphygmomanometry. *Circulation* **88**, 2460–2470.
24. Chobanian AV, Bakris GL, Black HR, *et al.* (2003) Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* **42**, 1206–1252.
25. Alberti KG, Zimmet P, Shaw J, *et al.* (2005) The metabolic syndrome – a new worldwide definition. *Lancet* **366**, 1059–1062.
26. Zhou BF & Cooperative Meta-Analysis Group of the Working Group on Obesity in China (2002) Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults – study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Biomed Environ Sci* **15**, 83–96.
27. Spiegelman D & Hertzmark E (2005) Easy SAS calculations for risk or prevalence ratios and differences. *Am J Epidemiol* **162**, 199–200.
28. Lee SK, Kim SH, Cho GY, *et al.* (2013) Obesity phenotype and incident hypertension: a prospective community-based cohort study. *J Hypertens* **31**, 145–151.

29. Jae SY, Babu AS, Yoon ES, *et al.* (2017) Impact of cardiorespiratory fitness and risk of systemic hypertension in nonobese versus obese men who are metabolically healthy or unhealthy. *Am J Cardiol* **120**, 765–768.
30. Phillips CM (2013) Metabolically healthy obesity: definitions, determinants and clinical implications. *Rev Endocr Metab Disord* **14**, 219–227.
31. Liu C, Wang C, Guan S, *et al.* (2019) The prevalence of metabolically healthy and unhealthy obesity according to different criteria. *Obes Facts* **12**, 78–90.
32. Levin G, Kestenbaum B, Ida Chen YD, *et al.* (2010) Glucose, insulin, and incident hypertension in the multi-ethnic study of atherosclerosis. *Am J Epidemiol* **172**, 1144–1154.
33. Song J, Nie SM, Chen X, *et al.* (2017) Association and interaction between triglyceride-glucose index and obesity on risk of hypertension in middle-aged and elderly adults. *Clin Exp Hypertens* **39**, 732–739.
34. Hajer GR, van Haeften TW & Visseren FL (2008) Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. *Eur Heart J* **29**, 2959–2971.
35. Park J, Kim SH, Cho GY, *et al.* (2011) Obesity phenotype and cardiovascular changes. *J Hypertens* **29**, 1765–1772.
36. Hall JE, do Carmo JM, da Silva AA, *et al.* (2015) Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. *Circ Res* **116**, 991–1006.
37. Mathieu P, Poirier P, Pibarot P, *et al.* (2009) Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease. *Hypertension* **53**, 577–584.
38. Lopes HF, Martin KL, Nashar K, *et al.* (2003) DASH diet lowers blood pressure and lipid-induced oxidative stress in obesity. *Hypertension* **41**, 422–430.

British Journal of Nutrition