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The effect of metabolic health and obesity phenotypes on risk of hypertension

A nationwide population-based study using 5 representative definitions of metabolic health

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Abstract

Although obesity is clearly identified as a risk factor for hypertension, the association between its different metabolic phenotypes and hypertension remains unclear. We aimed to investigate this association and compare the degree of association between metabolic health and obesity phenotypes defined by 5 representative criteria and hypertension risk.

This study used data from the China Health and Nutrition Survey 2009 wave, and the final analysis included 7632 subjects aged 18 to 85 years with available fasting blood samples and anthropometric measurements. Body mass index was used to define nonobese and obese status in subjects (cut-off value, 25 kg/m^2), and metabolic health state was respectively defined by 5 published criteria: the Adult Treatment Panel (ATP)-III, the Wildman, the Karelis, the homeostasis model assessment (HOMA), and the fasting blood glucose × triglyceride (TyG) criteria. Subjects were categorized into 4 phenotypes according to their metabolic health and obesity status: metabolically healthy nonobese (MHNO), metabolically unhealthy nonobese (MUNO), metabolically healthy obese (MHO), and metabolically unhealthy obese (MUO).

A total of 2171 subjects (28.4% of the study population) had hypertension, and hypertension prevalence was significantly increased as weight increased for both metabolically healthy and metabolically unhealthy subjects. Within the MHO phenotypes, the prevalence ranged from 22.7% to 38.6% according to the Wildman and HOMA criteria, respectively. Compared to the MHNO phenotype, the MHO phenotype had an increased risk of hypertension, and the adjusted odds ratios for hypertension in MHO subjects were 1.94 (95% confidence interval 1.60–2.35) using the ATP-III criteria, 1.98 (1.61–2.43) using the Wildman criteria, 2.37 (1.88–2.99) using the Karelis criteria, 2.26 (1.96–2.61) using the HOMA criteria, and 2.54 (2.14–3.00) using the TyG criteria, respectively. A similar significant pattern was found in the MUO and MUNO phenotypes for risk of hypertension. Furthermore, the MUO phenotype consistently revealed the strongest degree of association with hypertension, following by the MHO and the MUNO phenotype.

Both metabolically unhealthy status and obese status contributed to a higher risk of hypertension in Chinese adults. The MHO phenotype was not a benign condition and had substantial risk of hypertension compared to the MHNO phenotype. Thus, metabolic health status and obesity should be monitored together when managing hypertension risk.

Abbreviations: ATP-III = Adult Treatment Panel-III, BMI = body mass index, CHNS = China Health and Nutrition Survey, CI = confidence interval, CVD = cardiovascular disease, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HDL-C = high-density lipoprotein-cholesterol, HOMA = homeostasis model assessment, hsCRP = high-sensitivity C-reactive protein, MHNO = metabolically healthy nonobese, MHO = metabolically healthy obese, MUNO = metabolically unhealthy nonobese, MUNW = metabolically unhealthy normal weight, MUO = metabolically unhealthy obese, OR = odds ratio, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride, WC = waist circumference, WHtR = waist-to-height ratio.

Keywords: hypertension, metabolic health, obesity phenotype, the China Health and Nutrition Survey

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1. Introduction

Hypertension is a well-recognized major risk factor for cardiovascular diseases (CVDs) and premature mortality. It contributes to approximately 50% of incidents of stroke and ischemic heart disease, and approximately 7.6 million deaths, particularly in low-income and middle-income regions.[1,2] Obesity has become increasingly prevalent and is an epidemic with significant impact on public health, with up to 2.1 billion adults worldwide being reported overweight and obese in 2013.[3] Nowadays, obesity is believed to be closely associated with a great number of CVDs and metabolic disorders,[4] and has been reported to increases the risk of coronary artery disease, all-cause, and CVD mortality.[5] Recent research has introduced a novel obesity phenotype termed "metabolically healthy obese (MHO)," characterized by favorable cardiometabolic profiles whilst being categorized as obese. The studies showed MHO as a benign condition, not associated with an increased risk of CVD morbidity and mortality compared to normal-weight individuals.[6] Although obesity is a well-established risk factor for hypertension, the association between its different metabolic phenotypes and the risk of hypertension remains controversial. Some studies revealed a protective effect of MHO or metabolically unhealthy normal weight (MUNW) against hypertension,[7] whereas others concluded that MHO and MUNW phenotypes were associated with an increased risk of hypertension development.[8] As far as we know, no large-scale studies have investigated the strength of association of various metabolic health and obesity phenotypes with hypertension in a population-level study of Chinese adults. This study aims to fill this gap in knowledge and compare the degree of association between metabolic health and obesity phenotypes with hypertension risk using 5 established criteria for metabolic status definition in the literature.

2. Methods

2.1. Study population

This study used data from the 2009 wave of the China Health and Nutrition Survey (CHNS) for analysis. The CHNS is a large-scale, longitudinal, household-based survey designed to represent large provinces by a range of socioeconomic variables and to examine the effects of health and nutrition. A comprehensive description and the sampling procedures of the survey have been published elsewhere.[9] In brief, starting in 1989 this survey used a multistage, random cluster process to select households from 9 of the 31 mainland provinces; the original and new household members have been longitudinally assessed. Fasting blood samples from participants aged ≥7 years were collected for the first time in 2009. Survey protocols, instruments, and the process for obtaining informed consent for this study were approved by the institutional review committees of the University of North Carolina at Chapel Hill, the National Institute of Nutrition and Food Safety, the Chinese Center for Disease Control and Prevention, and the China-Japan Friendship Hospital, Ministry of Health. Among the 11,929 participants in the 2009 wave of the CHNS, 3501 men and 4131 women aged 18 to 85 years with available anthropometric measurements and fasting blood sample information were included in this study (Fig. 1).

2.2. Anthropometric and biochemical measurements

Anthropometry was measured following standardized procedures by well-trained examiners. Body weight and height were taken with participants bare footed and in light clothing, measured to the nearest 0.1 kg and 0.1 cm, respectively. Waist circumference (WC) was measured to the nearest 0.1 cm with an inelastic tape at the midpoint between the bottom of the rib cage and the top of the iliac crest at the end of an exhalation. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (meters). Systolic and diastolic blood pressures (SBP/DBP) were measured on the right arm, using mercury sphygmomanometers. Measures were collected in triplicate after a 10-minute seated rest and the mean of the 3 measurements used in the analyses.

A fasting blood sample was collected for each participant using a standardized process, then analyzed in a national central clinical laboratory in Beijing. Serum levels of fasting plasma glucose (FPG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C) concentrations, triglyceride (TG), and uric acid were measured using a biochemical autoanalyzer. Insulin resistance was estimated by the homeostasis model assessment (HOMA-IR) formula: HOMA-IR = fasting insulin ($mL \cdot U \cdot L^{-1}$) × FPG (mmol/L)/22.5. The fasting blood glucose × triglyceride (TyG) index was calculated as ln[TG (mg/dL) × FPG (mg/dL)/2]. Details of the laboratory analyses are reported in the "CHNS, Manual for Specimen Collection and Processing." Hypertension was defined as an SBP of ≥140 mm Hg, or a DBP of ≥90 mm Hg, or being previously diagnosed as hypertension by a physician or taking antihypertensive drugs currently.

2.3. Definitions of metabolic health and obesity phenotypes

In the present study, BMI was used to define nonobese and obese status in subjects (nonobese <25 kg/m^2 and obese ≥25 kg/m^2). We adopted 5 published criteria to define the metabolically unhealthy status: the Adult Treatment Panel-III (ATP-III) definition of metabolic syndrome of having >2 metabolic abnormalities (WC ≥90/80 cm for men/women, systolic/diastolic BP ≥130/85 mm Hg or use of antihypertensive drugs, TG ≥1.7 mmol/L or use of lipid-lowering drugs, fasting glucose ≥5.6 mmol/L or use of medications for diabetes, or HDL-C ≥1.0/1.3 mmol/L for men/women)[10]; the Wildman criterion of having >2 metabolic abnormalities [systolic/diastolic BP ≥130/85 mm Hg or use of antihypertensive drugs, TG ≥1.7 mmol/L or use of lipid-lowering drugs, fasting glucose ≥5.6 mmol/L or use of medications for diabetes, HOMA-IR >90th percentile, high-sensitivity C-reactive protein (hsCRP) >90th percentile, or HDL-C ≥1.0/1.3 mmol/L for men/women][11]; the Karelis criterion of having >2 metabolic factors (HOMA-IR ≥2.7, TG ≥1.7 mmol/L or use of lipid-lowering drugs, HDL-C ≥1.0/1.3 mmol/L for men/women, LDL-C ≥2.6 mmol/L, or hsCRP ≥3.0 mg/L)[12]; the HOMA index[5] of having HOMA-IR in the upper quartile of the HOMA index; and the TyG index of having TyG >8.82/8.73 for men/women.[13]According to these criteria for obesity and metabolic health, study subjects were categorized into one of the following 4 phenotypes: metabolically healthy nonobese (MHNO); metabolically unhealthy nonobese (MUNO); MHO; and metabolically unhealthy obese (MUO).

2.4. Statistical analyses

The characteristics of the study population were presented as the median (interquartile range) for continuous variables or as percentages for categorical variables. Differences in the characteristics of the 4 metabolically obesity phenotypes were evaluated using a 1-way analysis of variance test or Pearson chi-squared test, as

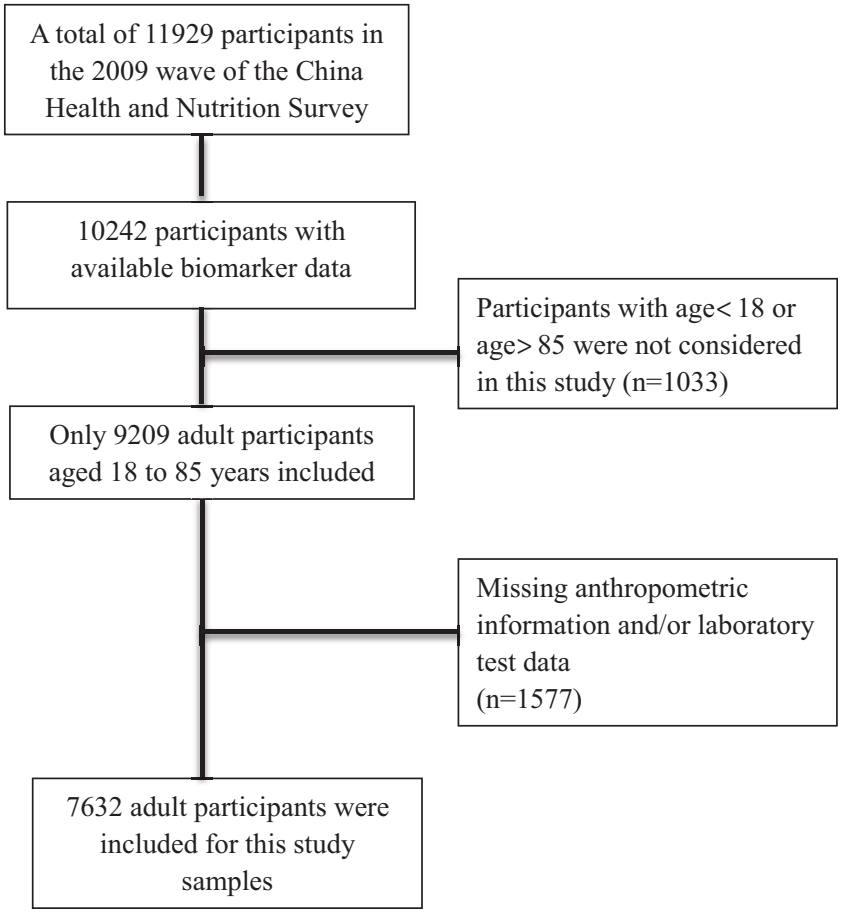

Figure 1. Flow chart of the participant selection process. A total of 11,929 individuals were recruited from the 2009 wave of the China Health and Nutrition Survey (CHNS). Of the 10,242 individuals participating laboratory test, 9209 adults aged ≥18 and ≤85 years, 1577 adults had missing data on laboratory test and/or anthropometric information, and as result were excluded. The final sample size was 7632 adults, which consisted of 3501 men and 4131 women.

appropriate. A multiple logistic regression model was used to calculate the adjusted odds ratios (ORs) for hypertension according to the metabolic health and obesity state; the model was adjusted for age, sex, smoking, alcohol status, diabetes, LDL-C, uric acid, and hsCRP. The MHNO phenotype was used as a reference and the results of the analyses presented as ORs with 95% confidence intervals (CIs). A sensitivity analysis was performed using WC and waist-to-height ratio (WHtR) as marker of (central) obesity, and obese status was defined by WC ≥90 cm in men and ≥85 cm in women or WHtR ≥0.5 for Chinese adult population.[14] All statistical analyses involved were conducted using R version 3.2.2 software (R Foundation for Statistical Computing, Vienna, Austria) with a P value $<.05$ considered as statistically significant.

3. Results

3.1. Characteristics of the sample population

The characteristics of the study population, according to the ATP-III criteria-based metabolic obesity phenotypes, are presented in Table 1. Of the 7632 subjects, 3775 (49.5%), 1678 (22%), 889 (11.6%), and 1290 (16.9%) subjects were classified into the MHNO, MUNO MHO, and MUO group, respectively. Compared with the MHNO phenotype, MHO subjects were more likely to be women, older, nonsmokers, and nondrinkers, but also to exhibit a less favorable risk profile, such as elevated BP, FPG, TC, and LDL-C levels. Another set of biomarkers, including TGs, BP, FPG, uric acid, and HOMA-IR, were lower in MHO than in MUO subjects (Table 1).

The prevalence of hypertension was significantly increased as weight increased for both metabolically healthy and metabolically unhealthy subjects. The highest prevalence of hypertension was consistently found in MUO phenotypes regardless of definitions, ranging from 43.8% to 54.7% according to the Karelis and ATP-III criteria, respectively. The MHO phenotype revealed a higher prevalence of hypertension than MUNO under the Karelis, HOMA-IR, and TyG criteria, with more than one-third of MHO subjects suffering from hypertension (Table 2). A sensitivity analysis, using WC and WHtR as obesity marker, showed highly consistent results, with the prevalence in MUO group ranging from 41.4% to 45.5% according to different metabolic health criteria (Supplementary Table 1, http://links.lww.com/MD/C495). Furthermore, when using WC as obesity marker, the hypertension prevalence was very similar across the 3 different metabolic health criteria.

3.2. Associations between hypertension and metabolic health-obesity phenotypes (according to 2 different criteria)

Table 2 summarizes the ORs of having hypertension according to metabolic obesity phenotypes defined by the 5 criteria. MHO subjects were nearly 2-fold more likely to have hypertension than

Table 1

Characteristics of the study subjects according to obesity status and metabolic health defined by Adult Treatment Panel-III criteria.

	Nonobese		Obese	
	Metabolically healthy (MHNO) (n = 3775)	Metabolically unhealthy (MUNO) (n = 1678)	Metabolically healthy (MHO) (n = 889)	Metabolically unhealthy (MUO) (n = 1290)
Age, y	46.5 (36.3–58.5)	55 (44.7–64.8)	49 (40.2–58.2)	53.7 (44.4–62.3)
Sex (female, %)	57.3	45.9	64.6	48.4
Smoker, %	29.3	38	20.1	31.9
Alcohol drinker, %	31.1	34.5	28.1	36.3
Urban resident, %	69.2*	67.6*	68.8*	66.4*
BMI, kg/m^2	21.4 (19.8–22.9)	22.6 (21.1–23.8)	26.5 (25.7–27.8)	27.3 (26–29)
WC, cm	77 (71–82.4)	81.8 (76–87)	89.8 (84.5–94.9)	93 (88–98.5)
HDL-C, mmol/L	1.5 (1.4–1.8)	1.2 (1.1–1.4)	1.4 (1.3–1.7)	1.1 (1–1.3)
LDL-C, mmol/L	2.8 (2.3–3.4)	3 (2.3–3.6)	3.1 (2.6–3.7)*	3.1 (2.6–3.8)*
DBP, mm Hg	76.7 (70–80.7)	82 (78–90)	80 (75.3–84)	86.7 (80–92)
SBP, mm Hg	117.3 (108.7–123.3)	130 (119.3–140.7)	120.5 (112–130)	130.7 (120.7–146)
FPG, mmol/L	4.9 (4.5–5.2)	5.6 (5–6)	5 (4.7–5.3)	5.5 (5–6.1)
TC, mmol/L	4.6 (4–5.2)	4.8 (4.2–5.5)*	4.9 (4.3–5.5)*	5 (4.5–5.7)
TG, mmol/L	1 (0.7–1.3)	1.9 (1.3–2.6)	1.1 (0.8–1.4)	2.2 (1.6–2.9)
Uric acid, mmol/L	266 (219–324)	319 (262–382)	278 (230–333)	342 (287–407)
HOMA-IR	1.9 (1.4–2.6)	2.8 (1.9–4.3)	2.5 (1.7–3.6)	3.5 (2.4–5.8)
hsCRP	1 (0–2)*	1 (1–3)†,‡	1 (1–3)*,†	2 (1–4)‡
HbA1c (%)	5.4 (5.1–5.7)	5.5 (5.2–5.9)	5.5 (5.3–5.8)	5.7 (5.4–6.1)
Diabetes, %	0.9	9.2	1	10.5
Dyslipidemia, %	13.1	53.2	19.8	66

Data are n (%) or median (interquartile range).

BMI = body mass index, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment of insulin resistance, hsCRP = high-sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, MHNO = metabolically healthy nonobese, MHO = metabolically healthy obese, MUNO = metabolically unhealthy nonobese, MUO = metabolically unhealthy obese, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride, WC = waist circumference.

*, †, ‡ Statistically insignificant difference.

their MHNO peers. The adjusted ORs for having hypertension in MHO subjects were 1.94 (95% CI 1.60–2.35) using the ATP-III criteria, 1.98 (95% CI 1.61–2.43) using the Wildman criteria, 2.37 (95% CI 1.88–2.99) using the Karelis criteria, 2.26 (95% CI 1.96–2.61) using the HOMA criteria, and 2.54 (95% CI 2.14–3.00) using the TyG criteria. Similarly, compared to the MHNO phenotype, subjects in the MUO and MUNO phenotypes demonstrated significantly higher ORs for hypertension; the corresponding ORs ranged from 2.75 to 7.02 and from 1.23 to 3.99, respectively. Furthermore, the degree of association with hypertension was stronger in the MHO phenotype than in the MUNO phenotype, for all except the ATP-III and Wildman criteria.

Furthermore, when adopting WC and WHtR as obesity maker (the sensitivity analysis), a highly similar pattern was found: MHO subjects were nearly 2-fold more likely to have hypertension than their MHNO peers and the adjusted ORs were similar across different criteria, whereas MUNO subjects were not significantly associated with hypertension compared to the MHNO phenotype when using WHtR as obesity marker.

4. Discussion

To the best of our knowledge, this is the first nationwide population-based study to investigate the association of different metabolic health and obesity phenotypes with hypertension in the Chinese adult population. Our results demonstrated that the MHO phenotype, irrespective of definitions, was not a benign condition and was associated with an approximately 2-fold

Table 2

Prevalence and odds ratios of hypertension according to metabolic health and obesity phenotypes defined by 5 criteria.

Obesity phenotypes	ATP-III criteria	Wildman criteria	Karelis criteria	HOMA-IR criteria	TyG criteria
Prevalence, %					
MHNO	13.9	13.2	18.5	21.9	19.8
MUNO	43.7	40.7	27.8	28.5	30.5
MHO	23.4	22.7	34.4	38.6	37.3
MUO	54.7	52.5	43.8	47.2	45.4
ORs for model*					
MHNO	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
MUNO	3.99 (3.45–4.63)	3.71 (3.21–4.3)	1.29 (1.12–1.49)	1.23 (1.03–1.47)	1.38 (1.19–1.6)
MHO	1.94 (1.6–2.35)	1.98 (1.61–2.43)	2.37 (1.88–2.99)	2.26 (1.96–2.61)	2.54 (2.14–3)
MUO	7.02 (5.97–8.25)	6.67 (5.67–7.85)	2.82 (2.41–3.29)	2.8 (2.34–3.33)	2.75 (2.34–3.22)

ATP-III = Adult Treatment Panel-III, HOMA-IR = homeostasis model assessment of insulin resistance, MHNO = metabolically healthy nonobese, MHO = metabolically healthy obese, MUNO = metabolically unhealthy nonobese, MUO = metabolically unhealthy obese, OR = odds ratio.

* Model was adjusted for age, sex, drinking, smoking, diabetes, LDL-C, uric acid, and high-sensitivity C-reactive protein (hsCRP).

increased risk of hypertension compared to the MHNO phenotype. The MUO phenotype was consistently associated with the highest risk, whereas being nonobese in combination with metabolically unhealthy status also had a significantly higher risk of hypertension compared to metabolically healthy subjects.

Recently, several studies have focused on the risk of hypertension in the different metabolic obesity phenotypes. These investigations consistently revealed an increased risk of hypertension incidence in MUO and MHO subjects, showing around a 2-fold and 1.5-fold higher risk in 3 respective Korean prospective studies,[7,8,15] and a 5-fold and 7-fold higher risk in a Chinese children and adolescent study,[16] respectively. The results of the present study are in line with previous reports suggesting that subjects with MUO and MHO phenotypes are nearly 7- and 2.5-fold more likely to develop hypertension, respectively, as compared to the MHNO phenotype.

However, there is still controversy over whether subjects in the MUNO phenotype carry an increased risk of hypertension compared to the MHNO phenotype. Based on a prospective cohort involving Korean middle-aged adults during an 8-year follow-up, Lee et al[7] reported that the MUNO phenotype defined by ATP-III criteria was not positively associated with an increased risk of hypertension incidence. Similarly, Ding et al[16] showed that, despite a high prevalence of MUNO status in Chinese children and adolescents, after a 6-year follow-up MUNO children and adolescents were not at a significantly increased risk of hypertension compared to the their healthy, normal-weight peers. These findings are contradictory to those of Kang et al and Ryoo et al, which both revealed a higher risk of hypertension development in MUNO subjects (approximately 70%) when compared to the healthy normal-weight phenotype. Consistent with both previous studies, a meta-analysis of 5 prospective cohort studies also confirmed that subjects with MUNO had an increased risk of subsequent hypertension events, with a pooled relative risk of 2.46.[17] Two aspects of our data are in full agreement with Kang et al's findings: firstly, this study showed significantly higher ORs in MUNO subjects irrespective of the definitions used, suggesting that the MUNO phenotype is a relatively malignant condition in this regard; secondly, we found that applying the Karelis, HOMA, and TyG criteria resulted in reduced ORs for MUNO subjects than their MHO peers. However, it was noteworthy stressing a potential bias when adopting the APT-III and Wildman criteria, because the BP parameters were used for defining both hypertension and metabolic status. This thus led to an overestimation of hypertension prevalence in MUO group and an underestimation in MHO group. Moreover, another consequence of this potential bias is that we found a higher strength of association between MUNO group and hypertension compared to their MHO peers, when adopting the APT-III and Wildman criteria. Above all, MUNO phenotype carry an increased risk of hypertension compared to the MHNO phenotype, regardless of metabolic health status definitions used.

4.1. Limitations and strengths

Several limitations of this study should be acknowledged. Firstly, since the present study was conducted only on Chinese population, extrapolation of results to other populations should be interpreted cautiously. Secondly, this study is a cross-sectional analysis and thus it does not explicitly infer causality in the relationship between metabolic obesity phenotypes and hypertension risk; further cohort studies are needed to clarify this aspect of our findings. Nevertheless, the strengths of this study are its population-based design and the large sample size, which guaranteed results with a reasonable statistical power to reflect the real association. A vigorous quality assurance program was utilized and the same strict methodology used to ensure the quality of data collection over the entire study period. Despite the current lack of consensus on the best definitions of metabolic health and obesity status, this study adopted 5 representative definitions of metabolic obesity from the literature to fully investigate their association with hypertension risk.

5. Conclusions

In conclusion, we demonstrated that both the metabolically unhealthy status and obese status contributed to have hypertension in Chinese adults by using a nationwide population-based study. We adopted 5 representative definitions of metabolic health and obesity phenotypes, showing that MUO subjects were consistently associated with the highest prevalence of hypertension. The MHO phenotype was not a benign condition and had substantial risk of hypertension compared to the MHNO phenotype; therefore, in clinical settings, it is important to take both metabolic health status and obesity into consideration when monitoring and managing hypertension risk.

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Methodology: Simiao Tian.
Writing – original draft: Simiao Tian.
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