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Predictive Value of Relative Fat Mass Algorithm for Incident Hypertension: a 6-year Prospective Study in a Chinese Population

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Abstract

Objectives Individuals with obesity especially excessive visceral adiposity have high risk for incident hypertension. Recently, a new algorithm named relative fat mass (RFM) was introduced to define obesity. Our aim was to investigate the whether it can predict hypertension in Chinese population, and to compare its predictive power with traditional indices such as body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHtR).

Design A 6-year prospective study.

Setting 9 provinces (Hei Long Jiang, Liao Ning, Jiang Su, Shan Dong, He Nan, Hu Bei, Hu Nan, Guang Xi, and Gui Zhou) in China.

Participants Those without hypertension in 2009 survey and respond in 2015 survey.

Intervention Logistic regression and sensitive analysis were performed to investigate the association between RFM and incident hypertension. Receiver operating characteristic (ROC) analysis was performed to compare the predictive ability of these indices and define their optimal cut-off value.

Main outcome measures Incident hypertension in 2015.

Results The prevalence of incident hypertension in 2015 based on RFM quartiles were 14.9%, 21.0%, 26.9% and 35.0% respectively (p for trend < 0.001). In overall population, the Odds ratio (OR) for the highest quartile compared to the lowest quartile for RFM was 2.062(1.594-2.668) in the fully adjusted model. In ROC analysis, RFM and WHtR had the highest AUC value in both sexes, but did not show statistical significance when compared to AUC value of BMI in male and AUC value of WC in female.

Conclusions RFM can be a powerful indictor for predicting incident hypertension in Chinese population, but it does not show superiority over BMI and WC in predictive power.

Strengths and limitations of this study

- Our study was the first study to reveal whether the newly invented RFM algorithm can independently predict incident hypertension and compare it predicting power with traditional obesity-related indices.

- We used a nationally representative sample and a prospective design to investigate the predictive power of RFM for incident hypertension.
- Potential bias may exist due to the exclusion of individuals whose data were incomplete.
- We can't validate and evaluate the performance of the RFM algorithm to estimate body fat percentage in our study population as the body composition estimates are lacking, which hinders the further interpretation of our results.

Introduction

During the last three decades, hypertension has been the leading cause for all-cause deaths worldwide [1]. An international survey indicated that the incident rate of hypertension was 40.8% in their multinational study population [2]. In China, 23.2% of adult population had hypertension and another 41.3% were in a pre-hypertension state, however, only 46.9% were aware of the diagnosis and minority were effectively controlled in those who were diagnosed [3]. Statistics present the grim reality, there is no doubt blood pressure-related morbidity and mortality will exert a huge burden. Thus, despite improvement in hypertension diagnosis and treatment, implementing effective measures to identify people at risk and prevent the incident of hypertension is extremely important.

Obesity is a significant risk factor for hypertension, various studies in different ethnic group has showed this association [4]. For example, the Framingham heart indicated that 34% of hypertension in men and 62% of hypertension in women can be ascribed to overweight and obesity [5]. On the other hand, weight loss intervention can significantly lower the blood pressure and serve as an effective method for the primary prevention of hypertension [6 7]. Currently, when considering the deleterious effect of obesity, excessive intra-abdominal or visceral adipose tissue not subcutaneous fat were regarded as the main cause for hypertension and other cardio-metabolic abnormalities [8-11]. Thus, a proper assessment of excessive adiposity especially central adiposity can effectively identify those at high risk for hypertension.

BMI and WC has been recommended to define obesity by several guidelines. However, BMI does not distinguish fat mass from lean mass and does not reflect fat distribution [12 13], WC can be a proxy for abdominal fat distribution but owing to its close relationship to body size, it may overestimate the risk in tall individuals and underestimate the risk

in short individuals [14].In 2018, a new algorithm named RFM had been introduced by Woolcott et al. to estimate whole-body fat percentage among adult individuals, they proved it was high correlated with abdominal obesity and can better predict whole-body fat percentage than BMI, which was validated by dual energy X-ray absorptiometry [15]. Moreover, the main component of RFM equation is height to waist ratio, the converse form of WHtR; as WHtR had been proved to be better than BMI and WC as predictor for cardiometabolic risk in the Asian population [16], RFM also show great potential. In our study, we performed a 6-year prospective study by using data from the China Health and Nutrition Survey, attempting to investigate whether RFM could be a better anthropometric index for hypertension risk prediction in Chinese population and contribute to the prevention of hypertension.

Method

Study subjects

The China Health and Nutrition Survey (CHNS) is an ongoing open cohort aiming at examining the health and nutritional condition and its influencing factors of the participants. To date, ten rounds of survey (1989, 1991, 1993, 1997, 2000, 2004, 2006, 2009, 2011, 2015) have been conducted. It was co-launched by Carolina Population Center at the University of North Carolina at Chapel Hill and the National Institute for Nutrition and Health at the Chinese Center for Disease Control and Prevention. All participants signed an informed consent form during the survey.

In this study, we conducted a prospective study among people aged more than 18 years by using the data form the 2009 and 2015 CHNS survey. Subjects who participated in both the 2009 and 2015 survey were enrolled in this study, those who didn't have hypertension in 2009 were set as baseline sample, and the presence of incident hypertension in 2015 was defined as the outcome. First, we excluded subjects aged less than 18 or pregnancy, and those whose medication history for hypertension and results of blood pressure measurement were both unavailable. Then, subjects lack anthropometric measurement data or serum biomarker data were excluded, and those who have missing data about smoking, drinking and outcome were also excluded. Last, those who had history of myocardial infarction or stroke, moderate to serve chronic kidney disease (eGFR < 60 mL/min/1.73 m^2), serve hepatic dysfunction (ALT ≥120 IU/L) were excluded. Finally, 3382 participants were included in our study (Fig. 1).

Data Collection

Characteristics of the participants including general personal characteristics, smoking status, alcohol consumption, medical history were obtained by using face to face interview. Each individual's Height and weight were measured by the investigators according to the standard of protocol, and BMI was calculated as weight in kilograms divided by the square of height in meters. When measure waist circumference, the tape was applied horizontally midway between the lower rib margin and the iliac crest. Hip circumference was measured at widest part of the protrusion. WHtR was waist circumference in centimeters divided by height in centimeters. RFM was calculated by using the established formula [15]:

$$RFM(male) = 64 - (20 \times (\frac{height(m)}{WC(m)}))$$

$$RFM(female) = 76 - (20 \times (\frac{height(m)}{WC(m)}))$$

Blood pressure was determined in duplicate to improve accuracy, and the average of the values was reported as the final results. For blood collection, participants were asked to fast for 6 to 8 hours. Blood were collected in EDTA-3K anticoagulant tube, then centrifugation at 3000g for 15 min to separate plasma from blood cells. Plasma samples were stored in cryovial at −70 ℃ condition and whole blood samples were stored at 2-8 ℃ condition. Whole blood was used for testing of glycated hemoglobin HbA1c by chromatography. Plasma were tested for alanine aminotransfease (ALT), triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), uric acid, creatinine (Cr), insulin by using automated biochemistry analyzer. ALT was tested by high-performance liquid chromatography method. HDL-C, LDL-C were determined by enzymatic method. TG were determined by CHOD-PAP method and TC were determined by GPO-PAP method. Uric acid was determined by enzymatic colorimetric method. Glucose was determined by GOD-PAP method. Insulin was determined by Radioimmunology method. Estimate glomerular filtration rate (eGFR) was calculated by using the CKD-EPI equation [17].

Definitions

Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, or subjects reported been diagnosed or treated with

anti-hypertensive drugs. Diabetes was defined as previously diagnosed with diabetes or fasting blood glucose≥7.0mmol/L or HbA1c≥6.5%. Mild decrease eGFR was defined as eGFR < 85ml/min/1.73m^2 in men and < 75ml/min/1.73m^2 in women. Hyperuricemia means serum uric acid > 420μmol/L in men and > 360μmol/L in women. Dyslipidemia was defined as the presence of any of the following: TG ≥ 1.70mmol/L or TC ≥ 5.18mmol/L or HDL-C < 1.04mmol/L or LDL-C≥3.37mmol/L.

Statistical Analysis

Continuous variables with a non-normal distribution were expressed as median (interquartile range), and categorical variables were expressed as percentages. Differences between groups were tested by Mann-Whitney U test for variables with skewed distributions and χ2-test for categorical variables. Multiple logistic regression analysis was conducted to examine the association of RFM and incident hypertension. RFM was stratified into four quartiles according to sex- specific cut point, odds ratio (OR) and its 95% confidence interval (CI) were estimated by four models: (a) crude model; (b) adjusted for age, sex; (c) adjusted for age, sex, smoking, alcohol drinking; (d) additionally adjusted for uric acid, eGFR, ALT, TG, TC, HDL-C, LDL-C, FPG. Receiver-operating characteristic curve analyses were conducted to compare predictive power of RFM with traditional indices including BMI, WC, WHtR. In ROC analysis, we defined the appropriate cut-off point of each anthropometric index for the prediction of incident hypertension, by using these indices as test variable and hypertension in 2015 as state variable, the cut-off values were determined by the maximizing the Youden index. The areas under the ROC curve of different indices were compared using the method developed by DeLong et al. [18]. All analyses were performed using Spass version 19.0. Two-tailed p values of < 0.05 were considered statistically significant.

Patient and public involvement

There were no patients or public involved in study design, outcome measurement and results interpretation.

Results

Baseline characteristics of participants

There were 3382 participants without hypertension at baseline. Baseline clinical characteristics are shown in Table 1. After 6-years of follow-up, 826 individuals developed hypertension. The incidence was 26.3% for men and 22.9% for women. As expected, those who developed hypertension showed a more adverse profile on cardiometabolic parameters—higher uric acid, ALT, FPG, TG, TC, LDL-C level and lower eGFR, LDL-Cholesterol level.

Baseline characteristics of the participants according to RFM quartiles are shown in Table 2. The prevalence of cardiometabolic risk factors such as hyperuricemia, dyslipidemia, and diabetes were increased in proportion to the quartiles of RFM.

Association between RFM and incident hypertension

Table 3 shows the incidence of hypertension according to quartiles of RFM. Participants with high levels of RFM at baseline were more likely to develop hypertension in the following up, incident cases of hypertension increased as the RFM increased (14.9%, 21.0%, 26.9% and 35.0% in the first, second, third, and fourth quartiles respectively). In unadjusted logistic regression models, compared to the first quartile of RFM levels, the ORs and 95% CI for incident hypertension in the second, the third, and the fourth quartiles were1.513(1.177-1.945), 2.094(1.643-2.667), and 0.060(2.417-3.874) respectively (p for trend < 0.001). After adjusted for age, sex (model 1) and age, sex, smoking, alcohol drinking (model 2), the associations remained significant. In the fully adjusted model considering additional potential confounders including uric acid, eGFR, ALT, TG, TC, HDL-C, LDL-C, and FPG (model 3), the ORs and 95% CI for incident hypertension comparing the second, third, and fourth quartiles to the first quartile of RFM levels were 1.235(0.953-1.601), 1.528(1.185-1.970), and 2.062(1.594-2.668) respectively (p for trend < 0.001).

ROC curves for the incidence of hypertension

In logistic regression analysis, we demonstrated RFM can predict incident hypertension. Aiming at comparing its predictive power with traditional anthropometric indices and delineating their optimal cut-points, a ROC analysis was conducted (figure 2). In both sexes, RFM and WHtR had the highest AUC value. In male, RFM had higher AUC value than WC and comparable value to BMI. However, there were no significant differences in AUC value of BMI as compared to WC. In female, RFM had higher AUC

value than BMI and comparable value to WC, WC had higher AUC value than BMI. All indices had higher AUC value in female than in male (Table 4).

In male population, the optimal cut-off value was 24.67 for RFM, 23.74 for BMI, 82.95 for WC, 0.51 for WHtR. In female population, the optimal cut-off value was 35.73 for RFM, 23.83 for BMI, 77.15 for WC, 0.50 for WHtR. In both sexes, RFM and WHtR had the highest Youden index values for predicting hypertension (Table 5).

Discussion

In our longitudinal study performed in initially non-hypersensitive individuals with 6 years of follow-up, we found an increased risk of incident hypertension across quartiles of the RFM after adjusted for several known risk factors, which indicate RFM is an independent and practicable predictor of hypertension in Chinese population.

When considering obesity and hypertension, visceral adiposity mediates the progression from a normotensive to hypertensive. The most robust evidence comes from the Dallas Heart Study, which measure adipose tissue through magnetic resonance imaging scanner, they demonstrated visceral adiposity but not total or subcutaneous adiposity was significantly associated with incident hypertension [19]. Excessive abdominal adiposity can result in adipocyte dysfunction, which was accompanied by abnormal proinflammatory cytokines and adipocytokines secretion and increased free fatty acids in the circulation. These factors can contribute to vascular dysfunction and systemic insulin resistance, and then leading to increased activation of the renin-angiotensin-aldosterone system (RAAS), increased sympathetic nervous system (SNS) activity [20]. Moreover, obesity can cause kidney injury. The compression of the kidneys by fat can induce inflammation and expansion of renal medullary extracellular matrix, inhibit renal tubular reabsorption and increase sodium reabsorption, leading to the development of low estimated GFR and further increases in blood pressure [21]. Thus, indices which can give a precise assessment of fat mass especially visceral adiposity may improve the sensitivity and specificity in detecting individuals with increased cardio-metabolic or hypertension risk.

The aim of developing the RFM algorithm was to better reflect estimates of whole-body fat percentage in clinical and epidemiological practice, it was proved having higher sensitivity and lower rates of misclassification in obesity estimation when compared to BMI in US population by its developers, and then validated better than BMI in Mexican

population [15] [22]. In predicting cardiometabolic risk, RFM also showed excellent performance. RFM had better discrimination power than BMI in identifying diabetes [15]. In a cohort study, RFM was better than BMI in predicting incident severe liver disease and overall mortality [23]. However, in our study performed in Chinese population, we found although RFM can be an effectively index in predicting hypertension, it was comparable to BMI in men and slightly better than BMI in women in predicting ability. Two reasons can account for this result. Firstly, the outcome in our study was different from other current published cross-sectional or cohort study about RFM, although obesity participate and serve as critical role in the pathophysiological processes of all these outcome diseases, the confounding factors may be different from each other. Secondly, according to a recent study performed in Korean population, RFM tend to overestimated the body fat percentage in their study population, and showed a better linear relationship with body fat percentage than BMI in men only. In ROC analysis, they found RFM was not superior to that of BMI in discriminating obese individuals [24]. As RFM was developed from Mexican-Americans, European-Americans, and African-Americans, and Asian populations tend to have higher body fat percentage than Caucasians at the same BMI level [25]. It is possible that the RFM algorithm gives a less accurate estimation of body fat percentage in Chinese population than in Western population.

RFM and WHtR had the same AUC value in the ROC analysis. The optimal cut-off of WHtR in our study were 0.51 for male and 0.50 for female, similar to the recommendations suggested by various studies to define central obesity (WHtR **>** 0.5), meanwhile, 0.5 had been demonstrated to be a good boundary value for men and women across ethnic groups according to the outcome measures related to diabetes and CVD [26-28]. When the WHtR value was 0.5, the corresponding value for RFM were 24 for men and 36 for women, very close to the optimal cut-off of RFM in our study. Based on these, we can conclude that a high level of consistency existed between the current RFM equation and WHtR, and RFM can be an alternative to WHtR in predicting incident hypertension.

In our study, BMI and WC showed similar power in male population, which should be explained. Indeed, WC can give a better quantity of visceral fat. However, same as our study, some studies reported that no difference between BMI and WC with regard to discriminating or predicting obesity-related diseases or mortality [29-32]. In many

circumstances especially in Asian populations, BMI and WC are highly correlated, there were reported studies reveal their ability were comparable in predicting abdominal adipose tissues which were measured by CT scan [33].

Our study has several strengths. First, our study was performed using nationally representative samples of the Chinese adult population, which were recruited from 9 different provinces in China. Second, to our best knowledge, we were the first longitudinal study to investigate whether the current RFM algorithm can be applied in hypertension prediction and compare it predicting power with traditional obesity-related indices. Third, in baseline population, we excluded the individuals with history of myocardial infarction or stroke, as well as those with moderate-to-serve renal insufficiency or liver dysfunction, which may affect the association between obesity and hypertension. This ensure the objectivity and accuracy of our research.

There are also limitations of our study. First, we exclude 762 individuals from this study duo to lack of data about the factors we needed to analysis, which may cause selection bias. Second, medical history taking and biomarker measurements were only carried out at the baseline, but these parameters may change over time. For example, lifestyle intervention and pharmacotherapy can result in weight loss and ameliorate metabolic disorders in some high-risk individuals and reduce the risk of developing hypertension. However, we failed to take these factors into consideration in our study. Third, although the blood pressure was measured in duplicate, white-coat hypertension may exist and affected our judgment of the outcome. Fourth, as the nature of observational study, when investigate about the association between RFM and incident hypertension, it's possible that some unknown or unmeasured factors confounded the association; however, in our logistic analysis, we had adjusted the main confounding factors, we don't think residual confounding will materially alter our conclusion. Fifth, as the participants in our study did not underwent dual-energy X-ray absorptiometry test or other tests which can give an assessment about body component, we couldn't evaluate the performance and accuracy of the RFM algorithm in Chinese population, this hinder the further interpretation of our results.

Conclusion

In conclusion, our study revealed that RFM is powerful indictor to predict incident hypertension in Chinese population. However, based on the based on the Youden index

in ROC analysis, RFM had the same predictive power with WHtR, and RFM do not show superiority in predictive power when compared with BMI and WC. The optimal cut-off for RFM was 24.67 and35.73 in men and women respectively. Individuals above the cut-off level show higher risk for hypertension and deserves early intervention to prevent it.

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Footnotes

Contributors: PY and XFY contributed to the study conception and study design. PY, TH, SLH contributed to the data analysis, interpretation of the data. PY contributed to drafting the manuscript. All authors read and approved the final manuscript.

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Table 1 Baseline characteristics of participates according to follow-up outcomes

	Incident hypertention		
	no (n=2556)	yes (n=826)	p value
Age	45.0(37.0-54.0)	52.0(44.0-59.0)	< 0.001
Men/Women	1138/1418	406/420	0.020
Alcohol consumer (%)	33	38.9	0.002
Smoking			0.324
Current smoker (%)	28.7	30.4	
Ex smoker (%)	2.0	2.7	
Non-smoker (%)	69.3	66.9	
Body weight (Kg)	57.7(52.0-65.2)	61.0(54.3-68.7)	< 0.001
BMI (kg/m^2)	22.38(20.50-24.59)	23.80(21.51-26.07)	< 0.001
WC (cm)	80.0(73.0-86.7)	84.0(77.5-90.0)	< 0.001
WHtR	0.50(0.46-0.54)	0.52(0.48-0.56)	< 0.001
RFM	30.15(23.75-36.72)	30.92(24.69-38.66)	< 0.001
SBP (mmHg)	116.0(108.0-121.3)	120.7(114.7-128.7)	< 0.001
DBP (mmHg)	76.7(70.0-80.0)	80.0(75.3-82.0)	< 0.001
eGFR (mL/min/1.73 m^2)	83.19(74.69-93.12)	80.36(72.06-89.68)	< 0.001
Cr (μmol/L)	82.0(74.0-93.0)	83.0(75.0-93.0)	0.503
Uric acid (μmol/L)	276.0(225.0-338.0)	290.0(234.0-352.2)	0.001
ALT (U/L)	18.0(13.0-25.0)	19.0(14.0-28.0)	< 0.001
FPG (mmol/L)	5.00(4.63-5.45)	5.15(4.76-5.64)	< 0.001
HbA1c (%)	5.4(5.1-5.7)	5.6(5.2-5.9)	< 0.001

TG (mmol/L)	1.13(0.78-1.73)	1.32(0.90-1.94)	< 0.001
TC (mmol/L)	4.63(4.05-5.27)	4.87(4.24-5.51)	< 0.001
HDL-C (mmol/L)	1.40(1.18-1.64)	1.40(1.16-1.64)	0.819
LDL-C (mmol/L)	2.78(2.27-3.38)	2.98(2.42-3.57)	< 0.001

Categorical variables were presented as a number (percentage), continuous variables with a skewed distribution were presented as medians (IQR). P values are for Mann-Whitney U test for or $\chi 2$-test.

BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass; SBP, systolic blood pressure; DBP, diastolic blood pressure, eGFR, estimate glomerular filtration rate; Cr, creatinine; ALT, alamine aminotransferase; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2 Baseline characteristics of participates according to RFM

	Quartile 1 n=850	Quartile 2 n=843	Quartile 3 n=848	Quartile 4 n=841	p value
Age	41.0(33.0-50.0)	46.0(38.0-54.0)	49.0(41.0-57.0)	51.0(43.0-58.0)	< 0.001
Men/Women	387/463	387/456	386/462	384/457	0.998
Alcohol consumer (%)	30.5	34.9	35.7	36.7	0.035
Current smoker (%)	29.2	29.3	29.0	28.9	0.290
Body weight (Kg)	52.4(47.7-57.5)	57.1(51.8-63.2)	60.6(55.0-67.3)	66.4(59.1-74.4)	< 0.001
BMI (kg/m^2)	19.97(18.73-21.21)	22.01(20.86-23.25)	23.63(22.09-24.93)	26.13(24.13-27.75)	< 0.001
WC (cm)	70.0(67.0-73.0)	78.0(75.0-80.0)	84.0(81.0-87.0)	92.0(88.5-96.5)	< 0.001
WHtR	0.44(0.42-0.45)	0.48(0.47-0.49)	0.52(0.51-0.53)	0.57(0.56-0.60)	< 0.001
SBP (mmHg)	110.7(102.7-120.0)	117.3(110.0-122.0)	119.7(110.0-125.3)	120.0(112.0-126.7)	< 0.001
DBP (mmHg)	73.3(69.3-80.0)	77.3(70.0-80.7)	79.3(71.3-81.0)	80.0(73.3-82.0)	< 0.001
eGFR (mL/min/1.73 m^2)	86.36(76.49-96.20)	81.86(74.50-92.29)	81.44(73.26-90.55)	80.72(72.15-89.74)	< 0.001
Cr (μmol/L)	83.0(75.0-93.0)	83.0(75.0-93.0)	82.0(75.0-93.0)	83.0(74.0-93.0)	0.860
Uric acid (μmol/L)	264.0(219.0-324.0)	274.0(222.0-333.0)	280.0(230.0-339.0)	302.0(244.0-372.0)	< 0.001
ALT (U/L)	15.0(11.0-21.0)	17.0(12.0-24.0)	19.0(14.0-26.0)	22.0(16.0-32.0)	< 0.001
FPG (mmol/L)	4.89(4.53-5.27)	4.95(4.62-5.37)	5.07(4.67-5.53)	5.22(4.84-5.76)	< 0.001

HbA1c (%)	5.3(5.0-5.6)	5.4(5.1-5.7)	5.5(5.2-5.8)	5.6(5.3-6.0)	< 0.001
TG (mmol/L)	0.94(0.69-1.28)	1.11(0.77-1.64)	1.25(0.85-1.92)	1.50(1.03-2.47)	< 0.001
TC (mmol/L)	4.40(3.84-4.95)	4.64(4.10-5.34)	4.79(4.17-5.40)	4.92(4.30-5.59)	< 0.001
HDL-C (mmol/L)	1.47(1.28-1.71)	1.45(1.22-1.69)	1.39(1.15-1.61)	1.28(1.09-1.50)	< 0.001
LDL-C (mmol/L)	2.58(2.11-3.14)	2.84(2.30-3.43)	2.91(2.39-3.49)	3.02(2.47-3.61)	< 0.001
Hyperuricemia (%)	5.2	9.5	12	17.4	< 0.001
Dyslipidemia (%)	30.4	48	56.4	69.3	< 0.001
Diabetes (%)	2.8	5.1	6.8	13.0	< 0.001

Categorical variables were presented as a number (percentage), continuous variables with a skewed distribution were presented as medians (IQR). P values are for Mann-Whitney U test for or $\chi 2$-test.

BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass; SBP, systolic blood pressure; DBP, diastolic blood pressure, eGFR, estimate glomerular filtration rate; Cr, creatinine; ALT, alamine aminotransferase; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 3 Odds ratios (ORs) and 95% confidence intervals (CI) for incident hypertension according to baseline quartiles of RFM

	Quartile 1 (n=850)	Quartile 2 (n=843)	Quartile 3 (n=848)	Quartile 4 (n=841)	p for trend
Incident hypertention	127	177	228	294	< 0.001
Unadjusted	1	1.513(1.177-1.945)	2.094(1.643-2.667)	3.060(2.417-3.874)	< 0.001
Model 1	1	1.296(1.003-1.676)	1.632(1.272-2.095)	2.292(1.795-2.926)	< 0.001
Model 2	1	1.280(0.990-1.656)	1.606(1.250-2.063)	2.253(1.763-2.879)	< 0.001
Model 3	1	1.235(0.953-1.601)	1.528(1.185-1.970)	2.062(1.594-2.668)	< 0.001

Model 1: adjusted for age, sex
Model 2: adjusted for age, sex, smoking, alcohol drinking
Model 3: adjusted for age, sex, smoking, alcohol drinking, uric acid, eGFR, ALT, TG, TC, HDL-C, LDL-C, FPG
eGFR, estimate glomerular filtration rate; ALT, alamine aminotransferase; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose.

Table 4 AUCs for each anthropometric index in predicting hypertension

	Men		Women	
	AUC(95%CI)	p value	AUC(95%CI)	p value
RFM	0.593(0.561-0.625)	< 0.001	0.647(0.617-0.677)	< 0.001
BMI	0.591(0.558-0.623)	< 0.001	0.615(0.584-0.646)	< 0.001
WC	0.579(0.547-0.612)	< 0.001	0.644(0.614-0.674)	< 0.001
WHtR	0.593(0.561-0.625)	< 0.001	0.647(0.617-0.677)	< 0.001

AUC, area under the curve; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass

Table 5 Optimal cutoff points for each anthropometric index in predicting hypertension

	Men				Women			
	Cut off	Sensitivity (%)	Specifity (%)	Youden index	Cut off	Sensitivity (%)	Specifity (%)	Youden index
RFM	24.67	0.51	0.65	0.16	35.73	0.76	0.47	0.22
BMI	23.74	0.48	0.67	0.15	23.83	0.53	0.67	0.20
WC	82.95	0.58	0.55	0.13	77.15	0.76	0.46	0.21
WHtR	0.51	0.51	0.65	0.16	0.50	0.76	0.47	0.22

AUC, area under the curve; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass

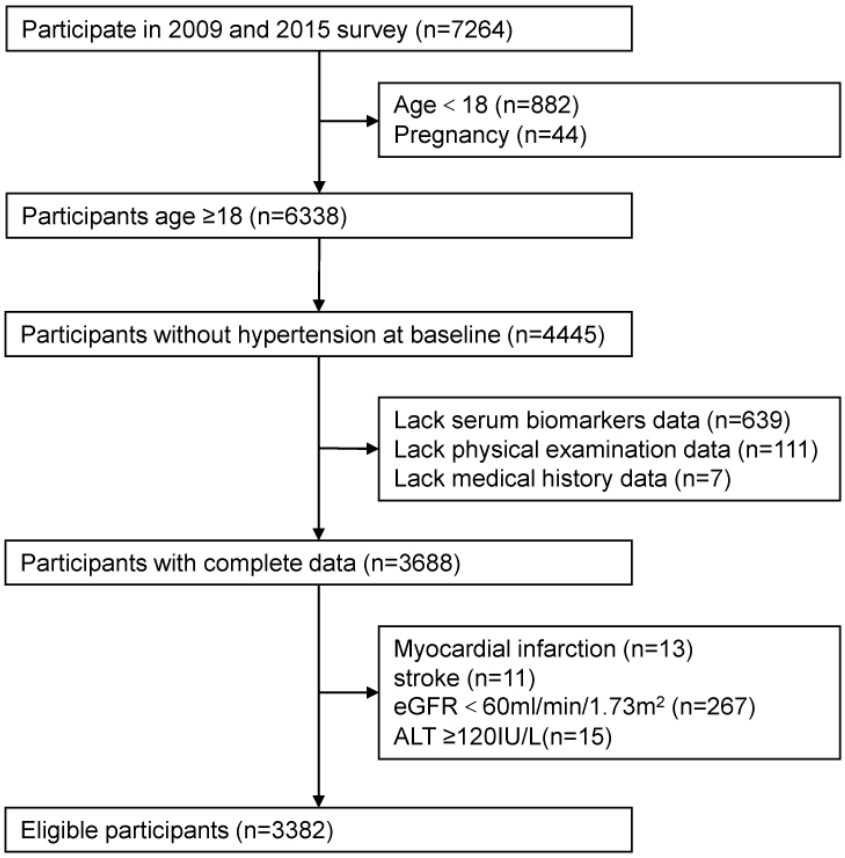

Figure 1 The flow chart of sample selection from the China Health and Nutrition Survey

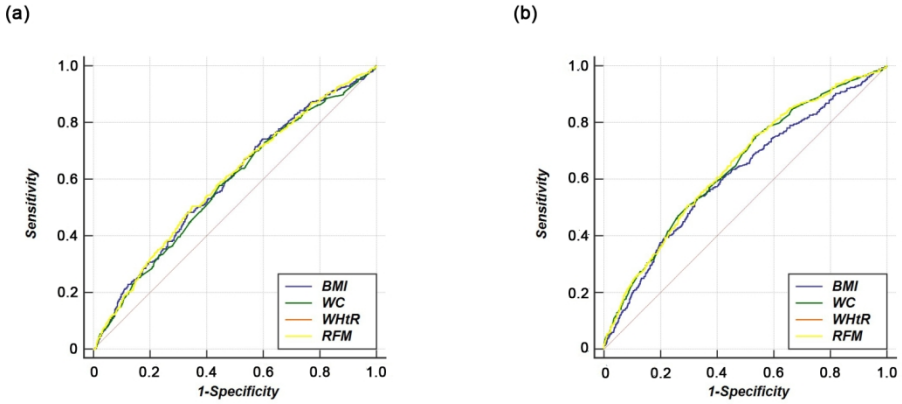

Figure 2 Receive-operating characteristic curves (ROC) of BMI, WC, WHtR, and RFM for incident hypertension.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	4
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	4

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	4
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,16,17,18
		(b) Indicate number of participants with missing data for each variable of interest	4
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	7,8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9,10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Predictive Value of Relative Fat Mass Algorithm for Incident Hypertension: a 6-year Prospective Study in Chinese Population

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Predictive Value of Relative Fat Mass Algorithm for Incident Hypertension: a 6-year Prospective Study in Chinese Population

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Abstract

Objectives Individuals with obesity especially excessive visceral adiposity have high risk for incident hypertension. Recently, a new algorithm named relative fat mass (RFM) was introduced to define obesity. Our aim was to investigate whether it can predict hypertension in Chinese population, and to compare its predictive power with traditional indices including body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHtR).

Design A 6-year prospective study.

Setting 9 provinces (Hei Long Jiang, Liao Ning, Jiang Su, Shan Dong, He Nan, Hu Bei, Hu Nan, Guang Xi, and Gui Zhou) in China.

Participants Those without hypertension in 2009 survey and respond in 2015 survey.

Intervention Logistic regression were performed to investigate the association between RFM and incident hypertension. Receiver operating characteristic (ROC) analysis was performed to compare the predictive ability of these indices and define their optimal cut-off values.

Main outcome measures Incident hypertension in 2015.

Results The prevalence of incident hypertension in 2015 based on RFM quartiles were 14.8%, 21.2%, 26.8% and 35.2% respectively (p for trend < 0.001). In overall population, the Odd ratio (OR) for the highest quartile compared to the lowest quartile for RFM was 2.032(1.567-2.634) in the fully adjusted model. In ROC analysis, RFM and WHtR had the highest AUC value in both sexes, but did not show statistical significance when compared to AUC value of BMI and WC in male and AUC value of WC in female. The pairwise comparation of AUC values for the prediction models contain each obesity index showed statistical insignificance.

Conclusions RFM can be a powerful indictor for predicting incident hypertension in Chinese population, but it does not show superiority over BMI, WC, and WHtR in predictive power.

Strengths and limitations of this study

- Our study was the first study to reveal whether the newly invented RFM algorithm can independently predict incident hypertension in Chinese population and

compare it predicting power with traditional obesity-related indices.

- We used a nationally representative sample and a prospective design to investigate the predictive power of RFM for incident hypertension.
- Potential bias may exist due to the exclusion of individuals whose data were incomplete.
- We can't validate and evaluate the performance of the RFM algorithm to estimate body fat percentage in our study population as the body composition estimates are lacking, which hinders the further interpretation of our results.

Introduction

During the last three decades, hypertension has been the leading cause for all-cause deaths worldwide [1]. An international survey indicated that the incident rate of hypertension was 40.8% in their multinational study population [2]. In China, 23.2% of adult population had hypertension and another 41.3% were in a pre-hypertension state, however, only 46.9% were aware of the diagnosis and minority were effectively controlled in those who were diagnosed [3]. Statistics present the grim reality, there is no doubt blood pressure-related morbidity and mortality will exert a huge burden. Thus, despite improvement in hypertension diagnosis and treatment, implementing effective measures to identify people at risk and prevent the incident of hypertension is extremely important.

Obesity is a significant risk factor for hypertension, various studies in different ethnic group has showed this association [4]. For example, the Framingham heart indicated that 34% of hypertension in men and 62% of hypertension in women can be ascribed to overweight and obesity [5]. On the other hand, weight loss intervention can significantly lower the blood pressure and serve as an effective method for the primary prevention of hypertension [6 7]. Currently, when considering the deleterious effect of obesity, excessive intra-abdominal or visceral adipose tissue not subcutaneous fat were regarded as the main cause for hypertension and other cardio-metabolic abnormalities [8-11]. Thus, a proper assessment of excessive adiposity (defined as the body fat percentage ≥25% in men and ≥35% in women according to the Western Pacific Regional Office and global World Health Organization reference standards [12]) especially central adiposity can effectively identify those at high risk for hypertension.

Body fat mass can be quantified with magnetic resonance imaging (MRI), computed

tomography (CT) and Dual energy X-ray absorptiometry (DXA). However, due to the high cost and limited availability, they are not ideal for large-scale epidemiological screening. In this context, anthropometric indices are widely used to assess body fatness and identifying individuals at risk of cardiometabolic diseases. Currently, there is no consensus about the best anthropometric index in predicting hypertension. Traditional indices such as BMI, WC and WHtR have been applied to assessing the risk of incident hypertension in Chinese population by several studies, and most of them revealed WHtR showed better performance when compared to BMI or WC [13-16] . Moreover, another six adiposity measures including conicity index (CI), lipid accumulation product (LAP), visceral adipose index (VAI), a body shape index (ABSI) and the body adiposity index (BAI) were also used to evaluate the hypertension risk, however, only LAP showed superiority when compared to traditional indices [17-20]; despite this, the equations of these indexes are relatively complex with numerous terms needed. Recently, a simple new algorithm named RFM had been introduced by Woolcott et al. to estimate whole-body fat percentage among adult individuals, they proved it was highly correlated with abdominal obesity and can better predict whole-body fat percentage than BMI, which was validated by dual energy X-ray absorptiometry [21]. Moreover, the main component of RFM equation is height to waist ratio, the converse form of WHtR. Thus, RFM shows great potential in cardiometabolic or hypertension risk assessment. In this study, we performed a 6-year prospective study by using data from the China Health and Nutrition Survey, attempting to investigate whether RFM could be a better anthropometric index for hypertension risk prediction in Chinese population and contribute to the prevention of hypertension.

Method

Study subjects

The China Health and Nutrition Survey (CHNS) is an ongoing open cohort aiming at examining the health and nutritional condition and its influencing factors of the participants. To date, ten rounds of survey (1989, 1991, 1993, 1997, 2000, 2004, 2006, 2009, 2011, 2015) have been conducted. It was co-launched by Carolina Population Center at the University of North Carolina at Chapel Hill and the National Institute for Nutrition and Health at the Chinese Center for Disease Control and Prevention. All participants signed an informed consent form during the survey. The cohort profile

provides detailed information on this survey [22].

Appropriate sample size was calculated using the OpenEpi software program (http://www.openepi.com/SampleSize/SSCohort.htm) before initiate the study. Considering 5% level of significance for a two-sided test, 80% power, unexposed/exposed ratio of 1.3, percent of unexposed with outcome = 15 and percent of exposed with outcome = 33 according to the results from the China hypertension survey [23]. Based on these settings, the estimated sample size required was at least 198 subjects.

In this study, we conducted a prospective study among people aged more than 18 years by using the data form the 2009 and 2015 CHNS survey. Subjects who participated in both the 2009 and 2015 survey were enrolled in this study, those who didn't have hypertension in 2009 were set as baseline sample, and the presence of incident hypertension in 2015 was defined as the outcome. First, we excluded subjects aged less than 18 or pregnancy, and those who were hypertensive at baseline. Then, those who had history of myocardial infarction or stroke, chronic kidney disease (eGFR < 60 mL/min/1.73 m^2), serve hepatic dysfunction (ALT ≥120 IU/L) were excluded. Last, subjects lack data about smoking, drinking, outcome and anthropometric measurement were excluded. Meanwhile, those who have missing data on biomarkers (n=443) were also excluded. Finally, 3406 participants were included in our study (Fig. 1), thus the sample of this study was sufficient. Compared to those who were included in the study, those who were excluded owing to missing data were slightly younger and higher percentage of males, there were no statistically significant differences in BMI, WC, biochemical parameters at baseline and the incidence of hypertension at 2015.

Data Collection

Characteristics of the participants including general personal characteristics, smoking status, alcohol consumption, medical history were obtained by using face to face interview. Each individual's Height and weight were measured by the investigators according to the standard of protocol, height was measured without shoes to the nearest 0.1 cm using a portable stadiometer, body weight was measured with subjects wearing light clothing without shoes, to the nearest 0.1 kg on a calibrated digital scale, BMI was calculated as weight in kilograms divided by the square of height in meters. When measure waist circumference, the tape was applied horizontally midway between the

lower rib margin and the iliac crest. WHtR was waist circumference in centimeters divided by height in centimeters. RFM was calculated by using the established formula [24]:

$$RFM(male) = 64 - (20 \times (\frac{height(m)}{WC(m)}))$$

$$RFM(female) = 76 - (20 \times (\frac{height(m)}{WC(m)}))$$

Blood pressure was determined in duplicate to improve accuracy, and the average of the values was reported as the final results. For blood collection, participants were asked to fast for 6 to 8 hours. Blood were collected in EDTA-3K anticoagulant tube, then centrifugation at 3000g for 15 min to separate plasma from blood cells. Plasma samples were stored in cryovial at −70 ℃ condition and whole blood samples were stored at 2-8 ℃ condition. Whole blood was used for testing of glycated hemoglobin HbA1c by chromatography. Plasma were tested for alanine aminotransfease (ALT), triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), uric acid, creatinine (Cr), insulin by using automated biochemistry analyzer. ALT was tested by high-performance liquid chromatography method. HDL-C, LDL-C were determined by enzymatic method. TG were determined by CHOD-PAP method and TC were determined by GPO-PAP method. Uric acid was determined by enzymatic colorimetric method. Glucose was determined by GOD-PAP method. Insulin was determined by Radioimmunology method. Estimate glomerular filtration rate (eGFR) was calculated by using the CKD-EPI equation [25].

Definitions

Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, or subjects reported been diagnosed or treated with anti-hypertensive drugs. Diabetes was defined as previously diagnosed with diabetes or fasting blood glucose≥7.0mmol/L or HbA1c≥6.5%. Hyperuricemia means serum uric acid > 420μmol/L in men and > 360μmol/L in women. Dyslipidemia was defined as the presence of any of the following: TG≥1.70mmol/L or TC≥5.18mmol/L or HDL-C < 1.04mmol/L or LDL-C≥3.37mmol/L.

Statistical Analysis

Continuous variables with a non-normal distribution were expressed as median (interquartile range), and categorical variables were expressed as percentages. Differences between groups were tested by Mann-Whitney U test for variables with skewed distributions and $\chi 2$-test for categorical variables. Logistic regression analysis was conducted to examine the association of RFM and incident hypertension. RFM was stratified into four quartiles according to sex- specific cut point, odds ratio (OR) and its 95% confidence interval (CI) were estimated by four models: (a) crude model; (b) adjusted for age, sex; (c) adjusted for age, sex, smoking, alcohol drinking; (d) additionally adjusted for uric acid, eGFR, ALT, TG, TC, HDL-C, LDL-C, FPG. Receiver-operating characteristic curve analyses were conducted to compare predictive power of RFM with traditional indices including BMI, WC, WHtR. In ROC analysis, we defined the appropriate cut-off point of each anthropometric index for the prediction of incident hypertension, by using these indices as test variable and hypertension in 2015 as state variable, the cut-off values were determined by the maximizing the Youden index. ROC analysis was also used to evaluate the performance of different models in predicting incident hypertension. The areas under the ROC curve of different indices were compared using the method developed by DeLong et al. [26]. Analyses were performed using Spass version 19.0 and MedCalc v18.2.1. Two-tailed p values of $<$ 0.05 were considered statistically significant.

Patient and public involvement

There were no patients or public involved in study design, outcome measurement and results interpretation.

Results

Baseline characteristics of participants

There were 3406 eligible participants without hypertension at baseline. Baseline characteristics are shown in Table 1. After 6-years of follow-up, 834 individuals developed hypertension. The incidence was 26.5% for men and 22.8% for women. As expected, those who developed hypertension showed a more adverse profile on cardiometabolic parameters—higher uric acid, ALT, FPG, TG, TC, LDL-C level and lower eGFR, LDL-C level.

Baseline characteristics of the participants according to RFM quartiles are shown in Table 2. The prevalence of cardiometabolic risk factors such as hyperuricemia, dyslipidemia, and diabetes were increased in proportion to the quartiles of RFM.

Association between RFM and incident hypertension

Table 3 shows the incidence of hypertension according to quartiles of RFM. Participants with high levels of RFM at baseline were more likely to develop hypertension in the following up, incident cases of hypertension increased as the RFM increased (14.8%, 21.2%, 26.8% and 35.2% in the first, second, third, and fourth quartiles respectively). In unadjusted logistic regression models, compared to the first quartile of RFM levels, the ORs and 95% CI for incident hypertension in the second, the third, and the fourth quartiles were 1.548 (1.205-1.989), 2.117(1.662-2.698), and 3.137(2.478-3.971) respectively (p for trend < 0.001). After adjusted for age, sex (model 1) and age, sex, smoking, alcohol drinking (model 2), the associations remained significant. In the fully adjusted model considering additional potential confounders including uric acid, eGFR, ALT, TG, TC, HDL-C, LDL-C, and FPG (model 3), the ORs and 95% CI for incident hypertension comparing the second, third, and fourth quartiles to the first quartile of RFM levels were 1.266(0.977-1.640), 1.513(1.172-1.953), and 2.032(1.567-2.634) respectively (p for trend < 0.001).

ROC curves for the incidence of hypertension

In logistic regression analysis, we demonstrated RFM can independently predict the onset of hypertension. Aiming at comparing its predictive power with traditional anthropometric indices and delineating their optimal cut-points, a ROC analysis was conducted (figure 2). In male, there were no significant differences in AUC value of RFMas compared to that of WC and BMI (Bonferroni-adjusted p-value > 0.05). In female, RFM had higher AUC value than that of BMI (Bonferroni-adjusted p-value = 0.047) and comparable value to that of WC (Bonferroni-adjusted p-value > 0.05). In both sexes, there were no significant differences in AUC value of BMI as compared to that of WC (Bonferroni-adjusted p-value > 0.05). All indices had higher AUC value in female than in male (Table 4).

In male population, the optimal cut-off value was 24.67 for RFM, 23.74 for BMI, 82.95 for WC, 0.51 for WHtR. In female population, the optimal cut-off value was 35.73 for RFM, 23.83 for BMI, 77.15 for WC, 0.50 for WHtR. In both sexes, RFM and WHtR had the highest Youden index values for predicting hypertension (Table 5).

Moreover, AUC was calculated for the regression models. The effect of each index of obesity plus other risk factors including age, smoking, alcohol drinking, uric acid, eGFR, ALT, TG, TC, HDL-C, LDL-C, and FPG in predicting hypertension were evaluated. For both male and female population, there were no statistical differences among the AUC values of the four models when compared in a pairwise manner (all Bonferroni-adjusted p-value > 0.05). (Table 6).

Discussion

In our longitudinal study performed in initially non-hypersensitive individuals with 6 years of follow-up, we found an increased risk of incident hypertension across quartiles of RFM after adjusted for several known risk factors, which indicate RFM is an independent and practicable predictor of hypertension in Chinese population.

When considering obesity and hypertension, visceral adiposity mediates the progression from a normotensive to hypertensive. The most robust evidence comes from the Dallas Heart Study, which measure adipose tissue through magnetic resonance imaging scanner, they demonstrated visceral adiposity but not total or subcutaneous adiposity was significantly associated with incident hypertension [27]. Excessive abdominal adiposity can result in adipocyte dysfunction, which was accompanied by abnormal proinflammatory cytokines and adipocytokines secretion and increased free fatty acids in the circulation. These factors can contribute to vascular dysfunction and systemic insulin resistance, and then leading to increased activation of the renin-angiotensin-aldosterone system (RAAS), increased sympathetic nervous system (SNS) activity [28]. Moreover, obesity can cause kidney injury. The compression of the kidneys by fat can induce inflammation and expansion of renal medullary extracellular matrix, inhibit renal tubular reabsorption and increase sodium reabsorption, leading to the development of low estimated GFR and further increases in blood pressure [29]. Thus, indices which can give a precise assessment of fat mass especially visceral adiposity may improve the sensitivity and specificity in detecting individuals with increased cardio-metabolic or hypertension risk.

The aim of developing the RFM algorithm was to better reflect estimates of whole-body fat percentage in clinical and epidemiological practice, it was proved having higher sensitivity and lower rates of misclassification in obesity estimation when compared to BMI in US population by its developers, and then validated better than BMI in Mexican

population [24] [30]. In predicting cardiometabolic risk, RFM also showed excellent performance. RFM had better discrimination power than BMI in identifying diabetes (AUC: 0.80 vs. 0.76 for men and AUC: 0.79 vs 0.73 for women) [24]. In a cohort study, RFM was better than BMI in predicting incident severe liver disease and overall mortality [31]. However, in our study performed in Chinese population, we found although RFM can be an effectively index in predicting hypertension, it was comparable to BMI in men and slightly better than BMI in women in predicting ability. Two reasons can account for this result. Firstly, the outcome in our study was different from other current published cross-sectional or cohort study about RFM, although obesity participate and serve as critical role in the pathophysiological processes of all these outcome diseases, the confounding factors may be different from each other. Secondly, according to a recent study performed in Korean population, RFM tend to overestimated the body fat percentage in their study population, and showed a better linear relationship with body fat percentage than BMI in men only. In ROC analysis, they found RFM was not superior to that of BMI in discriminating obese individuals [32]. As RFM was developed from Mexican-Americans, European-Americans, and African-Americans, and Asian populations tend to have higher body fat percentage than Caucasians at the same BMI level [33]. The efficiency of the RFM algorithm for estimating body fat percentage in Chinese population is unknown and needs further validation study.

RFM and WHtR had the same AUC value in the ROC analysis. The optimal cut-off of WHtR in our study were 0.51 for male and 0.50 for female, similar to the recommendations suggested by various studies to define central obesity (WHtR **>** 0.5), meanwhile, 0.5 had been demonstrated to be a good boundary value for men and women across ethnic groups according to the outcome measures related to diabetes and CVD [34-36]. When the WHtR value was 0.5, the corresponding value for RFM were 24 for men and 36 for women, very close to the optimal cut-off of RFM in our study. Based on these, we can conclude that a high level of consistency existed between the current RFM equation and WHtR, and RFM can be an alternative to WHtR in predicting incident hypertension.

Overall, in our study, the ROC analysis of the single index in predicting incident hypertension revealed that WC or WHtR did not show significant superiority over BMI. Meanwhile the AUCs calculated for the regression models in table 6 further

demonstrated this. Indeed, as BMI does not distinguish fat mass from lean mass and does not reflect fat distribution [37 38], WC and index based on WC may give a better quantity of visceral fat. However, same as our study, some studies reported that no difference between BMI and WC/WHtR with regard to discriminating or predicting hypertension [39-43], and some reported BMI showed a better performance [44 45], which should be explained. Aside from the different methodology (such as ROC analysis, Cox regression, Logistic regression) used to judge the performance, study design (cross-sectional, longitudinal) and covariates taken into consideration, we think two additional factors may explain the inconsistency between studies. Firstly, the morphological characteristics of the study participants, in many circumstances especially in Asian populations, BMI and WC are highly correlated, there were reported studies reveal their ability were comparable in predicting abdominal adipose tissues which were measured by CT scan [46], the high collinearity between BMI and WC-based indices may result in similar predictive power. Second, the inclusion criteria of the study, some studies were conducted in the overall population and did not excluded those with organ dysfunction such as myocardial infarction, heart failure, chronic kidney diseases. These diseases may lead to changes in hemodynamic load and total fluid volume which mediates the presence of hypertension, while BMI are sensitive to these changes and thus can provide information more than adiposity.

Our study has several strengths. First, our study was performed using nationally representative samples of the Chinese adult population, which were recruited from 9 different provinces in China. Second, to our best knowledge, we were the first longitudinal study to investigate whether the current RFM algorithm can be applied in hypertension prediction in Chinese population and compare it predicting power with traditional obesity-related indices. Third, in baseline population, we excluded the individuals with history of myocardial infarction or stroke, as well as those with chronic kidney disease or liver dysfunction, which may affect the association between obesity and hypertension. This ensure the objectivity and accuracy of our research.

There are also limitations of our study. First, we exclude 717 individuals from this study duo to lack of data about the factors we needed to analysis, which may cause selection bias. Second, medical history taking and biomarker measurements were only carried out at the baseline, but these parameters may change over time. For example, lifestyle intervention and pharmacotherapy can result in weight loss and ameliorate metabolic

disorders in some high-risk individuals and reduce the risk of developing hypertension. However, we failed to take these factors into consideration in our study. Third, although the blood pressure was measured in duplicate, white-coat hypertension may exist and affected our judgment of the outcome. Fourth, as the nature of observational study, when investigate about the association between RFM and incident hypertension, it's possible that some unknown or unmeasured factors confounded the association; however, in our logistic analysis, we had adjusted the main confounding factors, we don't think residual confounding will materially alter our conclusion. Fifth, as the participants in our study did not underwent dual-energy X-ray absorptiometry test or other tests which can give an assessment about body component, we couldn't evaluate the performance and accuracy of the RFM algorithm in Chinese population, this hinder the further interpretation of our results.

Conclusion

In conclusion, our study revealed that RFM is a powerful indictor to predict incident hypertension in Chinese population, the optimal cut-off of RFM was 24.67 and 35.73 for men and women respectively, individuals above the cut-off level show higher risk for hypertension and deserves early intervention to prevent it. However, based on the AUC values in ROC analysis, RFM did not show better performance compared to traditional obesity indices.

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Footnotes

Contributors: PY and XFY contributed to the study conception and study design. PY, TH, SLH contributed to the data analysis, interpretation of the data. PY contributed to drafting the manuscript. All authors read and approved the final manuscript.

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Table 1 Baseline characteristics of participates according to follow-up outcomes

	Incident hypertention		
	no (n=2572)	yes (n=834)	p value
Age	45.0(37.0-54.0)	52.0(44.0-59.0)	< 0.001
Men/Women	1144/1428	413/421	0.012
Alcohol consumer (%)	32.9	38.8	0.002
Smoking			0.303
Current smoker (%)	28.7	30.6	
Ex smoker (%)	2.0	2.6	
Non-smoker (%)	69.3	66.8	
Body weight (Kg)	57.7(52.0-65.2)	61.0(54.3-68.9)	< 0.001
BMI (kg/m^2)	22.37(20.50-24.58)	23.80(21.51-26.07)	< 0.001
WC (cm)	80.0(73.0-86.7)	84.0(77.9-90.0)	< 0.001
WHtR	0.50(0.46-0.54)	0.52(0.48-0.56)	< 0.001
RFM	30.18(23.75-36.70)	30.83(24.69-38.62)	< 0.001
SBP (mmHg)	116.0(108.0-121.3)	120.7(114.9-128.7)	< 0.001
DBP (mmHg)	76.7(70.0-80.0)	80.0(75.3-82.0)	< 0.001
eGFR (mL/min/1.73 m^2)	83.2(74.7-93.2)	80.4(72.1-89.7)	< 0.001
Cr (μmol/L)	82.0(74.0-93.0)	83.0(75.0-93.0)	0.394
Uric acid (μmol/L)	276.0(225.0-338.8)	290.0(234.0-353.0)	0.001
ALT (U/L)	18.0(13.0-25.0)	19.0(14.0-28.0)	< 0.001
FPG (mmol/L)	5.00(4.63-5.45)	5.15(4.76-5.64)	< 0.001
TG (mmol/L)	1.13(0.78-1.73)	1.31(0.90-1.92)	< 0.001

TC (mmol/L)	4.63(4.05-5.27)	4.87(4.23-5.51)	< 0.001
HDL-C (mmol/L)	1.40(1.18-1.64)	1.40(1.16-1.64)	0.804
LDL-C (mmol/L)	2.78(2.26-3.38)	2.98(2.42-3.57)	< 0.001

Categorical variables were presented as a number (percentage), continuous variables with a skewed distribution were presented as medians (IQR). P values are for Mann-Whitney U test for or $\chi 2$-test.

BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass; SBP, systolic blood pressure; DBP, diastolic blood pressure, eGFR, estimate glomerular filtration rate; Cr, creatinine; ALT, alamine aminotransferase; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2 Baseline characteristics of participates according to RFM

	Quartile 1 n=853	Quartile 2 n=851	Quartile 3 n=853	Quartile 4 n=849	p value
Age	41.0(32.0-50.0)	45.0(38.0-54.0)	49.0(41.0-57.0)	51.0(42.0-58.0)	< 0.001
Men/Women	387/463	387/456	386/462	384/457	0.999
Alcohol consumer (%)	30.5	34.9	35.9	36.3	0.045
Current smoker (%)	29.5	29.3	29.1	28.9	0.301
Body weight (Kg)	52.5(47.8-57.6)	57.0 (51.7 -63.1)	60.6(55.0-67.3)	66.4(59.1-74.4)	< 0.001
BMI (kg/m^2)	19.96 (18.71-21.21)	21.99 (20.84-23.25)	23.63(22.09-24.92)	26.13(24.12-27.75)	< 0.001
WC (cm)	70.0(67.0-73.0)	78.0(75.0-80.0)	84.0(81.0-87.0)	92.0(88.5-96.5)	< 0.001
WHtR	0.44(0.42-0.45)	0.48(0.47-0.49)	0.52(0.51-0.53)	0.57(0.56-0.60)	< 0.001
SBP (mmHg)	110.7(102.8 -120.0)	117.3(110.0-122.0)	120.0(110.0-125.3)	120.0(112.0-126.7)	< 0.001
DBP (mmHg)	73.3(69.3-80.0)	77.3(70.0-80.7)	79.3(71.3-81.0)	80.0(73.3-82.0)	< 0.001
eGFR (mL/min/1.73 m^2)	86.-5(76.5 -96.2)	81.9 (74.5-92.4)	81.4 (73.3 -90.6)	80.7 (72.2 -89.7)	< 0.001
Cr (μmol/L)	83.0(74.5-93.0)	83.0(75.0-93.0)	82.0(75.0-93.0)	83.0(74.0-93.0)	0.914
Uric acid (μmol/L)	265.0(219.0-324.0)	275.0(222.0-333.0)	279.0(230.0-338.0)	303.0(244.5 -372.0)	< 0.001
ALT (U/L)	15.0(11.0-22.0)	17.0(12.0-24.0)	19.0(14.0-26.0)	22.0(16.0-32.0)	< 0.001
FPG (mmol/L)	4.89(4.53-5.27)	4.95(4.62-5.38)	5.07(4.67-5.53)	5.22(4.84-5.76)	< 0.001
TG (mmol/L)	0.94(0.68-1.28)	1.11(0.77-1.65)	1.25(0.85-1.92)	1.49(1.03-2.46)	< 0.001

TC (mmol/L)	4.40(3.85-4.96)	4.64(4.10-5.34)	4.79(4.17-5.40)	4.91(4.30-5.57)	< 0.001
HDL-C (mmol/L)	1.47(1.28-1.72)	1.45(1.22-1.69)	1.39(1.15-1.61)	1.28(1.09-1.50)	< 0.001
LDL-C (mmol/L)	2.58(2.11-3.14)	2.83(2.29-3.43)	2.91(2.39-3.50)	3.00(2.47-3.61)	< 0.001
Hyperuricemia (%)	5.3	9.8	12.0	17.2	< 0.001*
Dyslipidemia (%)	32.5	49.2	57.6	69.4	< 0.001*
Diabetes (%)	2.8	5.1	6.8	13.0	< 0.001*

Categorical variables were presented as a number (percentage), continuous variables with a skewed distribution were presented as medians (IQR). p values for $\chi 2$-test or Kruskal-Wallis test. *p values for linear trend across quartiles (linear tendency $\chi 2$-test).
BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass; SBP, systolic blood pressure; DBP, diastolic blood pressure, eGFR, estimate glomerular filtration rate; Cr, creatinine; ALT, alamine aminotransferase; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 3 Odds ratios (ORs) and 95% confidence intervals (CI) for incident hypertension according to baseline quartiles of RFM

	Quartile 1 (n=853)	Quartile 2 (n=851)	Quartile 3 (n=853)	Quartile 4 (n=849)	p for trend
Incident hypertention	126	180	229	299	< 0.001
Unadjusted	1	1.548 (1.205-1.989)	2.117(1.662-2.698)	3.137(2.478-3.971)	< 0.001
Model 1	1	1.337 (1.035-1.728)	1.662(1.295-2.133)	2.360(1.849-3.013)	< 0.001
Model 2	1	1.320(1.021-1.707)	1.633(1.272-2.098)	2.321(1.817-2.966)	< 0.001
Model 3	1	1.266(0.977-1.640)	1.513(1.172-1.953)	2.032(1.567-2.634)	< 0.001

Quartiles of RFM for males: 1st Quartile≤20.0, 2nd Quartile = 20.1–23.4, 3rd Quartile =23.5–26.3, 4th quartile≥26.4

Quartiles of RFM for females: 1st Quartile≤33.1, 2nd Quartile= 33.2–36.7, 3rd Quartile = 36.8–39.8, 4th Quartile≥39.9

Model 1: adjusted for age, sex
Model 2: adjusted for age, sex, smoking, alcohol drinking
Model 3: adjusted for age, sex, smoking, alcohol drinking, uric acid, eGFR, ALT, TG, TC, HDL-C, LDL-C, FPG
eGFR, estimate glomerular filtration rate; ALT, alamine aminotransferase; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose.

Table 4 AUCs for each anthropometric index in predicting hypertension

	Men		Women	
	AUC(95%CI)	p value	AUC(95%CI)	p value
RFM	0.597 (0.572-0.621)	< 0.001	0.647(0.625-0.669)	< 0.001
BMI	0.593 (0.568-0.618)	< 0.001	0.615(0.592-0.637)	< 0.001
WC	0.583 (0.558-0.608)	< 0.001	0.644(0.622-0.666)	< 0.001
WHtR	0.597 (0.572-0.621)	< 0.001	0.647(0.625-0.669)	< 0.001

AUC, area under the curve; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass

Table 5 Optimal cutoff points for each anthropometric index in predicting hypertension

	Men				Women			
	Cut off	Sensitivity (%)	Specifity (%)	Youden index	Cut off	Sensitivity (%)	Specifity (%)	Youden index
RFM	24.67	0.51	0.65	0.16	35.73	0.75	0.47	0.22
BMI	23.74	0.48	0.67	0.15	23.83	0.53	0.67	0.20
WC	82.95	0.58	0.56	0.14	77.15	0.76	0.46	0.22
WHtR	0.51	0.51	0.65	0.16	0.50	0.75	0.47	0.22

AUC, area under the curve; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass

Table 6 Performance of different models in predicting incident hypertension

	Men		Women	
	AUC(95%CI)	p value	AUC(95%CI)	p value
RFM+other factors	0.660(0.636-0.684)	< 0.001	0.697 (0.676-0.718)	< 0.001
BMI+other factors	0.667(0.643-0.690)	< 0.001	0.702(0.680-0.723)	< 0.001
WC+other factors	0.660(0.636-0.684)	< 0.001	0.704(0.683-0.725)	< 0.001
WHtR+other factors	0.661(0.637-0.685)	< 0.001	0.698(0.677-0.719)	< 0.001

Other factors including age, smoking, alcohol drinking, uric acid, eGFR, ALT, TG, TC, HDL-C, LDL-C, FPG.
AUC, area under the curve; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass

figure legends

Figure 1 The flow chart of sample selection from the China Health and Nutrition Survey

Figure 2 Receive-operating characteristic curves (ROC) of BMI, WC, WHtR, and RFM for incident hypertension

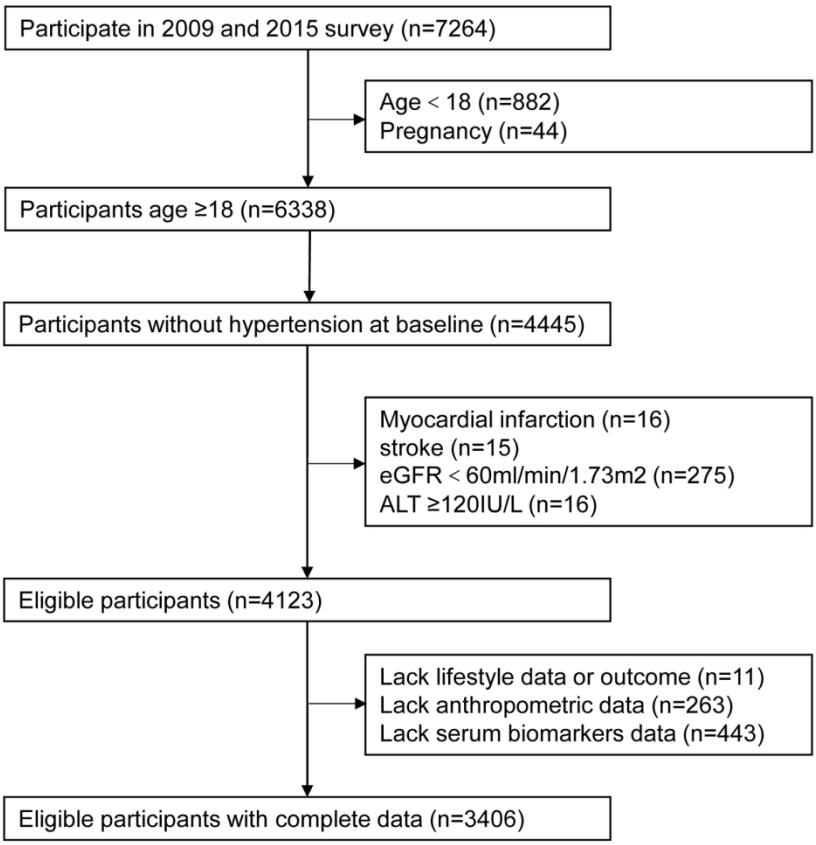

Figure 1 The flow chart of sample selection from the China Health and Nutrition Survey

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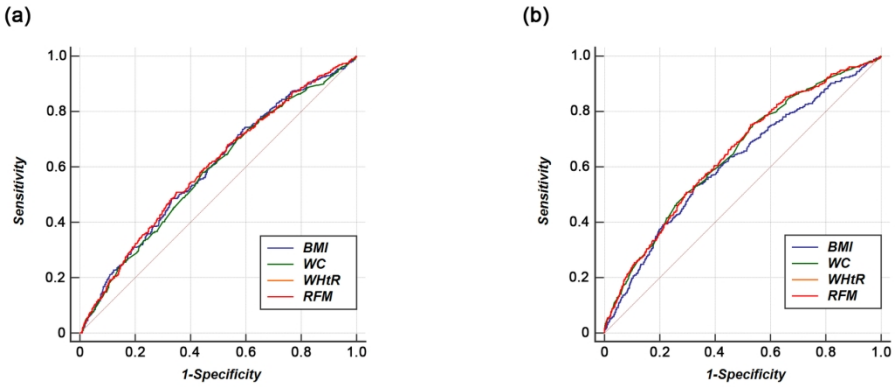

Figure 2 Receive-operating characteristic curves (ROC) of BMI, WC, WHtR, and RFM for incident hypertension

170x75mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	5

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	5
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10,11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Predictive Value of Relative Fat Mass Algorithm for Incident Hypertension: a 6-year Prospective Study in Chinese Population

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Abstract

Objectives Individuals with obesity especially excessive visceral adiposity have high risk for incident hypertension. Recently, a new algorithm named relative fat mass (RFM) was introduced to define obesity. Our aim was to investigate whether it can predict hypertension in Chinese population, and to compare its predictive power with traditional indices including body mass index (BMI), waist circumference (WC), and waist-to-height ratio (WHtR).

Design A 6-year prospective study.

Setting 9 provinces (Hei Long Jiang, Liao Ning, Jiang Su, Shan Dong, He Nan, Hu Bei, Hu Nan, Guang Xi, and Gui Zhou) in China.

Participants Those without hypertension in 2009 survey and respond in 2015 survey.

Intervention Logistic regression were performed to investigate the association between RFM and incident hypertension. Receiver operating characteristic (ROC) analysis was performed to compare the predictive ability of these indices and define their optimal cut-off values.

Main outcome measures Incident hypertension in 2015.

Results The prevalence of incident hypertension in 2015 based on RFM quartiles were 14.8%, 21.2%, 26.8% and 35.2% respectively (p for trend < 0.001). In overall population, the Odd ratio (OR) for the highest quartile compared to the lowest quartile for RFM was 2.032(1.567-2.634) in the fully adjusted model. In ROC analysis, RFM and WHtR had the highest AUC value in both sexes, but did not show statistical significance when compared to AUC value of BMI and WC in male and AUC value of WC in female. The pairwise comparation of AUC values for the prediction models contain each obesity index showed statistical insignificance.

Conclusions RFM can be a powerful indictor for predicting incident hypertension in Chinese population, but it does not show superiority over BMI, WC, and WHtR in predictive power.

Strengths and limitations of this study

- Our study was the first study to reveal whether the newly invented RFM algorithm can independently predict incident hypertension in Chinese population and

compare it predicting power with traditional obesity-related indices.

- We used a nationally representative sample and a prospective design to investigate the predictive power of RFM for incident hypertension.
- Physical examinations and biomarker measurements were only carried out at baseline and the follow-up recordings were lacking in this study.
- We can't validate and evaluate the performance of the RFM algorithm in estimating body fat percentage in our study population, which hinders the further interpretation of our results.

Introduction

During the last three decades, hypertension has been the leading cause for all-cause deaths worldwide [1]. An international survey indicated that the incident rate of hypertension was 40.8% in their multinational study population [2]. In China, 23.2% of adult population had hypertension and another 41.3% were in a pre-hypertension state, however, only 46.9% were aware of the diagnosis and minority were effectively controlled in those who were diagnosed [3]. Statistics present the grim reality, there is no doubt that blood pressure-related morbidity and mortality will exert a huge burden. Thus, despite improvement in hypertension diagnosis and treatment, implementing effective measures to identify people at risk and prevent the incident of hypertension is extremely important.

Obesity is a significant risk factor for hypertension, various studies in different ethnic group has showed this association [4]. For example, the Framingham heart indicated that 34% of hypertension in men and 62% of hypertension in women can be ascribed to overweight and obesity [5]. On the other hand, weight loss intervention can significantly lower the blood pressure and serve as an effective method for the primary prevention of hypertension [6 7]. Currently, when considering the deleterious effect of obesity, excessive intra-abdominal or visceral adipose tissue rather than subcutaneous fat were regarded as the main cause for hypertension and other cardio-metabolic abnormalities [8-11]. Thus, a proper assessment of excessive adiposity (defined as the body fat percentage ≥25% in men and ≥35% in women according to the Western Pacific Regional Office and global World Health Organization reference standards [12]) especially central adiposity can effectively identify those at high risk for hypertension. Body fat mass can be quantified with magnetic resonance imaging (MRI), computed

tomography (CT) and Dual energy X-ray absorptiometry (DXA). However, due to the high cost and limited availability, they are not ideal for large-scale epidemiological screening. In this context, anthropometric indices are widely used to assess body fatness and identifying individuals at risk of cardiometabolic diseases. Currently, there is no consensus about the best anthropometric index in predicting hypertension. Traditional indices such as BMI, WC and WHtR have been applied to assessing the risk of incident hypertension in Chinese population by several studies, and most of them revealed WHtR showed better performance when compared to BMI or WC [13-16] . Moreover, another six adiposity measures including conicity index (CI), lipid accumulation product (LAP), visceral adipose index (VAI), a body shape index (ABSI) and the body adiposity index (BAI) were also used to evaluate the hypertension risk, however, only LAP showed superiority when compared to traditional indices [17-20]; despite this, the equations of these indexes are relatively complex with numerous terms needed. Recently, a simple new algorithm named RFM had been introduced by Woolcott et al. to estimate whole-body fat percentage among adult individuals, they proved it was highly correlated with abdominal obesity and can better predict whole-body fat percentage than BMI, which was validated by dual energy X-ray absorptiometry [21]. Moreover, the main component of RFM equation is height to waist ratio, the converse form of WHtR. Thus, RFM shows great potential in cardiometabolic or hypertension risk assessment. In this study, we performed a 6-year prospective study by using data from the China Health and Nutrition Survey, attempting to investigate whether RFM could be a better anthropometric index for hypertension risk prediction in Chinese population and contribute to the prevention of hypertension.

Method

Study subjects

The China Health and Nutrition Survey (CHNS) is an ongoing open cohort aiming at examining the health and nutritional condition and its influencing factors of the participants. To date, ten rounds of survey (1989, 1991, 1993, 1997, 2000, 2004, 2006, 2009, 2011, 2015) have been conducted. It was co-launched by Carolina Population Center at the University of North Carolina at Chapel Hill and the National Institute for Nutrition and Health at the Chinese Center for Disease Control and Prevention. All participants signed an informed consent form during the survey. The cohort profile

provides detailed information on this survey [22].

Appropriate sample size was calculated using the OpenEpi software program (http://www.openepi.com/SampleSize/SSCohort.htm) before initiate the study. Considering 5% level of significance for a two-sided test, 80% power, unexposed/exposed ratio of 1.3, percent of unexposed with outcome = 15 and percent of exposed with outcome = 33 according to the results from the China hypertension survey [23], the estimated sample size required was at least 198 subjects.

In this study, we conducted a prospective study among people aged more than 18 years by using the data form the 2009 and 2015 CHNS survey. Subjects who participated in both the 2009 and 2015 survey were enrolled in this study, those who didn't have hypertension in 2009 were set as baseline sample, and the presence of incident hypertension in 2015 was defined as the outcome. First, we excluded subjects aged less than 18 or pregnancy, and those who were hypertensive at baseline. Then, those who had history of myocardial infarction or stroke, chronic kidney disease (eGFR < 60 mL/min/1.73 m^2), serve hepatic dysfunction (ALT ≥120 IU/L) were excluded. Last, subjects lack data about smoking, drinking, outcome and anthropometric measurement were excluded. Meanwhile, those who have missing data on biomarkers (n=443) were also excluded. Finally, 3406 participants were included in our study (Fig. 1), thus the sample of this study was sufficient. Compared to those who were included in the study, those who were excluded owing to missing data were slightly younger and there was a slightly higher percentage of males, there were no statistically significant differences between the two groups in BMI, WC, and biochemical parameters at baseline and in the incidence of hypertension at the final follow-up.

Data Collection

Characteristics of the participants including general personal characteristics, smoking status, alcohol consumption, and medical history were obtained by using face to face interview. Current smoker was defined as positive answers to the question "Have you ever smoke? Are you still smoking?". Alcohol consumer was defined as positive answers to "In the past year, have you ever drunk beer, liquor or wine? How often do you consume alcohol?". Each individual's Height and weight were measured by the investigators according to the standard of protocol, height was measured without shoes to the nearest 0.1 cm using a portable stadiometer, body weight was measured with

subjects wearing light clothing without shoes, to the nearest 0.1 kg on a calibrated digital scale, BMI was calculated as weight in kilograms divided by the square of height in meters. When measure waist circumference, the tape was applied horizontally midway between the lower rib margin and the iliac crest. WHtR was waist circumference in centimeters divided by height in centimeters. RFM was calculated by using the followingformula [24]:

$$RFM(male) = 64 - (20 \times (\frac{height(m)}{WC(m)}))$$

$$RFM(female) = 76 - (20 \times (\frac{height(m)}{WC(m)}))$$

Blood pressure was determined in duplicate to improve accuracy, and the average of the values was reported as the final results. For blood collection, participants were asked to fast for 6 to 8 hours. Blood were collected in EDTA-3K anticoagulant tube, then centrifugation at 3000g for 15 min to separate plasma from blood cells. Plasma samples were stored in cryovial at −70 ℃ condition and whole blood samples were stored at 2-8 ℃ condition. Whole blood was used for testing of glycated hemoglobin HbA1c by chromatography. Plasma were tested for alanine aminotransfease (ALT), triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), uric acid, creatinine (Cr), insulin by using automated biochemistry analyzer. ALT was tested by high-performance liquid chromatography method. HDL-C, LDL-C were determined by enzymatic method. TG were determined by CHOD-PAP method and TC were determined by GPO-PAP method. Uric acid was determined by enzymatic colorimetric method. Glucose was determined by GOD-PAP method. Insulin was determined by radioimmunology method. Estimate glomerular filtration rate (eGFR) was calculated by using the CKD-EPI equation [25].

Definitions

Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, or subjects reported been diagnosed or treated with anti-hypertensive drugs. Diabetes was defined as previously diagnosed with diabetes or fasting blood glucose≥7.0mmol/L or HbA1c≥6.5%. Hyperuricemia means serum uric acid > 420μmol/L in men and > 360μmol/L in women. Dyslipidemia was defined as the

presence of any of the following lipid alterations: TG≥1.70mmol/L or TC≥5.18mmol/L or HDL-C < 1.04mmol/L or LDL-C≥3.37mmol/L.

Statistical Analysis

Continuous variables with a non-normal distribution were expressed as median (interquartile range), and categorical variables were expressed as percentages. Differences between groups were tested by Mann-Whitney U test for variables with skewed distributions and $\chi 2$-test for categorical variables. Logistic regression analysis was conducted to examine the association of RFM and incident hypertension. RFM was stratified into four quartiles according to sex- specific cut point, odds ratio (OR) and its 95% confidence interval (CI) were estimated by four models: (a) crude model; (b) adjusted for age, sex; (c) adjusted for age, sex, smoking, alcohol drinking; (d) additionally adjusted for uric acid, eGFR, ALT, TG, TC, HDL-C, LDL-C, FPG. Receiver-operating characteristic curve analyses were conducted to compare the predictive power of RFM with traditional indices including BMI, WC, and WHtR. In ROC analysis, we defined the appropriate cut-off point of each anthropometric index for the prediction of incident hypertension, by using these indices as test variable and hypertension in 2015 as state variable, the optimal cut-off values were determined by the maximizing the Youden index. ROC analysis was also used to evaluate the performance of different models in predicting incident hypertension. The areas under the ROC curve of different indices were compared using the method developed by DeLong et al. [26]. Analyses were performed using Spass version 19.0 and MedCalc v18.2.1. Two-tailed p values of less than 0.05 were considered statistically significant.

Patient and public involvement

There were no patients or public involved in study design, outcome measurement and results interpretation.

Results

Baseline characteristics of participants

There were 3406 eligible participants without hypertension at baseline. Baseline characteristics are shown in Table 1. After 6-years of follow-up, 834 individuals developed hypertension. The incidence was 26.5% for men and 22.8% for women. As

expected, those who developed hypertension showed a more adverse profile on cardiometabolic parameters—higher uric acid, ALT, FPG, TG, TC, LDL-C level and lower eGFR level.

Baseline characteristics of the participants according to RFM quartiles are shown in Table 2. The prevalence of cardiometabolic risk factors such as hyperuricemia, dyslipidemia, and diabetes were increased in proportion to the quartiles of RFM.

Association between RFM and incident hypertension

Table 3 shows the incidence of hypertension according to quartiles of RFM. Participants with high levels of RFM at baseline were more likely to develop hypertension in the following up, as incident cases of hypertension increased as the RFM increased (14.8%, 21.2%, 26.8% and 35.2% in the first, second, third, and fourth quartiles respectively). In unadjusted logistic regression models, compared to the first quartile of RFM levels, the ORs and 95% CI for incident hypertension in the second, the third, and the fourth quartiles were 1.548 (1.205-1.989), 2.117(1.662-2.698), and 3.137(2.478-3.971) respectively (p for trend < 0.001). After adjusted for age, sex (model 1) and age, sex, smoking, alcohol drinking (model 2), the associations remained significant. In the fully adjusted model considering additional potential confounders including uric acid, eGFR, ALT, TG, TC, HDL-C, LDL-C, and FPG (model 3), the ORs and 95% CI for incident hypertension comparing the second, third, and fourth quartiles to the first quartile of RFM levels were 1.266(0.977-1.640), 1.513(1.172-1.953), and 2.032(1.567-2.634) respectively (p for trend < 0.001).

ROC curves for the incidence of hypertension

In logistic regression analysis, we demonstrated RFM can independently predict the onset of hypertension. Aiming at comparing its predictive power with traditional anthropometric indices and delineating their optimal cut-points, a ROC analysis was conducted (figure 2). In male, there were no significant differences in AUC value of RFM as compared to that of WC and BMI (Bonferroni-adjusted p-value > 0.05). In female, RFM had higher AUC value than that of BMI (Bonferroni-adjusted p-value = 0.047) and comparable value to that of WC (Bonferroni-adjusted p-value > 0.05). In both sexes, there were no significant differences in AUC value of BMI as compared to that of WC (Bonferroni-adjusted p-value > 0.05). All indices had higher AUC value in female than in male (Table 4).

In male population, the optimal cut-off value was 24.67 for RFM, 23.74 for BMI, 82.95

for WC, 0.51 for WHtR. In female population, the optimal cut-off value was 35.73 for RFM, 23.83 for BMI, 77.15 for WC, 0.50 for WHtR. In both sexes, RFM and WHtR had the highest Youden index values for predicting hypertension (Table 5).

Moreover, AUC was calculated for the regression models. The effect of each index of obesity plus other risk factors including age, smoking, alcohol drinking, uric acid, eGFR, ALT, TG, TC, HDL-C, LDL-C, and FPG in predicting hypertension were evaluated. For both male and female population, there were no statistical differences among the AUC values of the four models when compared in a pairwise manner (all Bonferroni-adjusted p-value > 0.05). (Table 6).

Discussion

In our longitudinal study performed in initially non-hypersensitive individuals with 6 years of follow-up, we found an increased risk of incident hypertension across quartiles of RFM after adjusted for several known risk factors, which indicate RFM is an independent and practicable predictor of hypertension in Chinese population.

When considering obesity and hypertension, visceral adiposity mediates the progression from a normotensive to hypertensive. The most robust evidence comes from the Dallas Heart Study, which measure adipose tissue through magnetic resonance imaging scanner, they demonstrated visceral adiposity but not total or subcutaneous adiposity was significantly associated with incident hypertension [27]. Excessive abdominal adiposity can result in adipocyte dysfunction, which was accompanied by abnormal proinflammatory cytokines and adipocytokines secretion and increased concentration of circulating free fatty acids. These factors can contribute to vascular dysfunction and systemic insulin resistance, and then leading to increased activation of the renin-angiotensin-aldosterone system (RAAS), increased sympathetic nervous system (SNS) activity [28]. Moreover, obesity can cause kidney injury. The compression of the kidneys by fat can induce inflammation and expansion of renal medullary extracellular matrix, inhibit renal tubular reabsorption and increase sodium reabsorption, leading to the development of low estimated GFR and further increases in blood pressure [29]. Thus, indices which can give a precise assessment of fat mass especially visceral adiposity may improve the sensitivity and specificity in detecting individuals with increased cardio-metabolic or hypertension risk.

The aim of developing the RFM algorithm was to better reflect estimates of whole-body

fat percentage in clinical and epidemiological practice, it was proved to have higher sensitivity and lower rates of misclassification in obesity estimation when compared to BMI in US population by its developers, and had been proved to be better than BMI in Mexican population [24 30]. In predicting cardiometabolic risk, RFM also showed excellent performance. RFM had better discrimination power than BMI in identifying diabetes (AUC: 0.80 vs. 0.76 for men and AUC: 0.79 vs 0.73 for women) [24]. In a cohort study, RFM was better than BMI in predicting incident severe liver disease and overall mortality [31]. However, in our study performed in Chinese population, we found although RFM can be an effectively index in predicting hypertension, it was comparable to BMI in men and slightly better than BMI in women in predicting ability. Two reasons can account for this result. Firstly, the outcome in our study was different from other current published cross-sectional or cohort study about RFM, although obesity participate and serve as critical role in the pathophysiological processes of all these outcome diseases, the confounding factors may be different from each other. Secondly, according to a recent study performed in Korean population, RFM tend to overestimated the body fat percentage in their study population, and showed a better linear relationship with body fat percentage than BMI in men only. In ROC analysis, they found RFM was not superior to that of BMI in discriminating obese individuals [32]. As RFM was developed from Mexican-Americans, European-Americans, and African-Americans, and Asian populations tend to have higher body fat percentage than Caucasians at the same BMI level [33]. The efficiency of the RFM algorithm for estimating body fat percentage in Chinese population is unknown and needs further validation study.

RFM and WHtR had the same AUC value in the ROC analysis. The optimal cut-off of WHtR in our study were 0.51 for male and 0.50 for female, similar to the recommendations suggested by various studies to define central obesity (WHtR **>** 0.5), meanwhile, 0.5 had been demonstrated to be a good boundary value for men and women across ethnic groups in assessing diabetes and CVD risk [34-36]. When the WHtR value was 0.5, the corresponding value for RFM were 24 for men and 36 for women, very close to the optimal cut-off of RFM in our study. Based on these, we can conclude that a high level of consistency existed between the current RFM equation and WHtR, and RFM can be an alternative to WHtR in predicting incident hypertension.

Overall, in our study, the ROC analysis of the single index in predicting incident

hypertension revealed that WC or WHtR did not show significant superiority over BMI. Meanwhile the AUCs calculated for the regression models in table 6 further demonstrated this. Indeed, as BMI does not distinguish fat mass from lean mass and does not reflect fat distribution [37 38], WC and index based on WC may give a better quantity of visceral fat. However, same as our study, some studies reported that no difference between BMI and WC/WHtR with regard to discriminating or predicting hypertension [39-43], and some reported BMI showed a better performance [44 45], which should be explained. Aside from the different methodology (such as ROC analysis, Cox regression, Logistic regression) used to judge the performance, study design (cross-sectional, longitudinal) and covariates taken into consideration, we think two additional factors may explain the inconsistency between studies. Firstly, the morphological characteristics of the study participants, in many circumstances especially in Asian populations, BMI and WC are highly correlated, there were reported studies reveal their ability were comparable in predicting abdominal adipose tissues which were measured by CT scan [46], the high collinearity between BMI and WC-based indices may result in similar predictive power. Second, the inclusion criteria of the study, some studies were conducted in the overall population and did not excluded those with organ dysfunction such as myocardial infarction, heart failure, chronic kidney diseases. These diseases may lead to changes in hemodynamic load and total fluid volume which mediates the presence of hypertension, while BMI are sensitive to these changes and thus can provide information more than adiposity.

Our study has several strengths. First, our study was performed using nationally representative samples of the Chinese adult population, which were recruited from 9 different provinces in China. Second, to our best knowledge, we were the first longitudinal study to investigate whether the current RFM algorithm can be applied in hypertension prediction in Chinese population and compare it predicting power with traditional obesity-related indices. Third, in baseline population, we excluded the individuals with history of myocardial infarction or stroke, as well as those with chronic kidney disease or liver dysfunction, which may affect the association between obesity and hypertension. This ensure the objectivity and accuracy of our research.

There are also limitations of our study. First, we exclude 717 individuals from this study duo to lack of data about the factors we needed in statistical analysis, which may cause selection bias. Second, medical history taking, physical examinations and biomarker

measurements were only carried out at the baseline, but these parameters may change over time. For example, lifestyle intervention and pharmacotherapy can result in weight loss and ameliorate metabolic disorders in some high-risk individuals and reduce the risk of developing hypertension. However, we failed to take these factors into consideration in our study. Third, although the blood pressure was measured in duplicate, white-coat hypertension may exist and affected our judgment of the outcome. Fourth, as the nature of observational study, when investigate about the association between RFM and incident hypertension, it's possible that some unknown or unmeasured factors confounded the association; however, in our logistic analysis, we had adjusted the main confounding factors, we don't think residual confounding will materially alter our conclusion. Fifth, as the participants in our study did not underwent dual-energy X-ray absorptiometry test or other tests which can give an assessment about body component, we couldn't evaluate the performance and accuracy of the RFM algorithm in Chinese population, this hinder the further interpretation of our results.

Conclusion

In conclusion, our study revealed that RFM is a powerful indictor to predict incident hypertension in Chinese population, the optimal cut-off of RFM was 24.67 and 35.73 for men and women respectively, individuals above the cut-off level show higher risk for hypertension and deserves early intervention to prevent it. However, based on the AUC values in ROC analysis, RFM did not show better performance compared to traditional obesity indices.

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Footnotes

Contributors: PY and XFY contributed to the study conception and study design. PY, TH, SLH contributed to the data analysis, interpretation of the data. PY contributed to drafting the manuscript. All authors read and approved the final manuscript.

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Table 1 Baseline characteristics of participates according to follow-up outcomes

	Incident hypertention		
	no (n=2572)	yes (n=834)	p value
Age	45.0(37.0-54.0)	52.0(44.0-59.0)	< 0.001
Men/Women	1144/1428	413/421	0.012
Alcohol consumer (%)	32.9	38.8	0.002
Smoking			0.303
Current smoker (%)	28.7	30.6	
Ex smoker (%)	2.0	2.6	
Non-smoker (%)	69.3	66.8	
Body weight (Kg)	57.7(52.0-65.2)	61.0(54.3-68.9)	< 0.001
BMI (kg/m^2)	22.37(20.50-24.58)	23.80(21.51-26.07)	< 0.001
WC (cm)	80.0(73.0-86.7)	84.0(77.9-90.0)	< 0.001
WHtR	0.50(0.46-0.54)	0.52(0.48-0.56)	< 0.001
RFM	30.18(23.75-36.70)	30.83(24.69-38.62)	< 0.001
SBP (mmHg)	116.0(108.0-121.3)	120.7(114.9-128.7)	< 0.001
DBP (mmHg)	76.7(70.0-80.0)	80.0(75.3-82.0)	< 0.001
eGFR (mL/min/1.73 m^2)	83.2(74.7-93.2)	80.4(72.1-89.7)	< 0.001
Cr (μmol/L)	82.0(74.0-93.0)	83.0(75.0-93.0)	0.394
Uric acid (μmol/L)	276.0(225.0-338.8)	290.0(234.0-353.0)	0.001
ALT (U/L)	18.0(13.0-25.0)	19.0(14.0-28.0)	< 0.001
FPG (mmol/L)	5.00(4.63-5.45)	5.15(4.76-5.64)	< 0.001
TG (mmol/L)	1.13(0.78-1.73)	1.31(0.90-1.92)	< 0.001

TC (mmol/L)	4.63(4.05-5.27)	4.87(4.23-5.51)	< 0.001
HDL-C (mmol/L)	1.40(1.18-1.64)	1.40(1.16-1.64)	0.804
LDL-C (mmol/L)	2.78(2.26-3.38)	2.98(2.42-3.57)	< 0.001

Categorical variables were presented as a number (percentage), continuous variables with a skewed distribution were presented as medians (IQR). P values are for Mann-Whitney U test for or $\chi 2$-test.

BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass; SBP, systolic blood pressure; DBP, diastolic blood pressure, eGFR, estimate glomerular filtration rate; Cr, creatinine; ALT, alamine aminotransferase; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2 Baseline characteristics of participates according to RFM

	Quartile 1 n=853	Quartile 2 n=851	Quartile 3 n=853	Quartile 4 n=849	p value
Age	41.0(32.0-50.0)	45.0(38.0-54.0)	49.0(41.0-57.0)	51.0(42.0-58.0)	< 0.001
Men/Women	387/463	387/456	386/462	384/457	0.999
Alcohol consumer (%)	30.5	34.9	35.9	36.3	0.045
Current smoker (%)	29.5	29.3	29.1	28.9	0.301
Body weight (Kg)	52.5(47.8-57.6)	57.0 (51.7 -63.1)	60.6(55.0-67.3)	66.4(59.1-74.4)	< 0.001
BMI (kg/m^2)	19.96 (18.71-21.21)	21.99 (20.84-23.25)	23.63(22.09-24.92)	26.13(24.12-27.75)	< 0.001
WC (cm)	70.0(67.0-73.0)	78.0(75.0-80.0)	84.0(81.0-87.0)	92.0(88.5-96.5)	< 0.001
WHtR	0.44(0.42-0.45)	0.48(0.47-0.49)	0.52(0.51-0.53)	0.57(0.56-0.60)	< 0.001
SBP (mmHg)	110.7(102.8 -120.0)	117.3(110.0-122.0)	120.0(110.0-125.3)	120.0(112.0-126.7)	< 0.001
DBP (mmHg)	73.3(69.3-80.0)	77.3(70.0-80.7)	79.3(71.3-81.0)	80.0(73.3-82.0)	< 0.001
eGFR (mL/min/1.73 m^2)	86.5(76.5 -96.2)	81.9 (74.5-92.4)	81.4 (73.3 -90.6)	80.7 (72.2 -89.7)	< 0.001
Cr (μmol/L)	83.0(74.5-93.0)	83.0(75.0-93.0)	82.0(75.0-93.0)	83.0(74.0-93.0)	0.914
Uric acid (μmol/L)	265.0(219.0-324.0)	275.0(222.0-333.0)	279.0(230.0-338.0)	303.0(244.5 -372.0)	< 0.001
ALT (U/L)	15.0(11.0-22.0)	17.0(12.0-24.0)	19.0(14.0-26.0)	22.0(16.0-32.0)	< 0.001
FPG (mmol/L)	4.89(4.53-5.27)	4.95(4.62-5.38)	5.07(4.67-5.53)	5.22(4.84-5.76)	< 0.001
TG (mmol/L)	0.94(0.68-1.28)	1.11(0.77-1.65)	1.25(0.85-1.92)	1.49(1.03-2.46)	< 0.001

TC (mmol/L)	4.40(3.85-4.96)	4.64(4.10-5.34)	4.79(4.17-5.40)	4.91(4.30-5.57)	< 0.001
HDL-C (mmol/L)	1.47(1.28-1.72)	1.45(1.22-1.69)	1.39(1.15-1.61)	1.28(1.09-1.50)	< 0.001
LDL-C (mmol/L)	2.58(2.11-3.14)	2.83(2.29-3.43)	2.91(2.39-3.50)	3.00(2.47-3.61)	< 0.001
Hyperuricemia (%)	5.3	9.8	12.0	17.2	< 0.001*
Dyslipidemia (%)	32.5	49.2	57.6	69.4	< 0.001*
Diabetes (%)	2.8	5.1	6.8	13.0	< 0.001*

Categorical variables were presented as a number (percentage), continuous variables with a skewed distribution were presented as medians (IQR). p values are for Kruskal-Wallis test or $\chi 2$-test. *p values for linear trend across quartiles (linear tendency $\chi 2$-test).
BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass; SBP, systolic blood pressure; DBP, diastolic blood pressure, eGFR, estimate glomerular filtration rate; Cr, creatinine; ALT, alamine aminotransferase; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 3 Odds ratios (ORs) and 95% confidence intervals (CI) for incident hypertension according to baseline quartiles of RFM

	Quartile 1 (n=853)	Quartile 2 (n=851)	Quartile 3 (n=853)	Quartile 4 (n=849)	p for trend
Incident hypertention	126	180	229	299	< 0.001
Unadjusted	1	1.548 (1.205-1.989)	2.117(1.662-2.698)	3.137(2.478-3.971)	< 0.001
Model 1	1	1.337 (1.035-1.728)	1.662(1.295-2.133)	2.360(1.849-3.013)	< 0.001
Model 2	1	1.320(1.021-1.707)	1.633(1.272-2.098)	2.321(1.817-2.966)	< 0.001
Model 3	1	1.266(0.977-1.640)	1.513(1.172-1.953)	2.032(1.567-2.634)	< 0.001

Quartiles of RFM for males: 1st Quartile≤20.0, 2nd Quartile = 20.1–23.4, 3rd Quartile =23.5–26.3, 4th quartile≥26.4

Quartiles of RFM for females: 1st Quartile≤33.1, 2nd Quartile= 33.2–36.7, 3rd Quartile = 36.8–39.8, 4th Quartile≥39.9

Model 1: adjusted for age, sex
Model 2: adjusted for age, sex, smoking, alcohol drinking
Model 3: adjusted for age, sex, smoking, alcohol drinking, uric acid, eGFR, ALT, TG, TC, HDL-C, LDL-C, FPG
eGFR, estimate glomerular filtration rate; ALT, alamine aminotransferase; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose.

Table 4 AUCs for each anthropometric index in predicting hypertension

	Men		Women	
	AUC(95%CI)	p value	AUC(95%CI)	p value
RFM	0.597 (0.572-0.621)	< 0.001	0.647(0.625-0.669)	< 0.001
BMI	0.593 (0.568-0.618)	< 0.001	0.615(0.592-0.637)	< 0.001
WC	0.583 (0.558-0.608)	< 0.001	0.644(0.622-0.666)	< 0.001
WHtR	0.597 (0.572-0.621)	< 0.001	0.647(0.625-0.669)	< 0.001

AUC, area under the curve; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass

Table 5 Optimal cutoff points for each anthropometric index in predicting hypertension

	Men				Women			
	Cut off	Sensitivity (%)	Specifity (%)	Youden index	Cut off	Sensitivity (%)	Specifity (%)	Youden index
RFM	24.67	0.51	0.65	0.16	35.73	0.75	0.47	0.22
BMI	23.74	0.48	0.67	0.15	23.83	0.53	0.67	0.20
WC	82.95	0.58	0.56	0.14	77.15	0.76	0.46	0.22
WHtR	0.51	0.51	0.65	0.16	0.50	0.75	0.47	0.22

AUC, area under the curve; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass

Table 6 Performance of different models in predicting incident hypertension

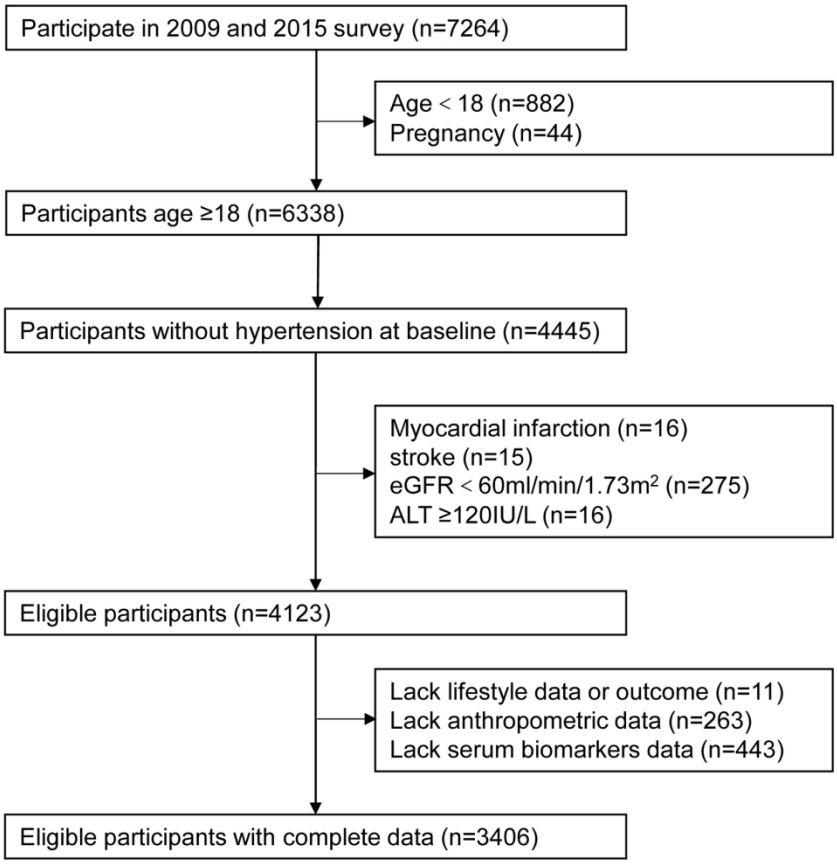
	Men		Women	
	AUC(95%CI)	p value	AUC(95%CI)	p value
RFM+other factors	0.660(0.636-0.684)	< 0.001	0.697 (0.676-0.718)	< 0.001
BMI+other factors	0.667(0.643-0.690)	< 0.001	0.702(0.680-0.723)	< 0.001
WC+other factors	0.660(0.636-0.684)	< 0.001	0.704(0.683-0.725)	< 0.001
WHtR+other factors	0.661(0.637-0.685)	< 0.001	0.698(0.677-0.719)	< 0.001

Other factors including age, smoking, alcohol drinking, uric acid, eGFR, ALT, TG, TC, HDL-C, LDL-C, FPG.
AUC, area under the curve; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass

figure legends

Figure 1 The flow chart of sample selection from the China Health and Nutrition Survey

Figure 2 Receive-operating characteristic curves (ROC) of BMI, WC, WHtR, and RFM for incident hypertension



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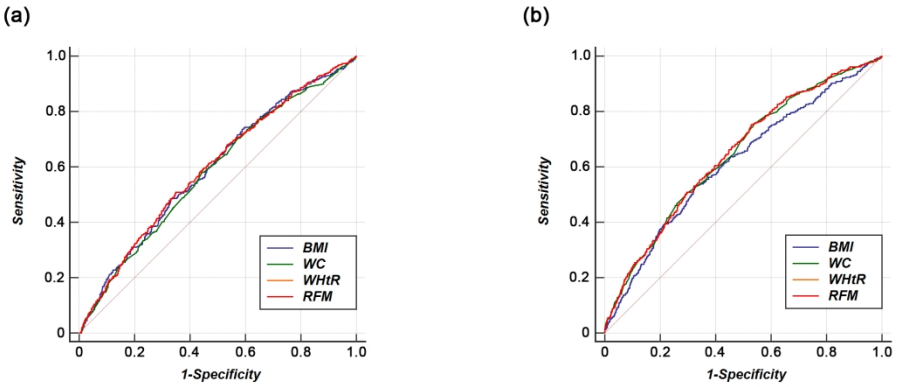

Figure 2 Receive-operating characteristic curves (ROC) of BMI, WC, WHtR, and RFM for incident hypertension

170x75mm (358 x 358 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	5

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	5
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10,11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.