Predicted Fat Mass, Lean Body Mass, and Risk of Hypertension: Results from a Chinese Male Cohort Study

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Abstract

Introduction: Few studies have deciphered whether lean body mass (LBM) or fat mass (FM) is predominantly responsible for the body mass index (BMI)-hypertension association. This study aimed to assess the associations of predicted LBM and FM with hypertension risk among Chinese male adults. Methods: A prospective cohort study was conducted among 2,812 male participants free of hypertension in the Fangchenggang Area Males Health and Examination Survey in 2009. We performed multivariable Cox models and restricted cubic spline to examine the associations of predicted LBM and FM with hypertension, and to further explore the mediating roles of lipid and glycemic traits in the relationship between predicted FM and blood pressure. Results: Of 1,238 participants included in the cohort study, 306 (24.8%) hypertension cases were identified during a median follow-up of 3.8 years, with an incidence rate of 7.0 per 100 person-years. A positive linear-shaped association was consistently observed between BMI and hypertension (p for trend <0.001). Multivariable-adjusted Cox models including predicted LBM and FM observed a positive association between predicted FM and hypertension. Compared with those in the lowest quartile of predicted FM, men in the highest quartile had a hazard ratio (HR) of 1.83 (95% confidence interval (CI): 1.13–2.97) for hypertension. The HR per standard deviation increase of BMI and predicted FM was 1.11 (95% CI: 1.04–1.19) above 23.1 kg/m² and 1.05 (95% CI: 1.02–1.15) above 14.6 kg, respectively. However, predicted LBM was not associated with hypertension. In addition, high-density lipoprotein cholesterol (HDL-c) and fasting blood glucose (FBG) mediated the relationship of predicted FM with systolic blood pressure, with a mediation ratio of 37.1% and 8.2%, respectively. Furthermore, total cholesterol (TC) and triglyceride (TG) positively mediated the association of predicted FM with diastolic blood pressure, with a mediation ratio of 9.5% and 9.9%, respectively. Conclusion: Higher predicted FM might play a central role in the positive linear relationship of the BMI-hypertension association in Chinese male adults, and the link from predicted FM to blood pressure was partially mediated by TC, TG, HDL-c, and FBG.

Keywords
Hypertension · Fat mass · Lean body mass · Body mass index · Mediated analyses
Introduction

Hypertension is the leading contributor to the global burden of cardiovascular disease (CVD), disability, and premature mortality [1]. Hypertension affects more than one billion people globally, and approximately 75% of these people live in low- and middle-income countries. In China, an estimated 23.2% of people ≥18 years of age have hypertension according to a national survey conducted in 2012–2015 [2], and approximately 50% of adults aged 35–75 years have hypertension, but less than one-twelve is in control of their blood pressure [3]. Among several modifiable risk factors for hypertension, increasing epidemiological evidence supports that obesity, assessed by body mass index (BMI), is a critical etiological factor in elevation of risk of hypertension [4, 5]. However, widespread controversy exists regarding the divergent estimates of the J- or U-shaped [6–8] linear association [5, 9] between BMI and blood pressure or hypertension, known as the obesity paradox. Recent studies [10, 11] have also argued that BMI is a crude indicator of obesity for being unable to discriminate between lean body mass (LBM) and fat mass (FM). It is indeed known that body compositions vary markedly in individuals with the same BMI. Therefore, understanding the independent roles of LBM and FM on BMI might have essential implications for interpreting the obesity paradox phenomenon in the BMI-hypertension association.

Previous literature to date has shown inconsistent correlations between body compositions and hypertension risk. It is well recognized that there is a positive association between excess FM and elevated blood pressure levels or hypertension risk in adults [12, 13]. In contrast, some studies debated that high blood pressure levels might be attributed to increased LBM rather than a higher FM [14]. Similarly, inconsistent estimates of LBM-related indices were observed, starting from an unfavorable role in blood pressure levels or hypertension [9, 15] to wholly no or an inverse association [16, 17]. Nevertheless, most of these studies were cross-sectional assessments that had limitations in exploring the causal correlation, focused on mono-factor quantitative impact, could not decipher the effects of LBM and FM on the BMI-hypertension association, or used less accurate surrogate measures (such as skinfold thickness). Thus, it remains elusive as to which of these two components is predominantly responsible for the BMI-hypertension association.

The direct measurement of LBM and FM requires expensive and sophisticated dual-energy X-ray absorptiometry or imaging technologies, making it impractical in extensive cohort studies. The National Health and Nutrition Examination Survey (NHANES) has recently developed and validated anthropometric equations for predicted LBM and FM involving a large US representative sample [18]. The validated equations have been proven to have a high predictive ability for different gender and are extensively used to address the associations of predicted LBM and FM with cardiovascular events and mortality [19, 20]. In this framework, we conducted a post hoc analysis of data from a Chinese male prospective cohort survey to examine the independent contributions of predicted LBM and FM with hypertension using these validated anthropometric equations, and to further explore the indirect effects of predicted FM on blood pressure via lipid and glycemic traits.

Materials and Methods

Study Population

The Fangchenggang Area Males Health and Examination Survey (FAMHES) is a population-based cohort study in Guangxi, China. FAMHES started in 2009, during which 4,303 Chinese men aged 17–88 years completed questionnaires face-to-face, underwent physical examinations, were collected overnight fasting venous blood specimens at baseline, and followed up until December 31, 2013 [21]. In this study, we excluded the participants who met the following criteria at baseline: (1) previously diagnosed as having cancer, CVD, stroke, or diabetes mellitus; (2) having impaired hepatic function (alanine transaminase >2 times upper limit of normal, chronic hepatitis, or liver cirrhosis); (3) having renal disease (creatinine >178 µmol/L); (4) taking any medication for losing weight; (5) without age, ethnicity, blood pressure, and anthropometric results. Next, based on the definition of hypertension, 2,812 men without hypertension at baseline were followed up for 4 years. Furthermore, we excluded participants who had one or more of the following criteria: (1) loss to follow-up or unwillingness to participate; (2) incomplete data. Finally, we included 1,238 eligible participants in the cohort study from 2009 to 2013. The flow chart for selecting participants is presented in online supplementary Figure S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000524653).

Ascertainment of Exposures

We calculated predicted LBM and FM using anthropometric prediction equations developed and validated by the NHANES, which included a large US representative sample of 7,531 men who underwent dual-energy X-ray absorptiometry [18]. The development and validation of the prediction equations have been well-described previously [19, 20], with information on age, race, height, weight, and waist circumference (WC). The prediction equations showed high predictive ability for LBM and FM in men without obvious bias, and detailed equations are depicted in online supplementary Table S1.
Ascertainment of Outcome

Blood pressure was measured twice by well-trained nurses using a validated oscillometric monitor on the right arm positioned at the heart level after the participant had rested for 5 min. The average of two readings was used for the analysis. According to the 2010 Chinese guideline for the management of hypertension [22], hypertension was defined as one of the following conditions: (1) previous diagnosis of hypertension by a doctor and/or the use of antihypertensive medications; (2) systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg.

Ascertainment of Covariates

Detailed information on demographic characteristics (including address, telephone number, birthplace, age, ethnicity, occupation, education, marriage status, and fertility status), lifestyle (namely, smoking and drinking status, dietary habit, physical activity [PA]), disease history, and medications were collected by a face-to-face interview in 2009 and updated every 2 years using biennial questionnaires. Smokers were defined as ≥1 cigarette/day for 6 months or longer. Drinkers were defined as ≥1 time/week for 6 months or longer [21]. PA was classified as sufficient PA (moderate-intensity PA ≥150 min/week or vigorous-intensity PA ≥60 min/week) and insufficient PA [23]. Dietary information included eggs, dairy products, salty food, sweet snacks, and high amount of saturated fatty or fried food. Participants were asked to choose one of five food intake frequencies: eat 5–7 times a week; eat 3–4 times a week; eat 1–2 times a week; eat less than once a week, and do not know. Dietary variety score (DVS) [24] was used to assess the dietary status of the participants, with total scores ranging from 0 to 20. Comprehensive information on DVS is provided in online supplementary Table S2.

Anthropometric measurements were conducted by trained staff using a standard protocol, and the measurements have been well-described previously [25]. BMI was calculated as weight (kg) divided by height squared (m²). According to the Chinese diagnosis criteria [26], underweight was defined as BMI < 18.5 kg/m², healthy weight as 18.5 ≤ BMI ≤ 23.9 kg/m², overweight as 24 ≤ BMI ≤ 27.9 kg/m², and obese as BMI ≥ 28 kg/m². WC was assessed mid-way between the lower rib margin and the iliac. Hip circumference was assessed midway between the higher gluteus maximus and the symphysis pubis. Levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and fasting blood glucose (FBG) were measured at the local hospital laboratory following standard laboratory procedures.

Statistical Analysis

We calculated the person-time of follow-up from the time at which the baseline predicted LBM and FM and BMI was available until the time of diagnosis of hypertension or the end of the study, whichever came first. The baseline characteristics of participants were described as proportions for categorical variables, as mean and standard deviation (SD) with normal distribution, or median and interquartile ranges with abnormal distribution for continuous variables.

We categorized predicted LBM and FM into quartiles, and predefined cut points for BMI (<18.5, 18.5–21.4, 21.5–23.9, 24.0–25.9, 26.0–27.9, and ≥28 kg/m²). For the main analysis, we constructed Cox proportional hazards models using the categorical variables of predicted LBM and FM, and BMI measured at baseline to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) on hypertension. In model 1, we adjusted for age and gender only, in model 2, we adjusted for height because predicted LBM and FM are correlated with height and vary greatly according to different body sizes; other potential confounders included age, ethnicity, FBG, DVS, smoking and drinking status, PA, family history of CVD, or cancer. In model 3, we further mutually adjusted for predicted LBM and FM based on model 2 to better evaluate their independent associations with hypertension. Further, we performed linear trend tests using the median value of each category of predicted LBM and FM as a continuous variable in models 1–3. In addition, we simultaneously entered predicted LBM and FM as continuous variables in model 3 to examine the HRs for hypertension per SD increase in these two components.

To further explore the effects of higher predicted LBM and FM on the higher BMI range, we examined the shape-shifting of the BMI-hypertension association when participants with high predicted LBM or FM (defined as those above the 97.5th, 95th, and 90th centiles of total participants) were excluded. Finally, we conducted restricted cubic spline (RCS) regression to analyze the dose-response associations of predicted LBM and FM with hypertension risk by five knots at the 5th, 27.5th, 50th, 72.5th, and 95th centiles and further explored the HRs of hypertension when the cutoff for each index was at the 50th centiles.

Moreover, we examined the indirect effects of predicted FM (ln-transformed) and blood pressure levels via lipid traits and FBG (ln-transformed) using bias-corrected bootstrapping models with 5,000 resamples while adjusting for potential confounders. Multiple linear regression coefficients were derived from predicted FM to the levels of lipid traits and FBG (a path), levels of lipid traits and FBG to SBP or DBP (b path), and the total effect (c path) and direct effect (c’ path) of predicted FM on SBP or DBP levels. A significant mediating effect was established when both of the bias-corrected bootstrapping confidence interval (BCCI) for a and b paths did not contain zero. The mediation ratio was explained by the contribution of the mediation on the total effect, which was calculated as (indirect effect/total effect) × 100. We used SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) and R4.0.2 for all analyses, and p < 0.05 (two-tailed) was considered statistically significant.

Results

Baseline Characteristics of Participants

Table 1 presents the baseline characteristics of the participants according to BMI categories. Of 1,238 eligible male participants included in the cohort study from 2009 to 2013, we identified 306 incident hypertension cases during 4,382.8 person-years of follow-up (median 3.8 years), with an incidence rate of 7.0 per 100 person-years. The average age of the participants was 38.7 years (range from 20 to 79 years), the average BMI was 23.1 kg/m², and the mean DVS was 12.4. Most of them were of Han ethnicity (79.6%), 53.4% were smokers, 48.5% were drinkers, 19.6% reported having sufficient PA, and the proportion with a family history of CVD and cancer were 3.8% and...
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2.0%, respectively. Predicted LBM and FM, and other obesity-related traits such as WC, hip circumference, SBP, DBP, TC, TG, LDL-c, and FBG increased gradually with higher BMI categories, whereas an opposite trend was observed in HDL-c (all \( p < 0.05 \)).

**Dose-Response Effects of Predicted LBM or FM on Hypertension**

Table 2 demonstrates the associations of predicted LBM and FM with hypertension. The multivariable-adjusted Cox proportion hazards model indicated that predicted FM was positively associated with hypertension, and the risk increased with each higher quartile (\( p \) for trend = 0.008, model 3). Compared with participants in the first quartile of predicted FM, those in the fourth quartile had an HR of 1.83 (95% CI: 1.13–2.97, model 3) for hypertension. Our study also revealed that the risk of hypertension increased among those with higher predicted LBM quartiles after adjusting for potential confounders (\( p \) for trend <0.001, model 2). However, the significant association disappeared when adjusting for the influence of predicted FM (HR: 1.58, 95% CI: 0.93–2.69; \( p \) for trend = 0.078; model 3). When we used predicted FM and LBM as a continuous covariate in the fully adjusted model 3, the increased risk of hypertension for a 1-SD increase in predicted FM and LBM were 1.07 (95% CI: 1.03–1.11) and 1.01 (95% CI: 0.96–1.06), respectively. Additionally, we found that men with a higher predicted LBM invariably had a higher FM or vice versa.

In the restricted cubic spline regression analysis, we still observed a positive linear relationship between predicted FM and hypertension in men (\( p \) for trend = 0.016, \( p \) for nonlinearity = 0.809); the curve increased rapidly when predicted FM was greater than 14.6 kg (Fig. 1a). Above 14.6 kg, the HR per SD increase in predicted FM was 1.05 (95% CI: 1.02–1.15), and the average BMI for men with 14.6 kg of predicted FM was 23.1 kg/m\(^2\). However, the association between predicted LBM and hypertension remained nonsignificant (\( p \) for overall = 0.982, \( p \) for nonlinearity = 0.961, Fig. 1b).

**Table 1. Baseline characteristics of study participants according to Chinese BMI categories**

| Characteristics\(^*\) | Overall \( n = 1,238 \) | Underweight \(<18.5 \text{ kg/m}^2\) \( n = 64 \) | Healthy weight \(18.5–23.9 \text{ kg/m}^2\) \( n = 708 \) | Overweight \(24.0–27.9 \text{ kg/m}^2\) \( n = 388 \) | Obese \(\geq 28.0 \text{ kg/m}^2\) \( n = 78 \) | \( p \) value |
|------------------------|-----------------------------|---------------------------------|---------------------------------|---------------------------------|-----------------------------|-----------------------------|
| Person-years (median, interquartile ranges) | 3.8 (3.7, 3.9) | 3.8 (3.7, 3.8) | 3.8 (3.7, 3.8) | 3.8 (3.7, 3.9) | 3.8 (3.8, 3.9) | 0.651 |
| Age, years | 38.7 (11.1) | 34.4 (13.1) | 38.7 (11.8) | 39.0 (9.3) | 40.7 (10.1) | 0.007 |
| Han ethnicity, % | 79.6 | 82.8 | 81.5 | 76.0 | 76.9 | <0.001 |
| BMI, \( \text{kg/m}^2 \) | 23.1 (3.1) | 17.7 (0.6) | 21.5 (1.5) | 25.6 (1.1) | 29.7 (1.6) | <0.001 |
| WC, cm | 80.5 (8.6) | 67.0 (3.6) | 76.5 (5.8) | 86.9 (4.6) | 95.4 (5.2) | <0.001 |
| HC, cm | 91.4 (6.1) | 82.0 (3.0) | 88.9 (4.1) | 95.4 (3.8) | 101.6 (5.9) | <0.001 |
| Predicted FM, kg | 14.6 (5.3) | 6.0 (1.7) | 12.0 (3.2) | 18.7 (2.4) | 24.7 (3.2) | <0.001 |
| Predicted LBM, kg | 49.1 (5.1) | 42.5 (2.5) | 47.1 (3.6) | 52.2 (3.8) | 57.8 (4.9) | <0.001 |
| SBP, mmHg | 74.5 (7.4) | 71.4 (7.7) | 73.7 (7.4) | 75.9 (6.9) | 77.4 (6.8) | <0.001 |
| TC, mmol/L | 5.7 (1.0) | 5.3 (0.9) | 5.6 (1.0) | 5.9 (1.0) | 6.1 (1.1) | <0.001 |
| TG, mmol/L | 1.4 (1.1) | 0.9 (0.3) | 1.2 (0.7) | 1.8 (1.4) | 2.3 (1.8) | <0.001 |
| HDL-c, mmol/L | 1.4 (0.3) | 1.6 (0.3) | 1.5 (0.3) | 1.3 (0.3) | 1.2 (0.2) | <0.001 |
| LDL-c, mmol/L | 2.9 (0.8) | 2.6 (0.6) | 2.8 (0.8) | 3.2 (0.8) | 3.4 (0.9) | <0.001 |
| FBG, mmol/L | 5.2 (0.5) | 5.1 (0.5) | 5.1 (0.5) | 5.2 (0.6) | 5.4 (0.5) | <0.001 |
| DVS | 12.4 (2.3) | 12.2 (2.6) | 12.4 (2.3) | 12.5 (2.4) | 12.0 (2.2) | 0.230 |
| Smokers, % | 53.4 | 59.4 | 53.0 | 51.3 | 62.8 | 0.217 |
| Drinkers, % | 48.5 | 34.4 | 47.5 | 51.3 | 56.4 | 0.035 |
| Sufficient PA, % | 19.6 | 9.4 | 16.7 | 25.5 | 25.6 | <0.001 |
| Family history of CVD, % | 3.8 | 4.7 | 3.5 | 3.6 | 6.4 | 0.621 |
| Family history of cancer, % | 2.0 | 0.0 | 2.7 | 1.3 | 1.3 | 0.245 |

\( SD \), standard deviation; BMI, body mass index; WC, waist circumference; HC, hip circumference; FM, fat mass; LBM, lean body mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FBG, fasting blood glucose; DVS, dietary variety score; PA, physical activity; CVD, cardiovascular disease. \(^*\)Indicates values are presented as mean (SD) unless stated otherwise.
Dose-Response Effects of BMI on Hypertension

When we analyzed BMI alone, a positive linear association was consistently observed between BMI and hypertension (model 2 in Table 3; Fig. 1c). Above 23.1 kg/m², the HR per SD increase in BMI was 1.11 (95% CI: 1.04–1.19). Due to the fact that both predicted LBM and FM increased invariably among those with a higher BMI range (online suppl. Table S3), we further examined their effects on BMI after excluding participants with high predicted LBM or FM. The linear and positive BMI-hypertension association still existed when we excluded participants above the 97.5th centiles of predicted LBM or FM. After exclusion of more participants above the 95th centiles of predicted LBM or the 90th centiles of predicted FM, the BMI-hypertension association lost significance in the highest BMI range (≥28 kg/m²). However, the risk of hypertension still increased with each higher BMI range (both \( p \) for trend <0.001). Detailed information is depicted in Table 3 and online supplementary Table S4.

Mediators of Predicted FM and Blood Pressure

As the results from mediation analysis shown in Table 4, HDL-c negatively mediated the association between predicted FM and SBP levels (\( \beta = -0.036, 95\% \) BCCI: −0.064 to −0.010), with a mediation ratio of 37.1%; while FBG had a positive mediation effect (\( \beta = 0.008, 95\% \) BCCI: 0.001–0.021), with a mediation ratio of 8.2%. Furthermore, TC (\( \beta = 0.024, 95\% \) BCCI: 0.007–0.044) and TG (\( \beta = 0.025, 95\% \) BCCI: 0.001–0.048) positively mediated the association between predicted FM and DBP levels, with a mediation ratio of 9.5% and 9.9%, respectively.

Discussion

Our prospective cohort study of Chinese male adults found a positive linear association between predicted FM and hypertension, suggesting that participants with higher FM had an elevated risk of developing hypertension than those with less FM. Furthermore, the effects of predicted FM on blood pressure may be partially mediated by TC, TG, HDL-c, and FBG levels. Although there was a linear trend, showing that high predicted LBM was positively correlated with hypertension, the association lost statistical significance when we took predicted FM into consideration based on other potential confounders.

LBM is mainly derived from skeletal muscles and has been widely believed to be protective against cardiometabolic diseases [27], all-cause mortality or longevity [28],

Table 2. HRs of hypertension according to predicted FM and LBM in study participants (FAMHS cohort study, 2009–2013)

| Variables | Predicted LBM, kg, mean (SD) | Predicted FM, kg, mean (SD) | BMI, kg/m², mean (SD) | Events, n | Incidence rate, % | HR (95% CI) |
|-----------|-----------------------------|----------------------------|----------------------|-----------|------------------|-------------|
|           | model 1*                    | model 2#                   | model 3&              |
| Quartile of predicted FM, kg |                             |                           |                      |           |                  |             |
| Q1 (<10.4) | 44.6 (3.0)                  | 8.0 (1.7)                  | 19.6 (1.3)           | 52        | 4.9              | 1.00 (reference) |
| Q2 (10.4–14.5) | 47.3 (3.3)             | 12.5 (1.2)                 | 22.1 (1.3)           | 75        | 6.1              | 1.21 (0.85–1.73) |
| Q3 (14.6–18.2) | 50.2 (3.3)               | 16.1 (1.3)                 | 24.0 (1.2)           | 95        | 7.5              | 1.43 (1.01–2.01) |
| Q4 (≥18.3) | 54.4 (4.5)                  | 21.4 (2.9)                 | 26.9 (2.1)           | 122       | 10.6             | 2.61 (1.82–3.75) |
| p for trend | <0.001                     | <0.001                     | 0.078                |
| Quartile of predicted LBM, kg |                             |                           |                      |           |                  |             |
| Q1 (<45.4) | 43.1 (1.8)                  | 9.7 (3.3)                  | 12.8 (3.4)           | 52        | 4.1              | 1.00 (reference) |
| Q2 (45.4–48.6) | 47.1 (1.0)             | 12.8 (3.4)                 | 15.7 (3.4)           | 75        | 6.1              | 2.23 (1.45–3.41) |
| Q3 (48.7–52.3) | 50.4 (3.3)               | 15.7 (3.4)                 | 23.8 (3.2)           | 95        | 7.5              | 2.34 (1.41–3.84) |
| Q4 (≥52.4) | 55.9 (3.9)                  | 20.1 (4.0)                 | 26.3 (2.4)           | 112       | 10.6             | 2.56 (1.72–3.83) |
| p for trend | <0.001                     | <0.001                     | <0.001               |
frailty, and physical dysfunction in the elderly [29]. Several possible mechanisms for these positive effects are related to better insulin sensitivity or glucose metabolism, and a reliable protein reserve [28, 30]. However, recent studies have shown that LBM could cause detrimental effects on blood pressure or hypertension in some populations. For example, a systematic review [14] found that higher muscle mass contributed toward more elevated blood pressure among American football players later in life when compared to those who were not athletes. Likewise, Ye et al. [13] indicated that different indices of total skeletal muscle, especially the arm LBM, are the risk determinants for elevated blood pressure, prehypertension, and hypertension in Chinese adults after adjusting for potential confounders. Similar findings were also observed in postmenopausal women [15] and children [12]. Potential mechanisms point to the muscle composition and muscle pressor reflexes [31], increased left ventricular hypertrophy and carotid intima-media thickness [32], and active sympathetic nervous system when accepting resistant skeletal muscle training [33]. Contrary to most of these findings that did not adjust for the dependent relationship between LBM and FM, our study found that predicted LBM is not an independent predictor of developing hypertension when the models mutually control for predicted FM. These inconsistent estimates might be caused by different statistical methods and study populations, potential confounders, or reverse causation biases.

Our findings on predicted FM were in accordance with previous evidence [12, 13, 18], whereby we found a positive linear-shaped association with risk of hypertension even after adjusting for predicted LBM in the models. Adipose tissue is not merely a fat storehouse but also functions as an endocrine organ to synthesize and release var-

**Fig. 1.** Dose-response relationships of body compositions and BMI with hypertension risk in men. Restricted cubic spline regression was conducted to analyze the dose-response relationships of FM (a), LBM (b), and BMI (c) with hypertension risk after adjusting for confounders in Table 2. For graphs (a, b), predicted FM and LBM were mutually adjusted. Reference point is the lowest value with the knots placed at 5th, 27.5th, 50th, 72.5th, and 95th centiles. The red line and red shadow represent HR and 95% CI, respectively.
### Table 3. HRs (95% CI) of hypertension according to BMI in study participants (exclusion of high predicted FM)

| BMI category | Events, n | Incidence rate, % | HR (95% CI) model 1* | HR (95% CI) model 2# | HR (95% CI) model 3& | HR (95% CI) model 4ѱ | HR (95% CI) model 5ζ |
|--------------|----------|------------------|----------------------|----------------------|---------------------|---------------------|---------------------|
| <18.5 kg/m²  | 6        | 2.5              | 0.64 (0.28–1.49)     | 0.62 (0.27–1.45)     | 0.63 (0.27–1.47)   | 0.63 (0.27–1.50)    | 0.62 (0.27–1.44)    |
| 18.5–21.4 kg/m² | 56    | 4.5              | 1.00 (reference)     | 1.00 (reference)     | 1.00 (reference)   | 1.00 (reference)    | 1.00 (reference)    |
| 21.5–23.9 kg/m² | 82    | 6.3              | 1.37 (0.97–1.92)     | 1.22 (0.87–1.72)     | 1.22 (0.87–1.72)   | 1.22 (0.87–1.72)    | 1.20 (0.85–1.69)    |
| 24.0–25.9 kg/m² | 78    | 8.9              | 1.86 (1.32–2.63)     | 1.73 (1.22–2.44)     | 1.72 (1.21–2.44)   | 1.71 (1.20–2.42)    | 1.72 (1.20–2.46)    |
| 26.0–27.9 kg/m² | 50    | 11.0             | 2.27 (1.55–3.33)     | 2.23 (1.51–3.28)     | 2.21 (1.50–3.27)   | 2.36 (1.59–3.49)    | 2.46 (1.55–3.92)    |
| ≥28 kg/m²     | 34      | 13.4             | 3.11 (2.03–4.76)     | 2.45 (1.59–3.78)     | 2.14 (1.28–3.58)   | 3.07 (1.70–5.56)    | 0.00 (0.00 to ∞)    |

| p for trend   | <0.001  | <0.001           | <0.001               | <0.001               | <0.001             | <0.001             | <0.001             |

BMI, body mass index; FM, fat mass; HR, hazard ratio; CI, confidence interval. * Unadjusted. # Adjusted for age, ethnicity (Han or non-Han), fasting blood glucose, dietary variety score, smokers (yes or no), drinkers (yes or no), physical activity (insufficient or sufficient), family history of cardiovascular disease (yes or no), family history of cancer (yes or no). & Based on model 2, additionally exclude participants with predicted fat mass above 97.5th centiles. ѱ Based on model 2, additionally exclude participants with predicted fat mass above 95th centiles. ζ Based on model 2, additionally exclude participants with predicted fat mass above 90th centiles.

### Table 4. Mediation analyses of predicted fat mass on SBP/DBP levels via lipid traits and FBG

| Path                  | Indirect effect# | Direct effect& | Total effect& | Mediation ratio, % |
|-----------------------|------------------|----------------|---------------|---------------------|
| FM-TC-SBP             | 0.012 (−0.003 to 0.030) | 0.085 (0.003–0.170) | 0.097 (0.014–0.180) | −37.1 |
| FM-TG-SBP             | 0.015 (−0.009 to 0.039) | 0.082 (−0.005 to 0.169) | 0.097 (0.014–0.180) | 8.2 |
| FM-HDL-c-SBP          | −0.036 (−0.064 to −0.010) | 0.132 (0.045–0.022) | 0.097 (0.014–0.180) | 9.5 |
| FM-LDL-c-SBP          | 0.010 (−0.012 to 0.032) | 0.087 (0.001–0.173) | 0.097 (0.014–0.180) | 9.9 |
| FM-FBG-SBP            | 0.008 (0.001–0.021) | 0.089 (0.005–0.172) | 0.097 (0.014–0.180) | 37.1 |
| FM-TC-DBP             | 0.024 (0.007–0.044) | 0.229 (0.137–0.322) | 0.252 (0.161–0.344) | −37.1 |
| FM-TG-DBP             | 0.025 (0.001–0.048) | 0.228 (0.133–0.323) | 0.252 (0.161–0.344) | 8.2 |
| FM-HDL-c-DBP          | −0.026 (−0.058 to 0.043) | 0.278 (0.102–0.347) | 0.252 (0.161–0.344) | 9.5 |
| FM-LDL-c-DBP          | 0.022 (−0.001 to 0.045) | 0.231 (0.137–0.325) | 0.252 (0.161–0.344) | 9.9 |
| FM-FBG-DBP            | 0.004 (−0.002 to 0.015) | 0.249 (0.157–0.340) | 0.252 (0.161–0.344) | −37.1 |

FM, fat mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FBG, fasting blood glucose. *Mediating effect models were constructed with predicted fat mass (ln-transformed) as predictors, SBP/DBP (ln-transformed) as dependent variable, and metabolic traits (ln-transformed) as mediators adjusted for age, ethnicity, predicted lean body mass, dietary variety score, smoking status, drinking status, physical activity, family history of cardiovascular disease, family history of cancer. # Indirect effects were showed as beta coefficients and bias corrected 95% confidence intervals (95% BCCIs). & Direct and total effects were showed as beta coefficients (95% confidence intervals). ¤Mediation ratio was calculated as (indirect effect/total effect) × 100.
ious cytokines and hormones, such as tumor necrosis factor-α, interleukin-6, C-reactive protein, leptin, adiponectin, and nonesterified fatty acids [34, 35]. Therefore, the links between excessive FM and hypertension are thought to be caused by an increase in low-grade inflammation, endothelial dysfunction, metabolic dysregulation, and free fatty acid circulation [36]. Besides, our study observed that predicted FM tended to increase in men with higher predicted LBM, and the average predicted FM of those with the lowest to the highest quartiles of predicted LBM ranged from 9.7 to 20.2 kg. These findings could further strengthen the central role of FM in the elevated risk of developing hypertension. Moreover, our findings revealed that the effects of predicted FM on SBP or DBP levels could be positively mediated by TG, TC, and FBG levels, while HDL-c levels negatively mediated the increased association between predicted FM and SBP levels, with the maximum mediation ratio. High concentrations of HDL-c are indeed considered antiatherogenic in healthy individuals because it stimulates endothelial nitric oxide production and reduces endothelial reactive oxygen species production [37, 38].

Consistent with previous literature [4, 5, 9], our findings supported a positive linear relationship between BMI and hypertension even after controlling for age, smoking, drinking, PA, and baseline diseases. To some extent, our study might shed new light on the linear-shaped association between BMI and hypertension when the shape of predicted LBM and FM and hypertension risk are taken together. The lower risk of hypertension among men in the lower BMI range (<24 kg/m²) is thought to be due to the protective effects of high predicted LBM that mediated the weak detrimental effects of predicted FM. As BMI increased up to 24–27.9 kg/m², the elevated hypertension risk is mainly attributed to the adverse effects of the increase in predicted FM. Lastly, we inferred that the high-risk combination associated with both predicted LBM and FM may have resulted in the markedly elevated risk of hypertension among those at the high end of BMI range (≥28 kg/m²). Indeed, our data showed that men with a higher BMI range are also characterized by an increase in predicted LBM and FM. Their impacts on the BMI-hypertension association were further confirmed after removing more participants at the higher levels of predicted LBM or FM, which led to the loss of the BMI-hypertension association at the high end of BMI eventually. Overall, our findings highlighted that both average body weight and healthy body compositions (such as healthy LBM or FM) are of equal importance in addressing the obesity paradox for hypertension. Promoting lifestyle interventions that target nutritional body compositions (e.g., healthy diet and regular exercise) is the next step to lower the incidence of hypertension. Of note, different from the WHO recommendations, our findings support the Chinese recommendations of maintaining an average body weight, defined by a BMI of 18.5–23.9 kg/m², for the prevention of hypertension among men and further suggested that the highest hypertension risk could be observed in obese people with BMI equal or greater than 28 kg/m².

The main strengths of our study are that the FAMHES was a well-established cohort study with repeated measures on physical examination, and detailed information on lifestyle and health status, which were updated every 2 years. These strengths allow us to adequately control confounders and improve the credibility of the results. Nevertheless, some inevitable limitations should be highlighted. First, the generalizability of our findings may be restricted with respect to children, females, or other races that exhibit different body sizes as the study participants were Chinese male adults. However, we believe that our main findings would provide an essential clue for broad populations. Second, we estimated the predicted LBM and FM using the anthropometric prediction equations developed and validated by the NHANES for a large US population sample, which may not be an ideal representation of the actual measurements. In fact, the predicted equations have been proven to have a high predictive ability for FM and LBM ($R^2 > 0.9$) and are extensively used to settle CVD and mortality [19, 20]. Besides, the correlations of predicted LBM or FM with other obesity-related biomarkers (e.g., TC, TG, LDL-c, HDL-c, and FBG) in our studies were similar to the original data of the NHANES (data not shown). Third, it is believed that the location of fat accumulation varies widely among individuals and has different effects on health. Although our present study could not address the associations between the distribution of body fat and hypertension due to the limited data, our findings pointed out the central role of FM in the BMI-hypertension association, which is helpful to provide a scientific basis for further research regarding the locations of fat accumulation and hypertension risk. Lastly, our study had a relatively short follow-up period and small sample size, resulting in only a few participants being defined as underweight or obese according to BMI categories. Nevertheless, we could partly minimize potential confounders due to the homogeneity of the study participants and comprehensive data on the risk factors.
Conclusions

In conclusion, our study supported that an increase in predicted FM, but not predicted LBM, plays a central role in the BMI-hypertension association in Chinese male adults, and the effects of predicted FM on blood pressure may be partially mediated by TC, TG, HDL-c, and FBG levels. Larger sample size and long-term follow-up longitudinal studies among broad populations are warranted to confirm our findings.

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Statement of Ethics

All subjects provided written informed consents, and the study was approved by the Ethics and Human Subject Committee of Guangxi Medical University, China, approval number is 2008 (KY-004).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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