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ORIGINAL RESEARCH

U-Shaped Association of Body Mass Index with the Risk of Peripheral Arterial Disease in Chinese Hypertensive Population

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Background: High body mass index (BMI) is a well-recognized risk factor for cardiovascular diseases. But its role in peripheral artery disease (PAD) remains perplexing. Our study aims to evaluate the association of BMI with PAD in the Chinese hypertensive population.

Methods: This is a cross-sectional study with enrollment data from the Chinese H-type Hypertension Registry.10896 hypertensive patients aged ≥18 years were included in the final analysis.

Results: The prevalence of PAD diagnosed by ABI in this study was 3.2% (n=351). A U-shaped association between BMI and PAD was found. Per SD increment (3.6 kg/m^2) on the left side of the BMI threshold (BMI < 25.7 kg/m^2) was associated with a 27% decrease in the adjusted risk of PAD [OR, 0.73; 95% confidence interval (CI) 0.60, 0.89; P=0.002]; BMI was significantly positively associated with the risk of PAD (OR, 1.52; 95% CI 1.52, 1.93; P=0.001) in those with BMI ≥25.7 kg/m^2.

Conclusion: In summary, a U-shaped association between BMI and the risk of PAD in the Chinese hypertensive population was found. BMI with the lowest risk of PAD was estimated to be 25.7 kg/m^2.

Keywords: peripheral arterial disease, body mass index, hypertension

Introduction

Peripheral arterial disease (PAD) is the third leading atherosclerotic disease after coronary heart disease and stroke,[1] mainly caused by the accumulation of lipid and fibrous material between the intima and media of lower limb arteries, resulting in luminal stenosis (focal or diffuse). It is well known for a sharp increase in the prevalence of PAD with advanced age.[2,3] With the aging of the Chinese population, PAD has become an increasingly severe clinical and social problem. Allison et al also showed ethnic differences were independent factors in the prevalence of PAD.[4] Compared to Whites, Blacks seem to be more vulnerable to PAD, while Asians seem to have a lower prevalence of PAD.[5]

The prevalence of PAD was higher in people with underweight, but the association between BMI and PAD was uncertain due to a variety of potential covariates.[6,7] A small prospective cohort study showed that obesity independently predicts severe PAD.[8] However, the recent observational study with more than 3 million sample size has found J-shaped relationship between BMI and PAD only in females.[9] Epidemiology of Dementia in Central Africa (EPIDEMCA) study recruited the elderly in the Central African Republic and the Republic of Congo, showed underweight and obesity were all associated with the risk of PAD.[10]

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Due to the inconsistent and the evidence of association between BMI and prevalence of PAD in the Chinese was still lacked. Our study aims to explore the association between BMI and the risk of PAD in Chinese hypertensive patients.

Methods

Study Design and Participants

The study population was drawn from the China Hypertension Registry (Registration number: ChiCTR1800017274), a real-world observational registry of hypertension designed to investigate the prevalence and treatment of hypertension in China and to assess prognostic risk factors. Details of the inclusion and exclusion criteria for the study have been published.[11] From March 2018 to August 2018, we recruited a total of 14,268 study participants in Wuyuan, Jiangxi Province, China as our study population, and finally analyzed the data of 10,802.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University (No. CH1059). All patients signed informed written consent before enrollment in this study.

Laboratory Biochemical Examination

All subjects were asked to do an overnight fast Venous blood samples were obtained from all study participants and analyzed by Biaojia Biotechnology Laboratory in Shenzhen, China. Lipids (including total cholesterol (TC, mmol/L), triglycerides (TG, mmol/L), high-density lipoprotein-cholesterol (HDL-C, mmol/L), low-density lipoprotein cholesterol (LDL-C, mmol/L)),[12,13] estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2), fasting blood glucose (FBG, mmol/L) and homocysteine (Hcy, μmol/L) were measured using automatic clinical analyzers (Beckman Coulter, USA) and the laboratory staff were blind to the research protocol.

Measurement of BMI

The height and weight of the subjects were measured by trained staff using standardized equipment in accordance with standard operation procedure. BMI = Weight (kg)/Height $(m)^2$.

Measurement of ABI and Definition of PAD

The ABI of each lower limb was calculated by dividing the systolic pressure of the ankle artery of the corresponding lower limb by the systolic pressure of the brachial artery. Subjects rested quietly in a warm room for more than 10 minutes and fully exposed their upper limbs and ankles. Trained technicians used the Omron Colin BP-203RPE III device (Omron Health Care, Kyoto, Japan) to simultaneously measure bilateral brachial and ankle arterial systolic pressures in supine subjects. And the software automatically calculates the bilateral ABI data according to the above calculation formula. All measurements were conducted in accordance with strict standard protocols. PAD was defined as an ABI $\leq$ 0.9 in either lower limb.[14] Subjects with ABI >1.4 were excluded because of abnormal elevation of ABI may due to calcification of the arterial wall.[15]

Other Variables

Variables included age (years), sex, systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg) measured by electronic sphygmomanometers after the subjects had rested for 10 minutes. Qualified researchers were trained to collect information by using standardized questionnaires, including smoking status (never, former, current), alcohol consumption (never, former, current), antihypertensive drugs (yes or no), the history of comorbid diseases including diabetes mellitus (yes or no), stroke (yes or no), and coronary heart disease (yes or no).

Statistical Analysis

Normally distributed variables were presented as mean ± standard deviation (SD); for non-normally distributed data the median and inter-quartile range (IQR) are given, and categorical variables as percentage (%). Population characteristics were described according to BMI classify. To reduce redundancy, variance inflation factors (VIF) were used to assess collinearity between independent variables before our data analysis, with a variable having VIF > 5 considered collinear with other variables. In comparison, LDL-C (VIF=5.9) had to be excluded from the next analysis because of its collinearity to other variables. The dose-response relationship between BMI and the risk of PAD was estimated using generalized additive regression model and smoothing curve (penalized spline method) with adjustment for age, sex, systolic and diastolic blood

pressure, pulse rate, smoking status, alcohol consumption, TC, TG, HDL-C, eGFR, Hcy, antihypertensive drugs, diabetes mellitus, stroke, coronary heart disease. If nonlinear was detected, threshold effect analysis was used for inflection points of BMI by using segmented regression model, LRT test and bootstrap resampling method. Multivariate logistic regression was used to analyze the relationship between BMI and the risk of PAD around threshold value. P value for interaction was used to compare whether there was a significant difference in the correlation between BMI and the risk of PAD before and after inflection point. In addition, possible modifications of the association between BMI and PAD were assessed for variables including sex, age, blood pressure controlled, pulse rate, Hcy, lipids profile, smoking status, history of diabetes mellitus and stroke.

All analyses in this study with P values <0.05 (two-tailed) were considered statistically significant. All analyses were statistically analyzed by EnpowerStats (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA) and R statistical software (http://www.r-project.org).

Results

Baseline Characteristics of Participants

As shown in Table 1, a total of 10,896 hypertensive patients with a mean age of 63.9 ± 9.3 years were included in this study. The prevalence of PAD was 3.2%, the mean BMI was 23.6 ± 3.6 kg/m^2, and 47.1% were male. BMI was stratified to four groups: underweight (BMI<18.5 kg/m^2), normal (BMI≥18.5, <25 kg/m^2), overweight (BMI≥25, >30 kg/m^2) and obesity (BMI≥30 kg/m^2) to describe demographic characteristics. The underweight of participants accounted for 6.3% of the total population, and obesity was only 4.2%. The prevalence of PAD in underweight was the highest (6.7%) and followed by obesity (4.4%), while overweight was only 2.3%. Compared with the other three groups, underweight participants were older, with higher tHcy, HDL-C, current smoking rate, and lower TC, TG, eGFR, the prevalence of diabetes mellitus and the use of the antihypertensive drug.

Association Between BMI and PAD

As shown in Figure 1, the relationship between BMI and the prevalence of PAD showed a U-shaped curve, and threshold saturation effect analysis showed that BMI value with the lowest risk of PAD was estimated to be 25.7 kg/m^2. We stratified BMI by 25.7 kg/m^2 and used logistic regression analysis models (Table 2). Per SD increment (3.6 kg/m^2) on the left side of the threshold (BMI< 25.7 kg/m^2), BMI was associated with a 27% decrease in the risk of PAD [adjusted odds ratio (OR), 0.73; 95% confidence interval (CI)0.60, 0.89; P= 0.002]; however, BMI was significantly positively associated with the risk of PAD (adjusted OR, 1.52; 95% CI 1.52, 1.93; P=0.001) in those with BMI ≥ 25.7 kg/m^2. Further adjusted lipid-lowering drugs as a sensitivity analysis, no change to the result suggested that the result was stable (Supplemental Table 1).

Stratified Analyses by Potential Effect Covariables

None of other covariables, including sex (male vs female), age (< 65 vs ≥ 65 years), blood pressure controlled [yes vs no (yes: SBP< 140 mmHg and DBP< 90 mmHg; otherwise no)], pulse rate (< 75 vs ≥ 75 bmp), smoking status (never vs former vs current), total Hcy (<15 vs ≥ 15μmol/L), total cholesterol (<5.2 vs.≥ 5.2mmol/L), HDL-C[abnormal vs normal (normal: male HDL-C≥1.04 mmol/L, female HDL-C≥1.3 mmol/L; abnormal: male HDL-C<1.04 mmol/L, female HDL-C<1.3 mmol/L)], diabetes mellitus (yes vs no), stroke (yes vs no) significantly modified the association between BMI and the risk of PAD, whether in the hypertensive population with BMI < 25.7 kg/m^2 or BMI ≥ 25.7 kg/m^2 (All stratified P-interactions were > 0.05) (Figure 2).

Discussion

In our analysis of this community-based hypertension registry study in China, we noted a U-shaped relationship between BMI and risk of PAD. The BMI value with lowest risk of PAD was estimated to be 25.7 kg/m^2.

A number of studies have reported the relationship between BMI and the risk of PAD. However, the association between BMI and PAD risk was not consistent. Epidemiological studies more than two decades ago reported a positive association between BMI and intermittent claudication in middle-aged males in Israel.[16] However, many population studies after adjusting for the relevant covariates fail to support the significant association between BMI and the prevalence of PAD.[4,17] In addition, the San Diego study reported an independent and significantly inverse association between BMI and prevalence of PAD (OR: 0.88) in multi-ethnic population.[18] Studies on the diabetic population in

Table 1 Population Characteristics of Stratified by Body Mass Index

Characteristics	Total	Body Mass Index (kg/m^2)				P-value
		Underweight: <18.5	Normal: ≥18.5, <25	Overweight: ≥25, <30	Obesity: ≥30	
N	10,896	691	6594	3157	454	
Age, y	63.9 ± 9.3	70.7 ± 8.3	64.9 ± 8.8	61.0 ± 9.1	58.7 ± 9.4	<0.001
BMI, kg/m^2	23.6 ± 3.6	17.4 ± 0.9	22.1 ± 1.7	26.8 ± 1.3	32.2 ± 3.0	<0.001
SBP, mmHg	148.5 ± 17.8	147.4 ± 20.0	148.7 ± 17.9	148.1 ± 17.0	149.5 ± 17.4	0.071
DBP, mmHg	89.0 ± 10.7	83.6 ± 11.6	88.4 ± 10.5	91.0 ± 10.4	92.3 ± 10.9	<0.001
Pulse rate, bpm	76.3 ± 14.2	77.1 ± 15.1	75.8 ± 14.4	77.0 ± 13.7	78.3 ± 11.8	<0.001
PAD, N(%)	351 (3.2)	46 (6.7)	212 (3.2)	73 (2.3)	20 (4.4)	<0.001
Lab Examination						
Homocysteine, μmol/L	18.0 ± 11.0	19.3 ± 10.8	18.1 ± 11.0	17.5 ± 10.9	17.7 ± 13.0	<0.001
Fasting blood glucose, mmol/L	6.2 ± 1.6	5.8 ± 1.1	6.1 ± 1.5	6.4 ± 1.9	6.5 ± 1.8	<0.001
Total cholesterol, mmol/L	5.1 ± 1.1	4.9 ± 1.1	5.1 ± 1.1	5.2 ± 1.1	5.2 ± 1.1	<0.001
Triglyceride, mmol/L	1.4 (1.0–2.1)	1.0 (0.8–1.3)	1.4 (1.0–1.9)	1.8 (1.3–2.6)	1.8 (1.3–2.6)	<0.001
HDL-C, mmol/L	1.6 ± 0.4	1.8 ± 0.5	1.6 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	<0.001
LDL-C, mmol/L	3.0 ± 0.8	2.6 ± 0.7	2.9 ± 0.8	3.1 ± 0.8	3.1 ± 0.8	<0.001
eGFR, mL/min/1.73m^2	88.7 ± 20.4	80.9 ± 21.7	88.3 ± 20.0	90.5 ± 20.4	93.4 ± 20.6	<0.001
Sex, N(%)						<0.001
male	5127 (47.1)	359 (52.0)	3193 (48.4)	1402 (44.4)	173 (38.1)	
female	5769 (52.9)	332 (48.0)	3401 (51.6)	1755 (55.6)	281 (61.9)	
Smoking status, N(%)						<0.001
Never	6277 (57.6)	317 (45.9)	3699 (56.1)	1956 (62.0)	305 (67.3)	
Former	1751 (16.1)	114 (16.5)	1052 (16.0)	526 (16.7)	59 (13.0)	
Current	2867 (26.3)	260 (37.6)	1843 (27.9)	675 (21.4)	89 (19.6)	
Alcohol consumption, N(%)						0.013
Never	6842 (62.8)	438 (63.4)	4075 (61.8)	2011 (63.7)	318 (70.2)	
Former	1584 (14.5)	98 (14.2)	974 (14.8)	452 (14.3)	60 (13.2)	
Current	2468 (22.7)	155 (22.4)	1544 (23.4)	694 (22.0)	75 (16.6)	
Diabetes mellitus, N(%)	1238 (11.4)	23 (3.3)	642 (9.7)	474 (15.0)	99 (21.8)	<0.001
Stroke, N(%)	706 (6.5)	43 (6.2)	441 (6.7)	205 (6.5)	17 (3.7)	0.104
CHD, N(%)	552 (5.1)	46 (6.7)	336 (5.1)	146 (4.6)	24 (5.3)	0.174
Antihypertensive drugs, N(%)	7154 (65.7)	406 (58.8)	4272 (64.8)	2162 (68.5)	314 (69.3)	<0.001
Lipid-lowering drugs, N(%)	381 (3.5)	7 (1.0)	199 (3.0)	154 (4.9)	21 (4.6)	<0.001

Notes: Values are N (%) or mean ± SD, except triglyceride presented as the median (IQR).

Abbreviations: BMI, body mass index, SBP, systolic blood pressure; DBP, diastolic blood pressure; PAD, peripheral vascular disease; HDL-C, high-density lipid cholesterol; FBG, fasting blood glucose; tHcy, total Homocysteine; eGFR, estimated glomerular filtration rate; CHD, coronary heart disease; IQR, inter-quartile range.

Taiwan showed that compared with diabetic patients without PAD, the BMI of patients with PAD was lower (23.5 ±3.2 vs.24.8±3.5 kg/m^2, P < 0.005). Heffron et al who gathered data from more than 20,000 sites (n= 3,250,350) in the United States from 2003 to 2008, recently reported BMI and the prevalence of PAD in females showed a J-shaped nonlinear relationship; a significant positive correlation between obesity and PAD in females, while only a slight positive correlation between obesity (BMI ≥ 40kg/m^2) and PAD in males (OR=2.98 vs 1.37).[9] Stepwise logistic regression analysis showed that the association between BMI and PAD was inverse.[19]

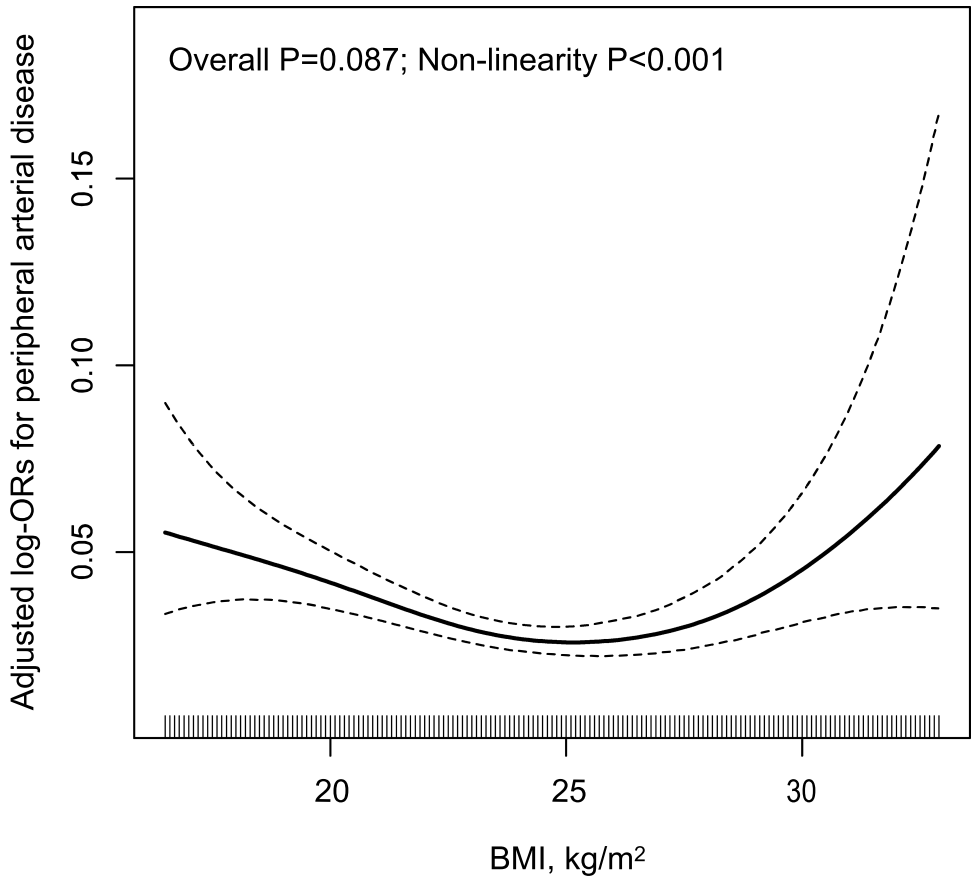

Figure 1 Smoothing curve of association between BMI and the risk of PAD. Adjusted for: age, sex, systolic and diastolic blood pressure, pulse rate, smoking status, alcohol consumption, total cholesterol, triglyceride, high density lipoprotein cholesterol, fasting blood glucose, estimated glomerular filtration rate, total homocysteine, antihypertensive drugs, diabetes mellitus, stroke, coronary heart disease.

To our knowledge, the U-shaped relationship between BMI and the risk of PAD shown in our study was the first reported in Chinese hypertensive population. Different from the very large sample population studies[9] in the United States, where participants were nearly 30% obese and 3.4% underweight, as well as study of the prevalence of PAD in African,[10] where obesity was only 4.5%, 34.1% underweight, we were 6.3% (691) underweight and only 4.2% (454) obesity, nearly 90% of the population was normal BMI and overweight. Over a third of the study population was underweight. A U-shaped relationship between BMI and the risk of PAD was observed. Compare to the subjects with normal BMI, underweight and obesity were statistically significant association with

Table 2 Association of BMI and the Risk of PAD Stratified by BMI Threshold

BMI, kg/m^2 (per SD Increment)	N	Events (%)	Crude Model OR (95% CI)	P value	Model 1 OR (95% CI)	P value	Model 2 OR (95% CI)	P value
Total participants	10896	351 (3.2)	0.75 (0.67, 0.84)	<0.001	1.02 (0.91, 1.15)	0.689	0.96 (0.85, 1.10)	0.559
<25.7	8027	278 (3.5)	0.55 (0.47, 0.66)	<0.001	0.83 (0.69, 1.00)	0.048	0.73 (0.60, 0.89)	0.002
≥25.7	2869	73 (2.5)	1.31 (1.04, 1.65)	0.020	1.38 (1.10, 1.73)	0.006	1.52 (1.20, 1.93)	0.001
P for interaction				<0.001		0.001		<0.001
Log Likelihood Ratio Tests								0.002

Notes: Crude model adjust for none; Model 1 adjust for age, sex, diabetes mellitus, smoking status; Model 2 adjust for: age, sex, systolic and diastolic blood pressure, pulse rate, smoking status, alcohol consumption, total cholesterol, triglyceride, high density lipoprotein cholesterol, estimated glomerular filtration rate, total homocysteine, antihypertensive drugs, diabetes mellitus, stroke, coronary heart disease.

Abbreviations: CI, confidence interval; BMI, Body Mass Index; PAD, peripheral arterial disease.

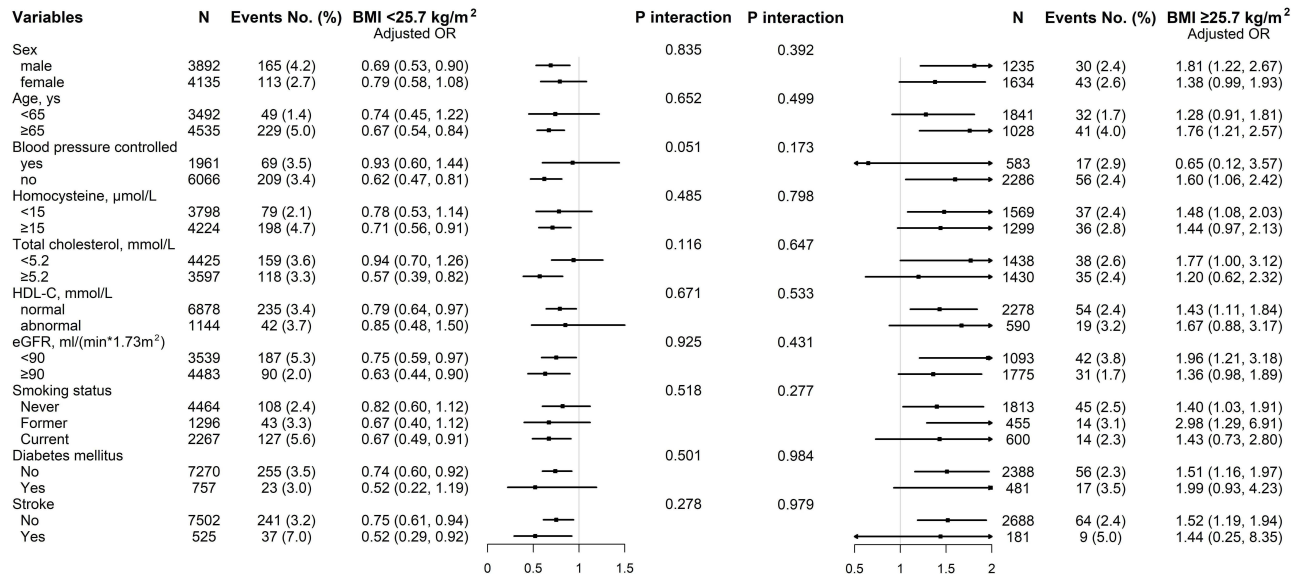

Figure 2 Subgroup analyses on the association between BMI and the risk of PAD. Adjusted for: age, sex, systolic and diastolic blood pressure, pulse rate, smoking status, alcohol consumption, total cholesterol, triglyceride, high density lipoprotein cholesterol, fasting blood glucose, estimated glomerular filtration rate, total homocysteine, antihypertensive drugs, diabetes mellitus, stroke, coronary heart disease, except for the stratifying variable.

the risk of PAD (OR, 2.09; 95% CI 1.35, 3.22; P= 0.0009; OR,1.90; 95% CI 1.04, 3.23; P= 0.0336), but not overweight (OR, 1.56; 95% CI 0.70, 2.51; P= 0.7342).[10] However, Heffron et al found a "J-shaped" relationship between BMI and PAD only in females, not in males, which may be due to the height and weight data used in this study for self-reporting of participants. Self-reported data may lead to personal BMI classification appear serious mistakes,[20] difficult to correct the mistakes,[21] especially in the stratified analysis according to gender.[22] Thus, self-report bias may have contributed to the fact that this study found a "J-shaped" relationship between BMI and PAD risk only in females, and not in males.

At present, few studies have elaborated on the possible mechanism of the correlation between BMI and PAD. A cross-sectional study of hemodialysis patients reported a lower prevalence of atherosclerosis and lower levels of inflammation (CRP) in patients with normal BMI and overweight compared with those with underweight and obesity.[23] Lower levels of inflammation and atherosclerosis may be associated with the lowest risk of PAD in this population (normal BMI and overweight).

Not only that, there have been also many reports on the U-shaped relationship between BMI and cardiovascular disease and death. A meta-analysis of 97 studies showed that obesity (all grades) and grades 2 and 3 obesity were significantly associated with all-cause mortality relative to normal BMI. However, overweight was associated with a significant reduction in all-cause mortality.[22] Among more than 1 million East Asian populations in the Asia Cohort Consortium BMI Project, including Chinese, Japanese, and Korean, the Cox proportional hazard regression model was used to analyze the relationship between BMI and mortality risk, which showed that the population with BMI between 22.6 and 27.5 had the lowest mortality risk.[24] Based on this, we speculate that the "U-shaped" relationship between BMI and peripheral atherosclerosis may, on one hand, explain the causes of the lowest cardiovascular disease risk and all-cause mortality in normal BMI/overweight.

Limitations and Future Directions

Nonetheless, these results must be interpreted with caution, and a number of limitations should be borne in mind. First, subjects in our analysis were middle-aged and elderly patients with hypertension. The U-shaped relationship between BMI and the risk of PAD was not necessarily applicable to the general population, but as an independent risk factor for PAD, exploring the relationship between BMI and the risk of PAD in the hypertensive population can serve the high-risk population more precisely. In addition, the association between BMI and the risk of PAD was still controversial. By design, our study was a cross-sectional study and cannot study the chronology of BMI and PAD. There might be a reverse causal relationship. The weight change caused by the disease may distort the

relationship between BMI and PAD. In the future, large prospective cohort studies on PAD were urgently needed. Final, the obesity rate in our study was low. It has no enough power to assess the relationship between different degrees of obesity or morbid obesity and the risk of PAD. However, our study reflects the real situation of hypertension population in Chinese hypertension, and the results obtained were more suitable for the application of hypertension in middle-aged and elderly people in China.

Conclusions

Our study reported the prevalence of PAD was 3.2%. The U-shaped association between BMI and the risk of PAD was found in Chinese middle-aged and elderly patients with hypertension. BMI with the lowest risk of PAD was estimated to be 25.7 kg/m^2 in our study.

Data Sharing Statement

The raw data used to support the findings of this study are available from the corresponding author upon request.

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Disclosure

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