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Relationship of Visceral Adiposity Index with New-Onset Hyperuricemia in Hypertensive Patients

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1. Abstract

1.1 Background: Visceral adiposity index is a new type of indicator that accurately reflects distribution and function of visceral fat. The relation between VAI and new-onset hyperuricemia remains largely understudied.

1.2. Purpose: This study sought to further investigate the prospective association between VAI and the risk of hyperuricemia by examining possible effect modifies in hypertensive patients.

1.3. Methods: We enrolled 11,622 hypertensive patients with normal uric acid (UA) concentrations [<360 μmol/L (6 mg/dL)] who participated the UA Sub-study of the China Stroke Primary Prevention Trial (CSPPT). Our primary outcome was new-onset hyperuricemia, which was defined as a UA concentration ≥420 μmol/L (7 mg/dL) in men or ≥360 μmol/L (6 mg/dL) in women at the exit visit.

1.4. Results: Over a median follow-up of 4.4 years, 741 (16.9%) participants developed new-onset hyperuricemia in the male and 1216 (16.8%) in the female.participants were stratified into quintiles according to VAI (per SD increment; quintile 1, lowest; quintile 5, highest). And when we used the lowest quintile 1 (Q1: <0.43) as a reference, the ORs for the second (Q2: 0.43-0.65), third (Q3: 0.65-0.92), fourth quintiles (Q4: 0.92-1.36) and fifth quintiles (Q5: ≥1.36) of (95%CI) for participants were 1.37 (1.15,1.64), 1.65 (1.39,1.97), 1.89 (1.58,2.25) and 2.75 (2.30,3.28), respectively (P for trend < 0.001).

1.5. Conclusion: There was a positive relationship between baseline VAI and the risk of new-onset hyperuricemia in a sample of Chinese hypertensive individuals.

2. Introduction

In recent years, an increasing trend in the prevalence of hyperuricemia has been observed in epidemiological studies [1-2]. Patients with hyperuricemia sustained increasing risk of gout, cardiovascular diseases (CVD), diabetes and chronic kidney disease (CKD) [3-6]. Hence, the discovery of more modifiable risk factors related to hyperuricemia is important for preventing hyperuricemia and reducing the risk of its related diseases. Obesity is a major global health challenge and is also an important risk factor for cancer, diabetes and CKD [7-9]. Several studies have suggested that it is not the extent of obesity but the distribution of adiposity tissue that plays a decisive role in the impact of obesity on these diseases [10,11]. In addition, previous study has found that an increase in visceral adiposity is associated with the higher risk prevalence of hyperuricemia [12]. There are several traditional methods like body mass index (BMI), waist-to-height ratio, waist circumference (WC), waist-to-hip ratio, but none of these can measure visceral adiposity accurately [13]. The visceral adiposity index (VAI) is as accurate as magnetic resonance imaging (the gold standard method) in measuring visceral adiposity [14], and therefore, can be

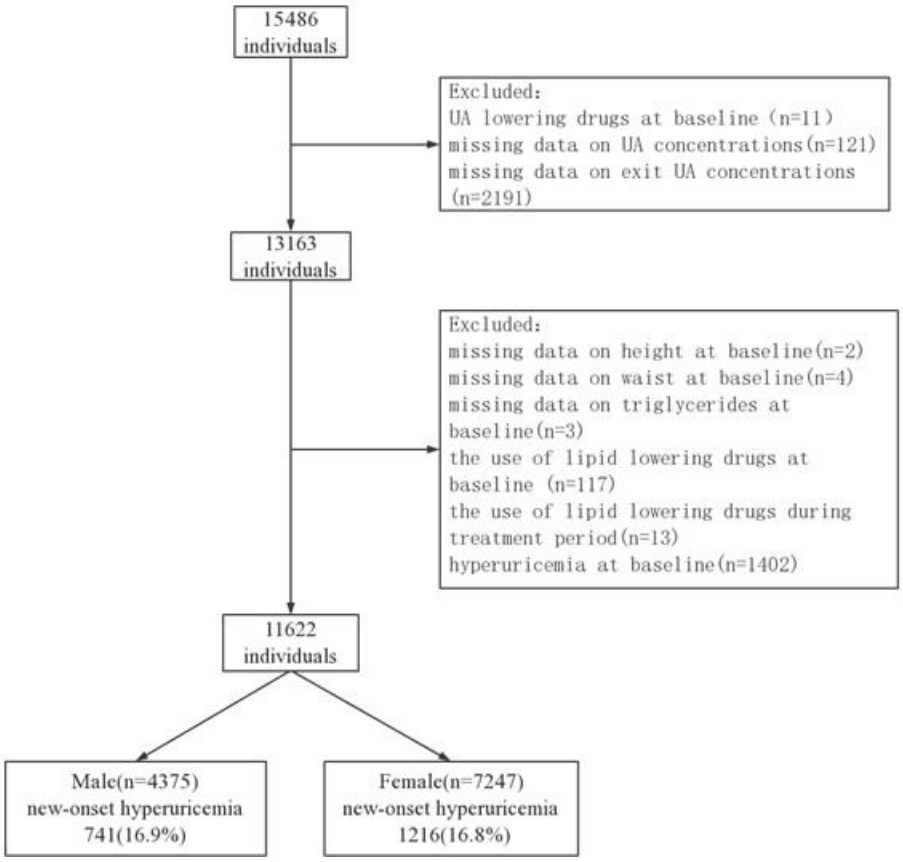
used as a valuable indicator of lipid accumulation and visceral adipose function for its convenience and accuracy. However, several cross-sectional studies [15,16] and only one prospective study [17] have evaluated the association between VAI and hyperuricemia, and reported inconsistent findings. Furthermore, few studies have been conducted in hypertensive population, who are proved to be at high risk for hyperuricemia [18].

To address the aforementioned gaps in the existing literature, we aimed to further investigate the prospective association between VAI and the risk of hyperuricemia by examining possible effect modifies in hypertensive patients who joined the UA Sub-study of the China Stroke Primary Prevention Trial (CSPPT) [19].

3. Methods

3.1. Study design and population

The study procedures has been described in previous studies [19-23], and are therefore only briefly explained here. The CSPPT was a multi-community, randomized, double-blind controlled trial with 20,702 hypertensive adults in 32 communities in Jiangsu and Anhui provinces of China, which was conducted from May 19, 2008 to August 24, 2013. The UA sub-study of the CSPPT enrolled 15,364 eligible participants with complete data on UA and without the usage of UA-lowering drugs at baseline from 20 communities in Jiangsu province. The current study is a post-hoc analysis of the UA Sub-study. The flow of the participants is presented in (Supplemental Figure 1).



Supplemental Figure 1: Flow chart of study participants

3.2. Intervention and follow-up

Eligible participants were randomly assigned, in a 1:1 ratio, to one of two treatment groups: a daily oral dose of one tablet containing 10mg enalapril and 0.8mg folic acid (single pill combination, the enalapril-folic acid group), or a daily oral dose of one tablet containing 10mg enalapril only (the enalapril group). Participants were scheduled for followed up every three months. At each follow-up visit, BP was measured; study drug adherence, concomitant medication use, adverse events and possible endpoint events were documented by trained research staff and physicians. During the trial period, if blood pressure (BP) was not adequately controlled, other classes of anti-hypertensive medications, mostly nitrendipine or hydrochlorothiazide, could be prescribed concomitantly. At the exit visit, final blood samples were collected and assessed.

3.3. Anthropometric Measurements

Height was measured without shoes to the nearest 0.1 cm on a portable stadiometer. Weight was measured in light indoor clothing without shoes to the nearest 0.1 kg. BMI was calculated as weight (kilograms)/height (meters) squared. WC was measured as the minimum circumference between the inferior margin of the ribcage

and the crest of the ileum [24-26] .

3.4. Laboratory assays

Serum concentrations of UA, fasting glucose, total homocysteine (tHcy) and lipids were measured with automatic analyzers (Beckman Coulter) at the core laboratory of the National Clinical Research Center for Kidney Disease, Nanfang Hospital, Guangzhou, China. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [27] .

3.5. Outcomes

The primary outcome was new-onset hyperuricemia in hypertensive participants with normal UA concentrations [<360μmol/L (6mg/dL)] at baseline. Hyperuricemia was defined as a UA concentration ≥420μmol/L (7mg/dL) in men or ≥360μmol/L (6mg/dL) in women [19,28,29].

3.6. Major definitions

The VAI, a reliable index based on WC, BMI, TG and HDL-C, was calculated using the following formulas [14]:

$$Females: VAI = \left(\frac{WC}{36.58 + (1.89 \times BMI)}\right) \times \left(\frac{TG}{0.81}\right) \times \left(\frac{1.52}{HDL-C}\right)$$

$$Males: VAI = \left(\frac{WC}{39.68 + (1.88 \times BMI)}\right) \times \left(\frac{TG}{1.03}\right) \times \left(\frac{1.31}{HDL-C}\right)$$

3.7. Statistical analyses

Baseline characteristics of study population are expressed as mean ± standard deviation (SDs) for continuous variables and as frequencies and percentages for categorical variables, respectively. To assess whether there were significant differences in baseline levels of participants by VAI quartiles, we used analysis of variance tests for continuous variables or chi-square tests for categorical variables.

The relationship of baseline VAI with primary was examined using multivariable logistic regression models, respectively, without and with adjustment for covariates including age, fasting glucose, total homocysteine (tHcy), estimated glomerular filtration rate (eGFR), SBP, smoking and drinking status, treatment group, as well as mean SBP during treatment period in Adjusted Model. As additional exploratory analysis, possible modifications on the association between VAI and new-onset hyperuricemia were also evaluated by stratified analyses and interaction testing.

A two-tailed P<0.05 was considered to be statistically significant in all analyses. Statistical analyses were performed using R software, version 3.6.3 (http://www. R-project.org/).

4. Results

4.1. Study participants and baseline characteristics

A total of the 11,622 participants with complete data on baseline VAI and exit UA, who were not using UA lowering drugs during the follow up period, as well as whose baseline UA levels were <360μmol/L (6mg/dL) in the UA Sub-study of CSPPT (Supplemental Figure 1) were included in the final analysis.

Baseline characteristics of the study participants by sex are shown in (Table 1). In the female, new-onset hyperuricemia patients were more likely to be older; tend to be current smoker; had higher BMI, WC, TG, TC, and tHcy levels, as well as higher time-averaged SBP during the treatment period; lower eGFR levels; higher frequency usage of antihypertensive drugs at baseline. In the male, new-onset hyperuricemia patients tend to be current alcohol drinker; had higher BMI, WC, TG, TC, and tHcy levels, as well as higher time-averaged SBP during the treatment period; lower eGFR

Table 1: Baseline characteristics by sex

† Values are presented as median (IQR).

Variables	Female				Male			
	Overall	non new-onset hyperuricemia	new-onset hyperuricemia	*P value*	Overall	non new-onset hyperuricemia	new-onset hyperuricemia	*P value*
N	7247	6031	1216		4375	3634	741	
Age, y	58.8 ±7.3	58.5 ±7.2	60.3 ±7.5	<0.001	60.6 ±7.5	60.6 ±7.4	60.7 ±7.8	0.670
Waist circumference, cm	85.0 ±9.4	84.6 ±9.3	87.3 ±9.4	<0.001	85.4 ±9.6	84.9 ±9.6	87.5 ±9.4	<0.001
Body mass index, kg/m2	25.9 ±3.6	25.7 ±3.5	27.0 ±3.7	<0.001	24.8 ±3.2	24.7 ±3.2	25.6 ±3.1	<0.001
Group (%)				0.030				0.819
enalapril only	3600 (49.7)	2961 (49.1)	639 (52.5)		2218 (50.7)	1839 (50.6)	379 (51.1)	
enalapril+folic acid	3647 (50.3)	3070 (50.9)	577 (47.5)		2157 (49.3)	1795 (49.4)	362 (48.9)	

Visceral adiposity index †	2.2 (1.5, 3.4)	2.2 (1.4, 3.3)	2.5 (1.7, 3.8)	<0.001	1.3 (0.8, 2.1)	1.3 (0.8, 2.0)	1.5 (1.0, 2.4)	<0.001
Smoking status, No. (%)				0.002				0.371
no	6906 (95.3)	5770 (95.7)	1136 (93.4)		1355 (31.0)	1115 (30.7)	240 (32.4)	
Former	96 (1.3)	70 (1.2)	26 (2.1)		715 (16.3)	587 (16.2)	128 (17.3)	
Current	244 (3.4)	190 (3.2)	54 (4.4)		2305 (52.7)	1932 (53.2)	373 (50.3)	
Alcohol drinking, No. (%)				0.849				0.008
no	6847 (94.5)	5698 (94.5)	1149 (94.5)		1494 (34.1)	1275 (35.1)	219 (29.6)	
Former	160 (2.2)	135 (2.2)	25 (2.1)		542 (12.4)	453 (12.5)	89 (12.0)	
Current	236 (3.3)	194 (3.2)	42 (3.5)		2339 (53.5)	1906 (52.4)	433 (58.4)	
Baseline SBP	169.5 ±20.8	168.2 ±20.0	175.8 ±23.1	<0.001	167.4 ±20.9	166.5 ±20.5	171.7 ±22.3	<0.001
Baseline DBP	94.2 ±11.5	93.8 ±11.2	96.1 ±12.4	<0.001	97.0 ±12.5	96.5 ±12.3	99.7 ±12.8	<0.001
Total cholesterol, mmol/L†	5.7 (5.0, 6.5)	5.7 (5.0, 6.4)	5.9 (5.2, 6.7)	<0.001	5.5 (4.8, 6.2)	5.4 (4.8, 6.2)	5.6 (4.9, 6.2)	0.015
Folate, ng/mL	8.2 ±3.2	8.2 ±3.3	8.0 ±2.9	0.209	6.8 ±3.0	6.8 ±3.0	6.8 ±2.9	0.832
Fasting glucose, mmol/L †	5.6 (5.2, 6.3)	5.6 (5.2, 6.3)	5.7 (5.2, 6.3)	0.079	5.6 (5.2, 6.2)	5.6 (5.2, 6.3)	5.6 (5.1, 6.1)	0.194
Triglycerides, mmol/L †	1.5 (1.1, 2.1)	1.5 (1.1, 2.1)	1.7 (1.3, 2.3)	<0.001	1.3 (0.9, 1.8)	1.3 (0.9, 1.8)	1.5 (1.1, 2.0)	<0.001
HDL-C, mmol/L	1.3 ±0.3	1.3 ±0.3	1.3 ±0.3	<0.001	1.4 ±0.4	1.4 ±0.4	1.3 ±0.4	0.132
eGFR, mL/min/1.73m2 †	97.4 (89.9, 103.2)	97.8 (90.8, 103.6)	94.3 (85.2, 101.1)	<0.001	94.8 (87.4, 101.5)	95.1 (88.0, 101.6)	93.1 (84.5, 100.7)	<0.001
Total homocysteine, μmol/L †	11.3 (9.6, 13.8)	11.2 (9.5, 13.7)	11.9 (10.1, 14.5)	<0.001	14.0 (11.8, 17.9)	13.9 (11.7, 17.7)	14.4 (12.0, 18.7)	0.010
SBP during treatment period	139.2 ±10.9	138.7 ±10.7	141.5 ±11.4	<0.001	139.5 ±10.8	139.3 ±10.8	140.5 ±10.6	0.004
DBP during treatment period	82.8 ±6.9	82.6 ±6.8	83.5 ±7.1	<0.001	84.5 ±7.6	84.3 ±7.5	85.4 ±7.9	<0.001

levels at baseline.

4.2. Relationship of VAI level with study outcome

During a median follow-up duration of 4.4 years, 741 (16.9%) participants developed new-onset hyperuricemia in the male and 1216 (16.8%) in the female.

Overall, there was a significant positive association between baseline VAI and the risk of new-onset hyperuricemia (per SD increment; odds ratio [OR], 1.32; 95% CI, 1.24, 1.41; (Figure 1). Subsequently, participants were stratified into quintiles according to VAI (per SD increment; quintile 1, lowest; quintile 5, highest). And when we used the lowest quintile 1 (Q1: <0.43) as a reference, the ORs for the second (Q2: 0.43-0.65), third (Q3: 0.65-0.92), fourth quintiles (Q4: 0.92-1.36) and fifth quintiles (Q5: ≥1.36) of (95%CI) for participants were 1.37 (1.15,1.64), 1.65 (1.39,1.97), 1.89 (1.58,2.25) and 2.75 (2.30,3.28), respectively (P for trend < 0.001). Similar results were found in males and females (Tables 2). Adjusted Model: Adjusted for age, sex, fasting glucose, total homocysteine (tHcy), estimated glomerular filtration rate (eGFR), systolic blood pressure (SBP), smoking and drinking status, treatment group, and mean SBP during the treatment period in the total population; Adjusted for age, fasting glucose, total homocysteine (tHcy), estimated glomerular filtration rate (eGFR), systolic blood pressure (SBP), smoking and drinking status, treatment group, and mean SBP during the treatment period in the males and females.

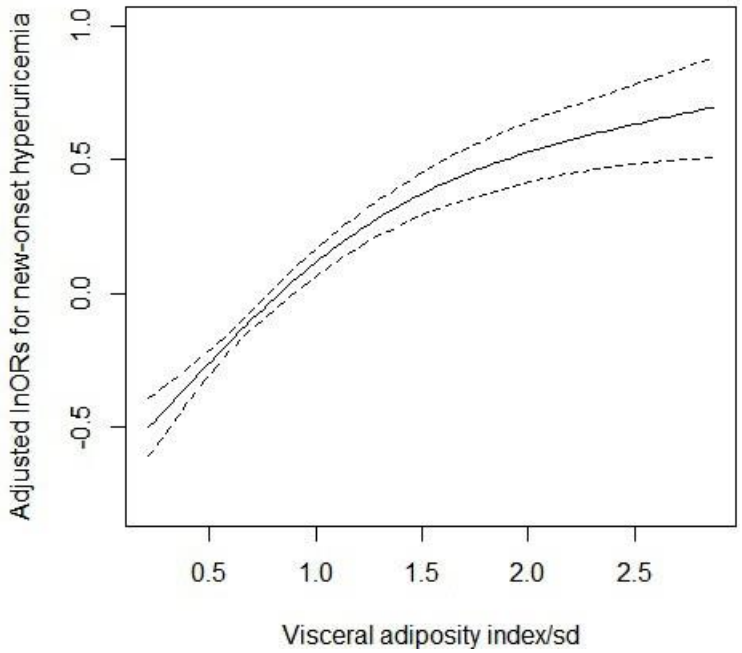


Figure 1: Smoothing curves illustrating the association between visceral adiposity index and new-onset hyperuricemia in the total population.

Table 2: The association between baseline visceral adiposity index and new-onset hyperuricemia

Visceral adiposity index/SD	N	Event(%)	Crude Model		Adjusted Model	
			OR(95%CI)	*P value*	OR(95%CI)	*P value*
Continuous	11622	1957(16.8)	1.20(1.14,1.27)	<0.001	1.32(1.24,1.41)	<0.001
Overall						
Quintiles						
Q1 (<0.43)	2325	290(12.5)	ref		ref	
Q2 (0.43~0.65)	2324	347(14.9)	1.23(1.04,1.46)	0.015	1.37(1.15,1.64)	<0.001
Q3 (0.65~0.92)	2324	396(17.0)	1.44(1.22,1.70)	<0.001	1.65(1.39,1.97)	<0.001
Q4 (0.92~1.36)	2324	414(17.8)	1.52(1.29,1.79)	<0.001	1.89(1.58,2.25)	<0.001
Q5 (≥1.36)	2325	510(21.9)	1.97(1.68,2.31)	<0.001	2.75(2.30,3.28)	<0.001
P for trend				<0.001		<0.001
Male						
Continuous	4375	741(16.9)	1.41(1.26,1.57)	<0.001	1.57(1.39,1.77)	<0.001
Quintiles						
Q1 (<0.43)	1635	220(13.5)	ref		ref	
Q2 (0.43~0.65)	980	170(17.3)	1.35(1.09,1.68)	0.007	1.48(1.18,1.85)	<0.001
Q3 (0.65~0.92)	774	140(18.1)	1.42(1.13,1.79)	0.003	1.56(1.23,1.98)	<0.001
Q4 (0.92~1.36)	553	101(18.3)	1.44(1.11,1.86)	0.006	1.71(1.30,2.23)	<0.001
Q5 (≥1.36)	433	110(25.4)	2.19(1.69,2.84)	<0.001	2.84(2.15,3.74)	<0.001
P for trend				<0.001		<0.001
Female						
Continuous	7247	1216(16.8)	1.16(1.08,1.24)	<0.001	1.23(1.14,1.32)	<0.001
Quintiles						
Q1 (<0.43)	690	70(10.1)	ref		ref	
Q2 (0.43~0.65)	1344	177(13.2)	1.34(1.00,1.80)	0.049	1.29(0.96,1.74)	0.095
Q3 (0.65~0.92)	1550	256(16.5)	1.75(1.32,2.32)	<0.001	1.67(1.25,2.22)	<0.001
Q4 (0.92~1.36)	1771	313(17.7)	1.90(1.44,2.50)	<0.001	1.88(1.42,2.50)	<0.001
Q5 (≥1.36)	1892	400(21.1)	2.37(1.81,3.11)	<0.001	2.63(1.98,3.47)	<0.001
P for trend				<0.001		<0.001

4.3. Stratified Analyses by Potential Effect Modifiers

We further performed stratified analyses to assess the relationship of baseline VAI (per SD increment) with the risk of new-onset hyperuricemia in various subgroups (Table 3). Significant group differences were observed among participants with different baseline age (<59.2 years: OR, 1.21; 95% CI, 1.12-1.32; versus ≥59.2 years: OR, 1.46; 95% CI, 1.32-1.61; P for interaction < 0.001), sex (male: OR, 1.57; 95% CI, 1.39-1.77; versus female: OR, 1.23; 95% CI, 1.14-1.32; P for interaction < 0.001) and total homocysteine (<12.3 μmol/L: OR, 1.21; 95% CI, 1.11-1.32; versus ≥12.3 μmol/L: OR, 1.47; 95% CI, 1.34-1.61; P for interaction = 0.003; (Table 3). If not stratified, adjusted for sex, age, fasting glucose, total homocysteine (tHcy), estimated glomerular filtration rate (eGFR), systolic blood pressure (SBP), smoking and drinking status, treatment group, and mean SBP during the treatment period.

Table 3: Stratified analysis of the impact of visceral adiposity index on new-onset hyperuricemia in the total population

Subgroup	No. of Events(%)	OR(95%CI)	*P for interaction*
Age(median), y			0.001
<59.2	5810(15.1)	1.21(1.12,1.32)	
≥59.2	5812(18.6)	1.46(1.32,1.61)	
Sex, n (%)			0.001
Male	4375(16.9)	1.57(1.39,1.77)	
Female	7247(16.8)	1.23(1.14,1.32)	
Fasting glucose(median), mmol/L			0.054
<5.6	5678(16.4)	1.24(1.12,1.37)	
≥5.6	5771(17.4)	1.36(1.25,1.47)	
Total homocysteine, μmol/L			0.003
<15	8446(15.9)	1.24(1.16,1.34)	
≥15	3087(19.7)	1.63(1.43,1.86)	
Baseline SBP(median)			0.557
<165.3	5731(13.6)	1.36(1.24,1.49)	
≥165.3	5891(20.0)	1.28(1.18,1.40)	
SBP during treatment period(median)			0.471
<138.3	5811(14.6)	1.40(1.27,1.53)	
≥138.3	5811(19.1)	1.26(1.16,1.38)	
Center, n (%)			0.090
ANQ	5818(17.5)	1.40(1.28,1.53)	
LYG	5804(16.2)	1.25(1.15,1.37)	

5. Discussion

The current study demonstrates that baseline VAI was positively associated with the risk of new-onset hyperuricemia during a median follow-up of 4.4 years in Chinese hypertensive patients. The positive relationship was independent of VAI components (BMI, WC, TG and HDL-C). Moreover, baseline age, tHcy and sex were significant modifiers of the association between VAI and new-onset hyperuricemia.

To our knowledge, inconsistent results have been reported regarding the relationship of VAI with hyperuricemia in several cross-sectional studies. Dong et al found that there was a significant positive relation of the VAI with hyperuricemia in the Chinese populations [15]. In contrast, Liu et al reported that VAI was not associated with the prevalence of hyperuricemia among Chinese population [16]. Only a prospective cohort study of 1936 healthy workers aged 6 to 82 years in Mexico had been conducted to examine the association between VAI and the risk of hyperuricemia, and showed that individuals in the highest VAI quartile had higher odds for hyperuricemia compared with individuals from the lowest quartile [17]. However, this study only adjusted for age, alcohol consumption, smoking status and physical activity, and did not consider the effect of other important confounders. As such , the study could not provide an accurate measurement for the independent relation of VAI with hyperuricemia. Similarly, our results suggest that there is the positive association between VAI and new-onset hyperuricemia among male and female.

The potential mechanisms by which higher VAI increases the risk of hyperuricemia is unclear, but it is biologically plausible. Many studies have shown that pathological visceral adipose tissue is considered to be metabolically active. In this condition, adipose tissue abnormally releases cytokines such as leptin and adiponectin [15,30,31]. Abnormal release of these adipocytokines may cause insulin resistance which may enhance renal proximal tubular reabsorption of UA with a subsequent increase in serum UA levels [32,33]. The increase in visceral adiposity accumulation provides excess free fatty acids - products of fatty breakdown - that may be associated with purine synthesis, which may accelerate UA production 34. Third, the visceral fat volume may be more accurate in reflecting the visceral fat accumulation. Further research is required to identify mechanisms underlying an association between

VAI and new-onset hyperuricemia.

In our study, the significant group differences were observed among participants with different baseline age, tHcy levels or different sex. In accordance with previous studies, age was confrmed as a signifcant risk factor for hyperuricemia in previous studies, the prevalence of hyperuricemia increased from the age of 60 years, and reached a plateau afer the age of 70 years [35-37]. As such, we found ≥59.2years and VAI levels could jointly increase the risk of hyperuricemia. In a study by Cohen et al, hyperhomocysteinemia had a significant association with hyperuricemia [38], and in another study, was highly prevalent in gout patients [39]. Previous studies have suggested that higher tHcy may result in parallel increases in intracellular S-adenosylhomocysteine, which could induce marked DNA damage, release purine nucleotides, and lead to UA synthesis [40-43]. Therefore, we speculate that VAI levels and higher tHcy levels could jointly increase DNA damage, and thereby increase the risk of hyperuricemia. Consistently, the stronger positive association was found in those male participants, and these participants also had a relatively higher hyperuricemia burden44. The SUA level was reported to be higher among men than among women, therefore we found VAI levels and male could jointly increase the risk of hyperuricemia.

Indeed, several limitations in our study that merit emphasis. First, in this post-hoc analysis, many covariates had been adjusted in the regression models; however, residual confounding from unmeasured or unrecorded factors may work. Second, this post-hoc analysis focused on Chinese hypertensive participates, so the generalizability of these findings to other types of populations remains to be unknown. Third, serum UA levels were measured only at baseline and exit visits. More frequent measurements of serum uric acid levels are needed to more accurately assess the relationship between VAI and new-onset hyperuricemia in the duration. Although there are many limitations, our results serve as the basis for future relevant randomized trials.

6. Conclusion

In conclusion, our results suggest that higher VAI is significantly associated with increased risk of new-onset hyperuricemia in Chinese hypertensive patients, independent of single VAI components. VAI can be easily measured and applied to clinical practice. Thus, VAI has important implications for primary prevention and early detection of new-onset hyperuricemia.

7. Contributors

7.1. Study conception and design: Binyan Wang, Xiping Xu, Shaojie Zhang;

7.2. Acquisition of data: Binyan Wang;

7.3. Analysis and interpretation of data: Shaojie Zhang;

7.4. Drafting of the manuscript: Shaojie Zhang;

All authors critically revised the manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

8. Funding

None.

9. Competing Interests

None.

10. Ethics approval

The present study was approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (FWA assurance number: FWA00001263).

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