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ORIGINAL ARTICLE

# Association of visceral adiposity index with new-onset type 2 diabetes and impaired fasting glucose in hypertensive Chinese adults

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## Abstract

**Purpose** Visceral adiposity index (VAI) is a reliable indicator for the distribution and function of adipose tissue in the body. The relation of VAI with new-onset type 2 diabetes and new-onset impaired fasting glucose (IFG) remains uncertain. We aimed to investigate the prospective relation of VAI with new-onset type 2 diabetes and new-onset IFG in Chinese hypertensive adults.

**Methods** A total of 14,838 hypertensive adults free of type 2 diabetes at baseline were included from the China Stroke Primary Prevention Trial. The primary outcome was new-onset type 2 diabetes, defined as physician-diagnosed diabetes or use of glucose-lowering drugs during follow-up, or fasting glucose ≥ 7.0 mmol/L at the exit visit. The secondary outcome was new-onset IFG, defined as fasting glucose < 6.1 mmol/L at baseline, while fasting glucose ≥ 6.1 mmol/L and < 7.0 mmol/L at the exit visit.

**Results** Over a median of 4.5 years' follow-up, 1612 (10.9%) participants developed type 2 diabetes. When VAI was categorized into quartiles, compared with participants in quartile 1–3 (< 2.80), significantly higher risk of new-onset type 2 diabetes (OR 1.30; 95% CI 1.08–1.56) and new-onset IFG (OR 1.28; 95% CI 1.08–1.52) was found in those in quartile 4 (≥ 2.80). Moreover, the positive associations were consistent in participants with or without single abnormal VAI components, including general obesity, abdominal obesity, elevated triglycerides and low high-density lipoprotein cholesterol (HDL-C) levels; or with different numbers of abnormal VAI components (all *P* interactions > 0.05).

**Conclusion** Our study suggested a positive relation of VAI with the risk of new-onset type 2 diabetes and new-onset IFG in Chinese hypertensive patients, independent of its components.

**Level of evidence** Level III, a well-designed cohort.

**Keywords** Visceral adiposity index · New-onset type 2 diabetes · New-onset impair fasting glucose · Hypertension

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## Introduction

Obesity and diabetes have become urgent public health problems in China and worldwide [1, 2]. In the recent nationally representative cross-sectional surveys in mainland China, the prevalence of obesity, including general obesity and abdominal obesity was 14.0% and 31.5% [3], and the prevalence of total diabetes and impaired fasting glucose (IFG) were 10.9% and 35.7%, respectively [4].

It has been reported that excess visceral fat, but not general adiposity, were independently related to prediabetes and type 2 diabetes [5–7]. However, traditional anthropometric measures such as body mass index (BMI) and waist circumference (WC) could not distinguish visceral adipose tissue from subcutaneous adipose tissue. Moreover, imaging modalities for assessing adipose tissue distribution, such as computed tomography and magnetic resonance imaging [8], are usually inconvenient and expensive, and had radiation hazard. Recently, the visceral adiposity index (VAI), an empirical mathematical model based on simple anthropometric (BMI and WC) and lipid parameters (triglycerides [TG] and high-density lipoprotein cholesterol [HDL-C]), was found to be strongly correlated with visceral adiposity measured by magnetic resonance imaging, and therefore, is considered to be a reliable sex-specified indicator of visceral adipose distribution and function [9–11]. Consistently, some of the previous studies have showed a positive association between VAI and risk of type 2 diabetes [12–20]. However, few previous studies have examined whether the effect of VAI on type 2 diabetes was independent of its components. More importantly, few studies have evaluated the prospective relationship of VAI with new-onset IFG.

To address this gap in knowledge, our current study aimed to assess the relationship of VAI with new-onset type 2 diabetes and new-onset IFG, and examine possible effect modifiers among hypertensive patients, using data from the China Stroke Primary Prevention Trial (CSPPT) [21].

## Subjects and methods

### Study population and study design

The study design, methods, and the major results for the CSPPT (unique identifier: NCT00794885) have been reported previously elsewhere [21–25]. Briefly, the CSPPT was a multi-community, randomized, double-blind controlled clinical trial with 20,702 hypertensive participants in 32 communities in China, which was conducted from May 19, 2008 to August 24, 2013. The aim of CSPPT was to confirm that combined use of enalapril–folic acid is more effective in preventing first stroke among patients with essential hypertension when compared to enalapril alone. Eligible participants were men and women who aged 40–75 years with hypertension, defined as seated resting systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg at both the screening and recruitment visit, or who were taking anti-hypertensive therapies. The major exclusion criteria included history of physician-diagnosed stroke, myocardial infarction, heart failure, post-coronary revascularization, or congenital heart disease.

The present study is a post hoc analysis of the CSPPT. The flow of the participants is presented in Supplemental Fig. 1. The CSPPT and this study were approved by the ethics committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (FWA assurance number FWA00001263). All participants provided written informed consent.

### 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 10 mg enalapril and 0.8 mg folic acid (the enalapril–folic acid group), or a daily oral dose of one tablet containing 10 mg enalapril only (the enalapril group).

Participants were followed-up every 3 months. At each follow-up visit, blood pressure was measured; study drug adherence, concomitant medication use, adverse events and possible endpoint events were documented by trained research staff and physicians. At the exit visit, final blood samples were collected and assessed.

### Anthropometric measurements and lifestyle assessments

Anthropometric measurements, including height, weight and WC were taken using standard operating procedures. Height was measured without shoes to the nearest 0.1 cm on a portable stadiometer. Weight was measured on a weight scale to the nearest 0.1 kg with subjects wearing light indoor clothing without shoes. BMI was calculated as weight (kg)/height$^2$ (m$^2$). WC was measured as the minimum circumference between the inferior margin of the ribcage and the crest of the ileum [26–28].

Current alcohol drinking was defined as consuming alcohol twice or more per week on average for more than 1 year. Current smoking was defined as smoking at least one cigarette per day or smoking > 18 packs per year.

### Laboratory assays

Serum fasting glucose, lipids, total homocysteine, and creatinine levels were measured with automatic clinical analyzers (Bachman Coulter) at the core laboratory of the National Clinical Research Center for Kidney Disease, Nanfang Hospital, Guangzhou, China.

### VAI assessment

The VAI was determined by gender-specific equations and calculated using the following formulas: males: [WC/(39.68 + (1.88 × BMI))] × (TG/1.03) × (1.31/HDL-C); females: [WC/(36.58 + (1.89 × BMI))] × (TG/0.81) × (1.52/HDL-C) [9]. Both serum concentrations of TG and HDL are presented in mmol/L.

Abnormal VAI components were defined as the presence of any of the following component: (1) general obesity based on the Asian parameters (BMI ≥ 28 kg/m$^2$); (2) abdominal obesity based on the Asian parameters (WC ≥ 80 cm for females and ≥ 90 cm for males); (3) elevated TG (≥ 1.7 mmol/L); (4) low HDL-C (< 1.04 mmol/L for males and < 1.30 mmol/L for females) [3, 29].

The Chinese VAI (CVAI) was estimated as follows: Males: − 267.93 + 0.68 × age + 0.03 × BMI + 4.00 × WC + 22.00 × Log10TG − 16.32 × HDL-C; Females : − 187.32 + 1.71 × age + 4.23 × BMI + 1.12 × WC + 39.76 × Log10TG − 11.66 × HDL-C [30].

### Study outcomes

The primary outcome was new-onset type 2 diabetes, defined as use of glucose-lowering drugs, or physician-diagnosed diabetes during follow-up, or new-onset fasting glucose ≥ 7.0 mmol/L at the exit visit.

The secondary outcomes include: (1) new-onset IFG, defined as fasting glucose < 6.1 mmol/L at baseline, while fasting glucose ≥ 6.1 mmol/L and < 7.0 mmol/L at the exit visit. The analysis of new-onset IFG included subjects with baseline fasting glucose < 6.1 mmol/L and without new-onset type 2 diabetes during follow-up; (2) physician-diagnosed diabetes, or use of glucose-lowering drugs during follow-up.

### Statistical analysis

Baseline characteristics are presented as the mean ± standard deviations (SDs) or proportions for continuous or categorical variables, respectively. The significant differences in population characteristics according to quartiles (< 1.08, 1.08– < 1.74, 1.74– < 2.80, ≥ 2.80) of baseline VAI were compared using ANOVA test, or Chi-squared tests accordingly.

The association between VAI and new-onset type 2 diabetes (primary outcome), new-onset IFG (secondary outcome 1), and physician-diagnosed diabetes or use of glucose-lowering drugs during follow-up (secondary outcome 2), were estimated using logistic regression models (primary outcome and secondary outcome 1) and Cox proportional hazard regression models (secondary outcome 2), respectively, without and with adjustment for age, sex, treatment group, study center, SBP, family history of diabetes, smoking status, alcohol drinking status, total cholesterol, fasting glucose, total homocysteine, estimated glomerular filtration (eGFR) at baseline, as well as time-averaged on-treatment SBP, the use of diuretics during follow-up in Model 1; and all the variables in Model 1 plus BMI, WC, TG, and HDL-C in Model 2. As additional exploratory analysis, possible modifications on the association between VAI and new-onset type 2 diabetes were also evaluated by stratified analyses and interaction testing.

Two-tailed $P < 0.05$ was considered statistically significant in the analysis. All statistical analyses were performed using R software, version 3.6.0 (http://www.R-project.org/, Accessed April 26, 2019).

## Results

### Study participants and characteristics

As illustrated in the flowchart (Supplemental Fig. 1), a total of 14,838 hypertensive participants of the CSPPT with complete data on BMI, WC, TG, and HDL-C at baseline, and fasting glucose at baseline and the exit visit, without lipid-lowering treatment at baseline or during the treatment period, as well as without diabetes (defined as: physician-diagnosed diabetes, using glucose-lowering drugs or with fasting glucose ≥ 7.0 mmol/L) at baseline were included in the final analysis.

Demographic and clinical characteristics of the study patients by quartiles of VAI are shown in Table 1. The mean age of the participants was 60 ± 7.4 years old; 40.7% of the participants was men. The median baseline VAI was 1.74 with an interquartile range of 1.08–2.80. Participants with higher VAI were more likely to be females and younger, and less likely to be smokers and alcohol drinkers, had a higher BMI, greater WC, and had higher DBP, TG, total cholesterol, fasting glucose and eGFR levels, had lower HDL-C, total homocysteine, and creatinine levels, had a higher frequency of family history of diabetes, and a higher use of anti-hypertensive or anti-platelet drugs at baseline; as well as higher time-averaged on-treatment SBP and DBP during the follow-up.

**Table 1** Characteristics of study participants by quartiles of baseline VAI[a]

| Variables | Baseline visceral adiposity index (VAI) quartiles | | | | *P* value[b] |
|---|---|---|---|---|---|
| | Q1(< 1.08) | Q2(1.08– < 1.74) | Q3(1.74– < 2.80) | Q4(≥ 2.80) | |
| *N* | 3710 | 3709 | 3709 | 3710 | |
| Male, *N* (%) | 2750 (74.1) | 1554 (41.9) | 1035 (27.9) | 707 (19.1) | < 0.001 |
| Age, (years) | 61.1 ± 7.4 | 60.2 ± 7.5 | 59.6 ± 7.4 | 59.3 ± 7.2 | < 0.001 |
| Enalapril–folic acid group, *N* (%) | 1866 (50.3) | 1872 (50.5) | 1830 (49.3) | 1838 (49.5) | 0.712 |
| BMI, (kg/m$^2$) | 22.8 ± 3.0 | 24.4 ± 3.4 | 25.6 ± 3.5 | 26.7 ± 3.4 | < 0.001 |
| WC, (cm) | 78.4 ± 8.4 | 82.5 ± 9.3 | 85.9 ± 9.4 | 89.0 ± 8.8 | < 0.001 |
| VAI | 0.8 ± 0.2 | 1.4 ± 0.2 | 2.2 ± 0.3 | 4.6 ± 3.5 | < 0.001 |
| BP, (mmHg) | | | | | |
| Baseline SBP | 166.6 ± 20.2 | 166.8 ± 20.3 | 166.9 ± 20.7 | 167.5 ± 20.1 | 0.332 |
| Baseline DBP | 93.9 ± 12.1 | 94.0 ± 12.0 | 94.4 ± 11.7 | 94.6 ± 11.5 | 0.020 |
| Time-averaged SBP during follow-up | 138.3 ± 10.3 | 138.7 ± 10.5 | 138.6 ± 10.6 | 139.4 ± 10.5 | < 0.001 |
| Time-averaged DBP during follow-up | 82.4 ± 7.3 | 82.7 ± 7.3 | 82.9 ± 7.3 | 83.3 ± 7.1 | < 0.001 |
| Current smoking, *N* (%) | 1601 (43.2) | 890 (24.0) | 591 (15.9) | 422 (11.4) | < 0.001 |
| Current alcohol drinking, *N* (%) | 1691 (45.6) | 847 (22.8) | 594 (16.0) | 418 (11.3) | < 0.001 |
| Family history of diabetes, *N* (%) | 100 (2.7) | 117 (3.2) | 158 (4.3) | 174 (4.7) | < 0.001 |
| Laboratory results | | | | | |
| HDL-C, (mmol/L) | 1.7 ± 0.4 | 1.4 ± 0.3 | 1.3 ± 0.3 | 1.1 ± 0.2 | < 0.001 |
| TG, (mmol/L) | 0.9 ± 0.2 | 1.3 ± 0.3 | 1.7 ± 0.4 | 2.7 ± 1.9 | < 0.001 |
| Total cholesterol, (mmol/L) | 5.3 ± 1.1 | 5.4 ± 1.1 | 5.6 ± 1.1 | 5.5 ± 1.2 | < 0.001 |
| Total homocysteine, (μmol/L) | 15.0 ± 8.5 | 14.2 ± 7.5 | 14.4 ± 8.9 | 14.2 ± 8.4 | < 0.001 |
| Fasting glucose, (mmol/L) | 5.3 ± 0.7 | 5.4 ± 0.7 | 5.4 ± 0.7 | 5.5 ± 0.7 | < 0.001 |
| Creatinine, (μmol/L) | 72.2 ± 16.3 | 67.4 ± 14.8 | 64.2 ± 14.8 | 59.3 ± 17.3 | < 0.001 |
| eGFR, (mL/(min.1.73m$^2$)) | 92.0 ± 11.9 | 92.2 ± 12.2 | 93.4 ± 12.5 | 96.6 ± 13.0 | < 0.001 |
| Medication use, *N* (%) | | | | | |
| Anti-hypertensive drug | 1405 (37.9) | 1652 (44.5) | 1778 (47.9) | 1942 (52.3) | < 0.001 |
| Anti-platelet drug | 85 (2.3) | 96 (2.6) | 107 (2.9) | 126 (3.4) | 0.028 |

*BMI* body mass index, *WC* waist circumference, *VAI* visceral adiposity index, *HDL-C* high-density lipoprotein cholesterol, *TG* triglyceride, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate

[a]Continuous variables are presented as the means ± SDs; categorical variables are presented as *N* (%)

[b]The *P* values indicate differences between any two groups

Additionally, participants with higher baseline VAI had a higher frequency in the use of diuretics during the treatment period (Supplemental Table 1).

## Association between visceral adiposity index (VAI) and study outcomes

During a median of 4.5 years' follow-up, 1612 (10.9%) participants developed type 2 diabetes. Of these, 161 were those with the use of glucose-lowering drugs, or physician-diagnosed diabetes during follow-up. Participants with new-onset type 2 diabetes tended to have higher VAI levels compared with those without new-onset type 2 diabetes (median, interquartile range; 2.12, 1.28–3.43 vs. 1.71, 1.06–2.72, $P < 0.001$). Higher VAI was also showed in patients with new-onset IFG (median, interquartile range; 1.86, 1.14–3.01 vs. 1.66, 1.03–2.63, $P < 0.001$), compared with those without new-onset IFG.

Consistently, when VAI was assessed as quartiles, a higher incidence risk of new-onset type 2 diabetes (primary outcome: adjusted OR 1.65; 95% CI 1.46, 1.86, $P < 0.001$), new-onset IFG (secondary outcome 1: adjusted OR 1.42; 95% CI 1.26, 1.59, $P < 0.001$), and physician-diagnosed diabetes, or use of glucose-lowering drugs during follow-up (secondary outcome 2: adjusted HR 2.35; 95% CI 1.68, 3.28, $P < 0.001$) were found in participants in quartile 4 (≥ 2.80), compared with those in quartiles 1–3 (< 2.80) (Table 2, Supplemental Table 2).

More importantly, further adjustment for BMI, WC, TG and HDL-C did not materially alter the relationship of higher VAI level (≥ 2.80) with new-onset type 2 diabetes (primary outcome: adjusted OR 1.30; 95% CI 1.08, 1.56, $P = 0.005$), new-onset IFG (secondary outcome 1: adjusted

**Table 2** Association between VAI and new-onset type 2 diabetes, new-onset IFG during follow-up

| Visceral Adiposity Index | Events/*N* (%) | Unadjusted model OR (95% CI) | *P* value | Adjusted model 1[a] OR (95% CI) | *P* value | Adjusted model 2[b] OR (95% CI) | *P* value |
|---|---|---|---|---|---|---|---|
| New-onset type 2 diabetes[c] | | | | | | | |
| Quartiles | | | | | | | |
| Q1 (< 1.08) | 299/3710 (8.1) | Ref | | Ref | | Ref | |
| Q2 (1.08– < 1.74) | 353/3709 (9.5) | 1.20 (1.02, 1.41) | 0.027 | 1.21 (1.02, 1.44) | 0.029 | 1.11 (0.91, 1.34) | 0.298 |
| Q3 (1.74– < 2.80) | 393/3709 (10.6) | 1.35 (1.15, 1.58) | < 0.001 | 1.43 (1.20, 1.70) | < 0.001 | 1.18 (0.93, 1.51) | 0.177 |
| Q4 (≥ 2.80) | 567/3710 (15.3) | 2.06 (1.77, 2.39) | < 0.001 | 2.05 (1.73, 2.44) | < 0.001 | 1.57 (1.13, 2.19) | 0.007 |
| *P* for trend | | < 0.001 | | < 0.001 | | 0.013 | |
| Q1-3 (< 2.80) | 1045/11, 128 (9.4) | Ref | | Ref | | Ref | |
| Q4 (≥ 2.80) | 567/3710 (15.3) | 1.74 (1.56, 1.94) | < 0.001 | 1.65 (1.46, 1. 86) | < 0.001 | 1.30 (1.08, 1.56) | 0.005 |
| New-onset IFG[d] | | | | | | | |
| Quartiles | | | | | | | |
| Q1 (< 1.04) | 418/2859 (14.6) | Ref | | Ref | | Ref | |
| Q2 (1.04– < 1.70) | 442/2859 (15.5) | 1.07 (0.92, 1.23) | 0.375 | 1.11 (0.95, 1.29) | 0.181 | 1.16 (0.98, 1.38) | 0.093 |
| Q3 (1.70– < 2.71) | 467/2859 (16.3) | 1.14 (0.99, 1.32) | 0.073 | 1.24 (1.06, 1.45) | 0.008 | 1.30 (1.04, 1.61) | 0.019 |
| Q4 (≥ 2.71) | 595/2860 (20.8) | 1.53 (1.34, 1.76) | < 0.001 | 1.61 (1.37, 1.88) | < 0.001 | 1.71 (1.27, 2.31) | < 0.001 |
| *P* for trend | | < 0.001 | | < 0.001 | | < 0.001 | |
| Q1-3 (< 2.71) | 1327/8577 (15.5) | Ref | | Ref | | Ref | |
| Q4 (≥ 2.71) | 595/2860 (20.8) | 1.44 (1.29, 1.60) | < 0.001 | 1.42 (1.26, 1.59) | < 0.001 | 1.28 (1.08, 1.52) | 0.005 |

[a]Model 1: adjusted for age, sex, group, study center, systolic blood pressure (SBP), family history of diabetes, smoking status, alcohol drinking status, total cholesterol, fasting glucose, total homocysteine, estimated glomerular filtration (eGFR) at baseline, as well as time-averaged on-treatment SBP, the use of diuretics during follow-up

[b]Model 2: adjusted for all the variables in the model 1, plus *BMI* body mass index, *WC* waist circumference, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol

[c]For the primary outcome, since there are four times assessments, we used the Bonferroni method and accepted $P < 0.0125$ as significant

[d]Subjects with baseline fasting glucose < 6.1 mmol/L and without new-onset type 2 diabetes during follow-up were included in the analysis

OR 1.28; 95% CI 1.08, 1.52, $P = 0.005$), and physician-diagnosed diabetes, or use of glucose-lowering drugs during follow-up (secondary outcome 2: adjusted HR 1.71; 95% CI 1.02, 2.88, $P = 0.042$) (Table 2, Supplemental Table 2). Of note, the association between VAI (quartile 4 versus 1–3) and primary outcome remained significant after Bonferroni multiple test correction for four tests (adjusted $P = 0.0125$).

Moreover, further adjustments for the use of CCB (calcium channel blockers) and anti-platelet medications during the treatment period also did not significantly change the results (Supplemental Table 3).

## Stratified analyses by VAI components

To further evaluate whether VAI components have a confounding effect on the association between VAI and the risk of new-onset type 2 diabetes, stratified analyses were performed as shown in Table 3. The results showed that the positive association between VAI and new-onset type 2 diabetes persisted in participants with or without general obesity, abdominal obesity, elevated TG, and decreased HDL-C. There were no significant interactions between VAI and single VAI components on new-onset type 2 diabetes (all *P* for interactions > 0.05). More importantly, the number of abnormal VAI components (≤ 1, 2, and ≥ 3) also did not modify the association between VAI and the risk of new-onset type 2 diabetes (*P* for interaction = 0.549) (Table 3).

Similar results were found for the new-onset IFG (Table 4).

## Stratified analyses by other potential effect modifiers

None of the other variables, including age (< 55 vs. ≥ 55 years), gender (male vs. female), treatment group (enalapril group vs. enalapril–folic acid group), baseline SBP (< 160 vs. ≥ 160 mmHg), time-averaged SBP (< 140 vs. ≥ 140 mmHg), current smoking status (yes vs. no), current alcohol drinking status (yes vs. no), total cholesterol (< 5.2 vs. ≥ 5.2 mmol/L) total homocysteine (< 15 vs. ≥ 15 μmol/L), eGFR (< 90 vs. ≥ 90 mL/min/1.73 $m^2$), Chinese VAI (median, < 108 vs. ≥ 108) significantly modified the associations between baseline VAI and the risk of new-onset type 2 diabetes (Fig. 1) or IFG (Supplemental Fig. 2) in hypertensive patients (all *P* for interactions > 0.05).

**Table 3** Stratified analysis of association between baseline VAI and new-onset type 2 diabetes diabetes by VAI components

| Subgroups[b] | Q1-3 events (%) | Q4 events (%) | Unadjusted model OR (95%CI) | Adjusted model[a] OR (95% CI) | *P* for interaction |
|---|---|---|---|---|---|
| General obesity | | | | | 0.420 |
| Yes | 213 (13.4) | 236 (19.8) | 1.60 (1.31, 1.96) | 1.38 (1.08, 1.77) | |
| No | 832 (8.7) | 331 (13.1) | 1.58 (1.38, 1.81) | 1.24 (1.01, 1.53) | |
| Abdominal obesity | | | | | 0.790 |
| Yes | 538 (11.3) | 493 (16.3) | 1.52 (1.33, 1.74) | 1.31 (1.08, 1.58) | |
| No | 507 (7.9) | 74 (10.8) | 1.41 (1.09, 1.82) | 1.26 (0.92, 1.71) | |
| Elevated TG | | | | | 0.191 |
| Yes | 844 (9.0) | 512 (15.3) | 1.39 (1.17, 1.66) | 1.23 (1.01, 1.50) | |
| No | 201 (11.5) | 55 (15.5) | 1.86 (1.38, 2.50) | 1.57 (1.13, 2.18) | |
| Low HDL-C | | | | | 0.756 |
| Yes | 256 (10.2) | 461 (15.4) | 1.61 (1.36, 1.89) | 1.22 (0.99, 1.51) | |
| No | 789 (9.2) | 106 (14.8) | 1.73 (1.39, 2.15) | 1.28 (0.98, 1.67) | |
| Number of abnormal VAI components | | | | | 0.549 |
| ≤ 1 | 669 (8.4) | 23 (11.7) | 1.46 (0.94, 2.27) | 1.33 (0.82, 2.14) | |
| 2 | 239 (10.7) | 131 (12.8) | 1.23 (0.98, 1.55) | 1.43 (1.10, 1.86) | |
| ≥ 3 | 137 (15.3) | 413 (16.6) | 1.10 (0.89, 1.36) | 1.19 (0.93, 1.51) | |

[a]If not stratified, adjusted for age, sex, group, study center, systolic blood pressure (SBP), family history of diabetes, smoking status, alcohol drinking status, total cholesterol, fasting glucose, total homocysteine, estimated glomerular filtration (eGFR), body mass index (BMI), waist circumference (WC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) at baseline, as well as time-averaged on-treatment SBP, the use of diuretics during follow-up

[b]General obesity was defined as BMI ≥ 28 kg/m$^2$; abdominal obesity was defined as WC ≥ 80 cm for females and ≥ 90 cm for males; elevated TG was defined as TG ≥ 1.7 mmol/L; low HDL-C was defined as HDL-C < 1.04 mmol/L for males and HDL-C < 1.30 mmol/L for females; abnormal VAI components were defined as the presence of the following components: (1) general obesity; (2) abdominal obesity; (3) elevated TG; (4) low HDL-C

## Discussion

The present study first showed that VAI was positively associated with the risk of increased incidence of new-onset type 2 diabetes and new-onset IFG in Chinese hypertensive patients. The positive association was independent of the VAI components (BMI, WC, TG and HDL-C). In addition, the results were consistent in participants with different baseline characteristics.

Consistently, some of the previous studies have reported that higher VAI levels were associated with an increased risk of type 2 diabetes [12–20]. A systematic review included seven studies in Asia, four in prospective design and three in a cross-sectional design, also indicated that VAI is positively associated with diabetes [31]. However, none of the previous studies had investigated whether the effect of VAI on type 2 diabetes was independent of its components. Moreover, this issue has not been well examined in the hypertensive patients, a subpopulation with a high risk for developing diabetes [32].

IFG is another important abnormal glucose metabolism condition, which can be reversed into normal glucose condition and is also more prevalent in hypertensive patients [32, 33]. In Chinese hypertensive adults, the prevalence of IFG was about 40.7% [34]. IFG was significantly associated with the development of diabetes [35]. Therefore, early detection and primary prevention of IFG may be essential strategies to reduce the incidence of type 2 diabetes and its related complications. For instance, only one prior study in cross-sectional design, which included 280 non-smokers, overweight or obese Mexican adults, reported a positive association between VAI and IFG [36]. However, the prospective relationship of VAI with IFG remains unknown.

Nevertheless, CVAI, a new indicator of visceral adiposity, was also developed in a previous study in Chinese adults [28]. As were reported, VAI was significantly correlated with visceral adipose volume measured by magnetic resonance imaging, while CVAI was well associated with visceral adipose area measured by computed tomography [9, 28]. In the present study, we first found that there was a significantly positive relation of VAI levels with both new-onset type 2 diabetes and new-onset IFG in hypertensive patients, independent of BMI, WC, TG, HDL-C. More importantly, although commonly WC and the BMI are assessed and is easy to do, in the field, our study further showed that the positive relation of VAI with new-onset type 2 diabetes or new-onset IFG was consistent in participants with or without general obesity, abdominal obesity, elevated TG, decreased

**Table 4** Stratified analysis of association between baseline VAI and new-onset IFG by VAI components

| Subgroups[b] | Q1-3 events (%) | Q4 events (%) | Unadjusted model OR (95%CI) | Adjusted model[a] OR (95% CI) | *P* for interaction |
|---|---|---|---|---|---|
| General obesity | | | | | 0.415 |
| Yes | 224 (20.2) | 194 (23.3) | 1.19 (0.96, 1.49) | 1.18 (0.92, 1.52) | |
| No | 1103 (14.8) | 401 (19.8) | 1.42 (1.26, 1.62) | 1.32 (1.09, 1.60) | |
| Abdominal obesity | | | | | 0.218 |
| Yes | 612 (17.7) | 485 (21.3) | 1.26 (1.11, 1.44) | 1.24 (1.03, 1.48) | |
| No | 715 (14.0) | 110 (18.7) | 1.42 (1.14, 1.77) | 1.47 (1.11, 1.93) | |
| Elevated TG | | | | | 0.195 |
| Yes | 211 (17.5) | 522 (20.6) | 1.22 (1.02, 1.46) | 1.20 (0.99, 1.46) | |
| No | 1116 (15.1) | 73 (22.5) | 1.62 (1.24, 2.12) | 1.50 (1.12, 2.02) | |
| Low HDL-C | | | | | 0.154 |
| Yes | 288 (15.6) | 462 (20.2) | 1.37 (1.17, 1.61) | 1.16 (0.95, 1.42) | |
| No | 1039 (15.4) | 133 (23.1) | 1.64 (1.34, 2.02) | 1.41 (1.10, 1.81) | |
| Number of abnormal VAI components | | | | | 0.157 |
| ≤ 1 | 918 (14.4) | 37 (21.9) | 1.67 (1.15, 2.42) | 1.77 (1.18, 2.65) | |
| 2 | 290 (18.0) | 175 (20.0) | 1.14 (0.92, 1.40) | 1.34 (1.05, 1.70) | |
| ≥ 3 | 119 (20.7) | 383 (21.1) | 1.02 (0.81, 1.29) | 1.13 (0.87, 1.45) | |

[a]If not stratified, adjusted for age, sex, group, study center, systolic blood pressure (SBP), family history of diabetes, smoking status, alcohol drinking status, total cholesterol, fasting glucose, total homocysteine, estimated glomerular filtration (eGFR), body mass index (BMI), waist circumference (WC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) at baseline, as well as time-averaged on-treatment SBP, the use of diuretics during follow-up

[b]General obesity was defined as BMI ≥ 28 kg/m$^2$; abdominal obesity was defined as WC ≥ 80 cm for females and ≥ 90 cm for males; elevated TG was defined as TG ≥ 1.7 mmol/L; low HDL-C was defined as HDL-C < 1.04 mmol/L for males and HDL-C < 1.30 mmol/L for females; abnormal VAI components were defined as the presence of the following components: (1) general obesity; (2) abdominal obesity; (3) elevated TG; (4) low HDL-C

HDL-C and elevated CVAI, indicating that higher VAI could reflect more risk factors or detrimental mechanisms associated with abnormal glucose metabolism, which are not signified by BMI, WC, TG, HDL-C, and even CVAI separately. The possible mechanisms include, first, excess visceral adiposity tissue produces excess inflammatory cytokines and adipokines or leads to lower leptin concentration. Those will contribute to the pathogenesis of insulin resistance, an initial process to IFG and diabetes [37–39]. Second, visceral lipid accumulation in hypertrophic adipocytes initiates a state of cellular stress, implicates in the activation of the c-Jun N-terminal kinase (JNK) pathway, blocking normal insulin receptor signaling and the activation of the pro-inflammatory pathway that leads to the production of pro-inflammatory cytokines, results resulting in diminished glucose uptake, free fatty acid esterification, and storage which associated with incident dysglycemia [40–42]. Third, the visceral fat volume may be more accurate in reflecting the visceral fat accumulation. Overall, our findings suggest that VAI may be an important and independent risk factor for evaluating the risk of new-onset type 2 diabetes and new-onset IFG. However, future studies are needed to further investigate the underlying mechanisms.

The major strength of the present study was to provide an opportunity to assess the prospective relation of baseline VAI with new-onset type 2 diabetes and new-onset IFG in hypertensive patients with the largest sample size of its kind, an adjustment for comprehensive covariables, and a series of stratified analyses, including the components of VAI (BMI, WC, TG and HDL-C) and CVAI. However, the present study has some limitations. First, this was a post hoc analysis of the CSPPT, although the adjustments for a broad range of confounding in the analysis, unmeasured or unrecorded variables of residual confounding cannot be excluded. Second, our present research was conducted in hypertensive participants, the generality of the results to other populations remains to be considered. Third, although the physician-diagnosed diabetes and the use of glucose-lowering drugs during treatment period were recorded every 3 months in the CSPPT, fasting glucose only assessed at the baseline and the exit visit. More frequent measurements of fasting glucose levels would have allowed a more accurate assessment of its progression. Finally, we did not measure the adipokine, islets β cell function, insulin levels and direct inflammatory markers, which would help explore the potential

| Variables | Size | Q1-3 Events(%) | Q4 Events(%) | OR(95%CI) | P for interaction |
|---|---|---|---|---|---|
| Age, yr | | | | | 0.068 |
| <55 | 4042 | 239 (8.1) | 173 (15.9) | 1.55 (1.20,2.00) | |
| ≥55 | 10796 | 806 (9.9) | 394 (15.0) | 1.22 (1.00,1.48) | |
| Gender | | | | | 0.865 |
| male | 6046 | 535 (10.0) | 121 (17.1) | 1.28 (0.98,1.67) | |
| female | 8792 | 510 (8.8) | 446 (14.9) | 1.31 (1.08,1.59) | |
| Group | | | | | 0.305 |
| Enalapril group | 7432 | 507 (9.1) | 287 (15.3) | 1.38 (1.11,1.71) | |
| Enalapril-folic Acid group | 7406 | 538 (9.7) | 280 (15.2) | 1.22 (0.99,1.52) | |
| Baseline SBP, mmHg | | | | | 0.338 |
| <160 | 5603 | 376 (8.8) | 207 (15.5) | 1.40 (1.11,1.77) | |
| ≥160 | 9235 | 669 (9.7) | 360 (15.2) | 1.25 (1.02,1.53) | |
| Time-averaged SBP, mmHg | | | | | 0.189 |
| <140 | 8712 | 536 (8.1) | 282 (13.7) | 1.41 (1.14,1.74) | |
| ≥140 | 6126 | 509 (11.4) | 285 (17.3) | 1.20 (0.97,1.50) | |
| Current smoking | | | | | 0.145 |
| yes | 3504 | 303 (9.8) | 82 (19.4) | 1.59 (1.15,2.19) | |
| no | 11331 | 741 (9.2) | 485 (14.8) | 1.26 (1.04,1.51) | |
| Current alcohol drinking | | | | | 0.809 |
| yes | 3550 | 302 (9.6) | 68 (16.3) | 1.26 (0.90,1.76) | |
| no | 11281 | 742 (9.3) | 499 (15.2) | 1.31 (1.08,1.58) | |
| Total cholesterol, mmol/L | | | | | 0.103 |
| <5.2 | 6336 | 433 (9.0) | 247 (16.2) | 1.46 (1.16,1.83) | |
| ≥5.2 | 8501 | 612 (9.7) | 320 (14.6) | 1.20 (0.98,1.47) | |
| tHcy,μmol/L | | | | | 0.143 |
| <15 | 10675 | 713 (9.0) | 433 (15.6) | 1.37 (1.13,1.67) | |
| ≥15 | 4156 | 332 (10.3) | 134 (14.4) | 1.13 (0.87,1.47) | |
| eGFR,mL/min*1.73m$^2$ | | | | | 0.369 |
| <90 | 4663 | 354 (9.3) | 115 (13.5) | 1.20 (0.92,1.58) | |
| ≥90 | 10170 | 691 (9.5) | 452 (15.8) | 1.36 (1.12,1.65) | |
| Chinese VAI | | | | | 0.677 |
| <108 | 7419 | 560 (7.9) | 27 (9.3) | 1.19 (0.76,1.86) | |
| ≥108 | 7419 | 485 (12.1) | 540 (15.8) | 1.31 (1.08,1.57) | |

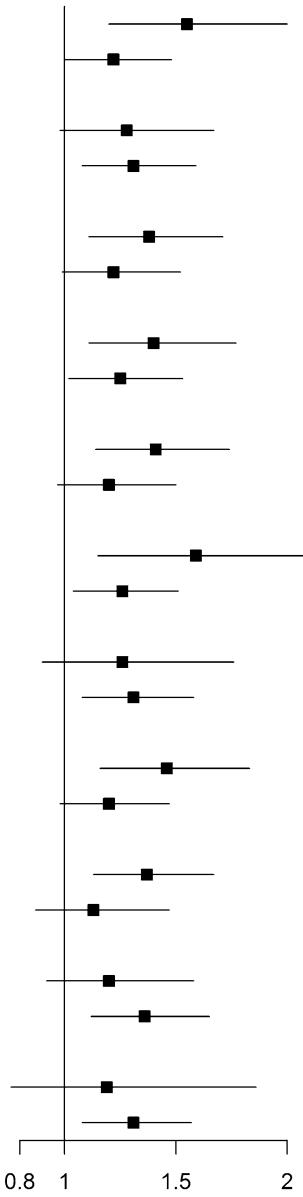


**Fig. 1** Stratified analysis of association between baseline VAI (≥2.80 vs. VAI<2.80) and new-onset type 2 diabetes by other variables[a]. [a]Adjusted, if not stratified, for age, sex, group, study center, systolic blood pressure (SBP), family history of diabetes, smoking status, alcohol drinking status, total cholesterol, fasting glucose, total homocysteine, estimated glomerular filtration (eGFR), body mass index (BMI), waist circumference (WC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) at baseline, as well as time-averaged on-treatment SBP, the use of diuretics during follow-up

mechanism and pathophysiological process of VAI and diabetes. Overall, our study is hypothesis-generating, further studies are needed to confirm the findings.

In conclusion, our study suggested a positive relation of VAI with new-onset type 2 diabetes and new-onset IFG in hypertensive population, independent of the components of VAI. If further confirmed, VAI measurements along with other known risk factors, would further help identify hypertensive patients at high risk of developing abnormal glucose metabolisms.

## What is already known on this subject?

Previous studies have reported that higher VAI levels were associated with increased risk of type 2 diabetes. However, none of the previous studies had investigate whether the effect of VAI on type 2 diabetes was independent of its components, and the prospective relationship of VAI with IFG remains unknown.

## What this study adds?

Our study suggested a positive relation of VAI with new-onset type 2 diabetes and new-onset IFG in hypertensive population, independent of the components of VAI. If further confirmed, VAI measurements along with other known risk factors, would further help identify hypertensive patients at high risk of developing abnormal glucose metabolisms.

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**Author contributions** CZ and XQ designed research and wrote paper, XQ, CZ conducted research, CZ and CL analyzed data, all authors revise and approved the final manuscript.

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**Data availability** Data described in the manuscript, code book, and analytic code will be made available from the corresponding authors on request, after the request is submitted and formally reviewed and approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China.

## Declarations

**Conflict of interest** Dr. Xiping Xu reports Grants from the National Key Research and Development Program [2016YFE0205400, 2018ZX09739010, 2018ZX09301034003], the Science and Technology Planning Project of Guangzhou, China [201707020010], the Science, Technology, and Innovation Committee of Shenzhen [JSGG20170412155639040, GJHS20170314114526143, JSGG20180703155802047], and the Economic, Trade and Information Commission of Shenzhen Municipality [20170505161556110, 20170505160926390]. Dr. Jing Nie reports grants from the National Key R&D program of China [2020YFC2005000]. Dr. Xianhui Qin reports Grants from the National Natural Science Foundation of China [81973133, 81730019]. No other disclosures were reported.

**Ethical approval** This study was approved by the ethics committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (FWA assurance number FWA00001263).

**Consent to participate** All participants provided written informed consent.

**Consent for publication** All authors agreed with the content and that all gave explicit consent to submit.

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