



ORIGINAL RESEARCH

# Association of Chinese Visceral Adiposity Index and Its Dynamic Change With Risk of Carotid Plaque in a Large Cohort in China

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**BACKGROUND:** We aimed to evaluate the association between the Chinese visceral adiposity index (CVAI) and its dynamic change and risk of carotid plaque based on a large Chinese cohort.

**METHODS AND RESULTS:** This cohort included 23 522 participants aged 20 to 80 years without elevated carotid intima-media thickness and carotid plaque at baseline and who received at least 2 health checkups. CVAI was calculated at baseline and at every checkup. The dynamic change in CVAI was calculated by subtracting CVAI at baseline from that at the last follow-up. Cox proportional hazard regression model was used to estimate hazard ratios (HRs) and 95% CIs. The restricted cubic spline was applied to model the dose-response association between CVAI and carotid plaque risk. During the 82 621 person-years of follow-up, 5987 cases of carotid plaque developed (7.25/100 person-years). We observed a significant positive correlation between CVAI and carotid plaque risk (HR, 1.53; 95% CI, 1.48–1.59 [ $P < 0.001$ ]) in a nonlinear dose-response pattern ( $P_{\text{nonlinearity}} < 0.001$ ). The sensitivity analyses further confirmed the robustness of the results. The association was significant in all subgroup analyses stratified by sex, hypertension, and fatty liver disease except for the diabetes subgroup. The association between CVAI and carotid plaque risk was much higher in men than in women. No significant association was identified between change in CVAI and carotid plaque risk.

**CONCLUSIONS:** CVAI was positively associated with carotid plaque risk in a nonlinear dose-response pattern in this study. Individuals should keep their CVAI within a normal level to prevent the development of carotid plaque.

**Key Words:** carotid plaque ■ Chinese visceral adiposity index ■ cohort study ■ dynamic change

Atherosclerosis is an inflammatory process that causes complex lesions or plaques to protrude into the arterial lumen.<sup>1</sup> With the rupture and fragmentation embolization of the plaques, it can cause malignant cerebrovascular events and seriously threaten human health.<sup>2</sup> Carotid plaque is a potential marker of atherosclerosis and can effectively predict the presence of atherosclerosis and cardiovascular events.<sup>3</sup> It has been proposed that about one third of Chinese adults have carotid plaque, and its progression rate with age is more extreme than that of

European countries.<sup>4</sup> Therefore, it is urgent to identify effective tools to detect and intervene carotid plaque in advance to reduce the health burden of the population.

Studies have shown that visceral obesity is an independent risk factor for the increased risk of carotid atherosclerosis.<sup>5,6</sup> Direct measurement of visceral obesity using imaging techniques is expensive and often not feasible in public health. Several clinical proxies are commonly used, such as body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) to assess visceral obesity.

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For Sources of Funding and Disclosures, see pages 11 and 12.

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## CLINICAL PERSPECTIVE

### What Is New?

- The Chinese visceral adiposity index (CVAI) is associated with carotid plaque risk for both sexes and in individuals with and without hypertension and fatty liver disease and those without diabetes.
- The association between CVAI and risk of carotid plaque is in a nonlinear pattern.

### What Are the Clinical Implications?

- CVAI might be a useful and applicable indicator for predicting carotid plaque risk in the clinic for the public.
- The risk of incident carotid plaque increased by 53% per 1-SD increase in baseline CVAI (hazard ratio, 1.53; 95% CI, 1.48–1.59). Therefore, individuals should keep their CVAI within a normal level to prevent carotid plaque.

## Nonstandard Abbreviations and Acronyms

<b>ABSI</b>	a body shape index
<b>CVAI</b>	Chinese visceral adiposity index
<b>LAP</b>	lipid accumulation product
<b>VAI</b>	visceral adiposity index
<b>WC</b>	waist circumference
<b>WHR</b>	waist-to-hip ratio
<b>WHtR</b>	waist-to-height ratio

However, these indicators can neither accurately distinguish between muscle and fat mass, nor between peripheral fat and abdominal fat, or are too sensitively influenced by height and weight, which could not effectively evaluate the body's external morphology and internal tissue composition.

There is evidence of significant differences in body fat distribution between various ethnicities.<sup>7</sup> Furthermore, the Asian population seems to be more inclined to visceral fat accumulation at lower BMIs.<sup>8</sup> Considering these characteristics, the Chinese visceral adiposity index (CVAI) was developed to predict visceral adipose area in Chinese adults. The CVAI was proven to be a reliable index for the evaluation of visceral fat in a cross-sectional study of 485 participants and was further validated in 6495 participants recruited from Shanghai, and it showed better performance than BMI and WC.<sup>9</sup>

Visceral adipose tissue was the primary region of adiposity associated with atherosclerosis and especially may cause more risk in men.<sup>5,10</sup> Abdominal fat assessment may be a powerful tool for detecting the

subclinical status of carotid atherosclerosis.<sup>6</sup> However, the relationship between CVAI and carotid plaque risk is not yet clear. In addition, whether a change in CVAI ( $\Delta$ CVAI) affects future carotid plaque risk has been of interest and remains unclear. Therefore, we performed this study to estimate the association between CVAI and  $\Delta$ CVAI and carotid plaque risk in a Chinese cohort.

## METHODS

### Study Patients

The data that support the findings of this study are available from the corresponding author on reasonable request. The data were obtained from a longitudinal cohort in which participants underwent a comprehensive annual/biennial health screening examination at Beijing Xiaotangshan Hospital from 2009 to 2016. Participants were considered eligible if they were aged  $\geq 20$  and  $< 80$  years, were free of elevated carotid intima-media thickness and carotid plaque at the baseline health examination, and completed at least 2 health checkups ( $n=24\ 288$ ). Individuals with cancer ( $n=314$ ), coronary heart disease ( $n=315$ ), stroke ( $n=74$ ), or myocardial infarction ( $n=63$ ) at baseline were excluded from the current study. Finally, a total of 23 522 participants entered into this study. The institutional review board of the Xiaotangshan Hospital approved this study (No. 202006). Only routine health check information was used for data analysis, so the requirement for informed consent from participants was waived.

### Carotid Ultrasound Assessment

The vascular ultrasonography examination was performed by experienced radiologists who had  $>3$  years of experience in carotid ultrasound and were blinded to all clinical information using a 3.5-MHz transducer (logic Q700 MR, GE). Radiologists have unified training and diagnosis criteria and regular evaluation of the consistency of examination results among radiologists. The consistency of inspection results was typically evaluated every 3 months. For consistency assessments, all agreement rates were  $>95\%$ , with the largest being 99.5%. Both sides of the internal carotid artery and common carotid artery were examined, and each side was measured 3 times. If the lesions on both sides were not consistent, the more serious side of the lesion prevailed. The recording frequency of ultrasound images of the common carotid artery was 5 to 10 MHz, and the acquisition frequency of ultrasound images of the carotid bulb and proximal carotid artery was 9 MHz. The diastolic images were recorded on all ultrasound images to reduce cardiac cycle variability.

Carotid plaque was interpreted as the presence of focal wall thickening that was at least 0.5 mm, or 50% greater than that of the surrounding vessel wall,

or as a focal region with carotid intima-media thickness  $>1.5$  mm that protrudes into the lumen, which was distinct from the adjacent boundary.<sup>11</sup>

## Data Collection

Information on demographic characteristics (eg, age and sex), lifestyles (eg, cigarette smoking and alcohol drinking), personal medical history, and use of medications were obtained at baseline and follow-up checkups for all participants by face-to-face standardized questionnaire interviews; anthropometry, clinical, and biochemical measures were collected by well-trained doctors and nurses. Height and weight were measured via standard methods with participants wearing light clothes without shoes. BMI was calculated by dividing weight (kg) by height squared ( $m^2$ ). WC was measured twice at 1.0 cm horizontally above the navel as the participants exhaled with legs about 25- to 30-cm apart. WHR was calculated as WC divided by hip circumference. WHtR was calculated as WC divided by height. A body shape index (ABSI),<sup>12</sup> lipid accumulation product (LAP),<sup>13</sup> and visceral adiposity index (VAI)<sup>14</sup> were calculated as follows, with triglyceride and high-density lipoprotein cholesterol (HDL-C) levels expressed as millimole per liter:  $ABSI = WC / (BMI^{2/3} \times height^{1/2})$ ;  $LAP = (WC - 65) \times triglycerides$  for men,  $LAP = (WC - 58) \times triglycerides$  for women;  $VAI = (WC / (39.68 + (1.88 \times BMI))) \times (triglycerides / 1.03) \times (1.31 / (HDL - C))$  for men;  $VAI = (WC / (36.58 + (1.89 \times BMI))) \times (triglycerides / 0.81) \times (1.52 / (HDL - C))$  for women. Systolic and diastolic blood pressures were measured 3 times with a 30-second interval using an electronic sphygmomanometer (HEM-770AFuzzy, Omron) on the right arm of patients in a seated position after at least 5 minutes of rest.

Overnight fasting blood samples were collected after at least 12-hour fasting and used to measure serum uric acid, serum alanine aminotransferase, and aspartate aminotransferase by an automated analyzer. Fasting plasma glucose was determined by the glucose dehydrogenase method (Merck). Serum levels of triglycerides, total cholesterol, HDL-C, and low-density lipoprotein cholesterol were detected by enzymatic colorimetry on the Roche Cobas C 710 automatic biochemical analyzer (Supplied by Beijing Barry Medical Equipment Co., Ltd) according to the instructions of the manufacturer. The quality-control products PUND and PNUX were provided by Bio-Rad (supplied by Beijing Jingyang Tenghui Technology Development Co., Ltd). Estimated glomerular filtration rate was calculated as follows:  $(mL/min \text{ per } 1.73 \text{ m}^2) = 175 \times creatinine^{-1.234} \times age^{-0.179}$  (if women,  $\times 0.79$ ), with creatinine level in mg/dL and age in years.<sup>15</sup>

## Diabetes, Hypertension, and Fatty Liver Disease Definition

Diabetes was defined with any of the following criteria: glycated hemoglobin  $\geq 6.5\%$ , fasting glucose level

$\geq 126$  mg/dL, 2-hour plasma glucose  $\geq 200$  mg/dL, or the use of antidiabetes medication according to the criteria of the American Diabetes Association.<sup>16</sup>

Hypertension was defined with any of the following criteria: (1) self-report of a physician's diagnosis of hypertension, (2) use of antihypertensive medication during the past 2 weeks, or (3) systolic blood pressure  $\geq 140$  mm Hg and/or diastolic blood pressure  $< 90$  mm Hg.<sup>17</sup>

Individuals underwent abdominal ultrasonography at baseline and every follow-up examination. The diagnosis of fatty liver disease was the presence of at least 2 or 3 abnormal findings on abdominal ultrasonography: diffusely increased echogenicity ("bright") liver with liver echogenicity greater than kidney or spleen, vascular blurring, and deep attenuation of the ultrasound signal.<sup>18</sup>

## Chinese VAI

CVAI was calculated using the sex-specific formulas previously described,<sup>9</sup> with triglyceride and HDL-C levels expressed as millimole per liter. The visceral adiposity area was estimated by CVAI as follows:

$$\text{For Men: } CVAI = -267.93 + 0.68 \times \text{age} + 0.03 \times BMI + 4.00 \times WC + 22.00 \times \log_{10} TG - 16.32 \times HDL - C.$$

$$\text{For Women: } CVAI = -187.32 + 1.71 \times \text{age} + 4.23 \times BMI + 1.12 \times WC + 39.76 \times \log_{10} TG - 11.66 \times HDL - C.$$

Participants were categorized into 4 groups based on the quartiles of CVAI:  $< 49.63$ , 49.63 to 85.14, 85.14 to 116.12, and  $\geq 116.12$ . The optimal cutoff value of CVAI was determined by the area under the receiver operating characteristic curve (cutoff value = 86.229). The dynamic  $\Delta CVAI$  was calculated by subtracting baseline CVAI from that of the previous follow-up. Participants were further classified by quintiles of  $\Delta CVAI$  as follows:  $\leq -9.429$  (large decrease),  $-9.429$  to 0.668 (moderate decrease), 0.668 to 8.724 (stable), 8.724 to 18.606 (moderate increase), and  $> 18.606$  (large increase).

## Statistical Analysis

Baseline characteristics of the study participants are described based on the quartiles of CVAI. Numerical variables were reported as mean  $\pm$  SD, and categorical variables were expressed as frequency (percentage).

Person-years of follow-up were calculated from the date of the first entry visit to the date of the last confirmed follow-up, or the date of carotid plaque diagnosis. Three Cox proportional hazards models were established to assess the associations of CVAI and other adiposity indices (WHR, WHtR, LAP, ABSI, BMI,

and VAI) with carotid plaque risk. The proportionality assumption was tested and verified.<sup>19</sup> Hazard ratios (HRs) and 95% CIs were calculated in 3 models: model 1 was the crude model; model 2 was adjusted for sex,<sup>20,21</sup> fasting plasma glucose,<sup>22,23</sup> blood pressure information (systolic and diastolic),<sup>24,25</sup> serum liver enzymes alanine aminotransferase and aspartate aminotransferase,<sup>26,27</sup> uric acid,<sup>28,29</sup> estimated glomerular filtration rate,<sup>30,31</sup> resting heart rate,<sup>32,33</sup> lifestyle (cigarette smoking and alcohol drinking),<sup>34</sup> and the medication history of hypolipidemic drugs and hypoglycemic drugs at baseline; and model 3 was further adjusted for white blood cell count at baseline.<sup>35,36</sup> These covariates were included in the Cox models taking into account the univariate Cox regression results and their potential confounding effects between CVAI and

carotid plaque risk.  $P_{\text{trend}}$  was evaluated among baseline CVAI quartiles by imputing the median values for every quartile as continuous variables in Cox models. We also estimated the risk of carotid plaque associated with a 1-SD increase of CVAI. To describe the dose-response association between CVAI and incident carotid plaque, we used restricted cubic splines incorporated into the Cox models.

To assess the robustness of the results, sensitivity analysis was performed by removing individuals with carotid plaque that occurred during the first 2 years of follow-up. In addition, subgroup analyses were also performed by sex and personal medical history (eg, hypertension, diabetes, fatty liver disease, and medication history of hypoglycemic drugs). We performed crossover analyses in Cox model to evaluate CVAI and

**Table 1. Characteristics at Baseline by Follow-Up Outcomes**

Baseline characteristics	CVAI quartiles				P for trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
No. of participants	5712	5921	5988	5901	
Women, No. (%)	4674 (81.83)	3208 (54.18)	1663 (27.77)	620 (10.51)	<0.001
Age, y	34.87±8.49	42.34±9.06	45.53±10.17	47.62±11.26	<0.001
Height, m	162.95±6.93	165.35±7.87	168.20±7.81	171.16±7.15	<0.001
Weight, kg	56.80±6.77	66.03±7.34	73.72±7.85	84.63±10.32	<0.001
BMI, kg/m <sup>2</sup>	21.38±2.06	24.14±2.06	26.05±2.17	28.85±2.77	<0.001
Hip circumference, cm	91.10±4.37	94.90±4.19	97.70±4.40	102.31±5.34	<0.001
WC, cm	71.69±5.19	80.77±4.40	87.58±3.93	96.63±6.05	<0.001
Resting heart rate, beats per min	76.75±10.2	75.62±9.79	75.84±9.59	77.32±10.09	<0.001
UA, μmol/L	265.13±62.73	307.66±75.43	354.23±78.68	387.86±80.39	<0.001
TC, mmol/L	4.45±0.80	4.81±0.87	5.04±0.92	5.10±0.97	<0.001
Triglycerides, mmol/L	0.84±0.37	1.27±0.67	1.83±1.20	2.61±2.04	<0.001
LDL-C, mmol/L	2.57±0.65	2.96±0.71	3.16±0.74	3.14±0.76	<0.001
HDL-C, mmol/L	1.60±0.34	1.42±0.32	1.29±0.27	1.17±0.24	<0.001
eGFR, mL/min per 1.73 m <sup>2</sup>	60.06±19.09	65.78±22.83	72.86±21.81	78.46±20.00	<0.001
ALT, U/L	15.46±10.03	20.88±15.14	26.72±18.42	34.21±29.07	<0.001
AST, U/L	18.27±5.86	20.43±8.72	22.46±10.59	24.55±12.94	<0.001
FPG, mmol/L	4.98±0.47	5.25±0.81	5.54±1.10	5.90±1.42	<0.001
SBP, mm Hg	108.41±11.76	115.96±13.90	121.52±14.1	127.31±14.78	<0.001
DBP, mm Hg	67.18±7.97	73.14±9.16	77.61±9.39	81.52±9.70	<0.001
WBC count, 10 <sup>9</sup> /L	5.72±3.60	5.96±4.51	6.20±3.13	6.59±2.09	<0.001
Cigarette smoking, No. (%)	866 (15.16)	1621 (27.38)	2501 (41.77)	2988 (50.64)	<0.001
Alcohol drinking, No. (%)	1050 (18.38)	2095 (35.38)	3072 (51.30)	3640 (61.68)	<0.001
Hypertension, No. (%)	126 (2.21)	751 (12.68)	1603 (26.77)	2681 (45.43)	<0.001
Diabetes, No. (%)	33 (0.58)	176 (2.97)	441 (7.36)	837 (14.18)	<0.001
Fatty liver, No. (%)	146 (2.56)	1123 (18.97)	2741 (45.77)	4487 (76.04)	<0.001
Hypolipidemic drugs, No. (%)	3 (0.05)	15 (0.25)	25 (0.42)	47 (0.80)	<0.001
Hypoglycemic drugs, No. (%)	5 (0.09)	26 (0.44)	50 (0.84)	69 (1.17)	<0.001

Values are expressed as mean±SD unless otherwise indicated. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CVAI, Chinese visceral adiposity index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; UA, uric acid; WBC, white blood cell; and WC, waist circumference.

diabetes interaction effects on the risk of carotid plaque with four types of HR ( $HR_e$ ,  $HR_g$ ,  $HR_{eg}$ , and  $HR_i$ ). The area under the receiver operating characteristic curve (AUC) was used to test the ability of baseline CVAI, WHR, WHtR, LAP, ABSI, BMI, VAI, WC, triglycerides, and HDL-C levels in predicting carotid plaque incidence at follow-up. Differences between AUCs were tested with the z statistic. We used a multiple imputation method to fill the missing values in the analyses.<sup>37</sup> Statistical significance was considered with a 2-sided  $P < 0.05$ , and the subgroup analyses with Bonferroni adjustment for post hoc comparisons were considered with a 2-sided  $P < 0.025$ . All statistical analyses were performed with R version 3.5.2 (The R Foundation).

## RESULTS

### Baseline Information

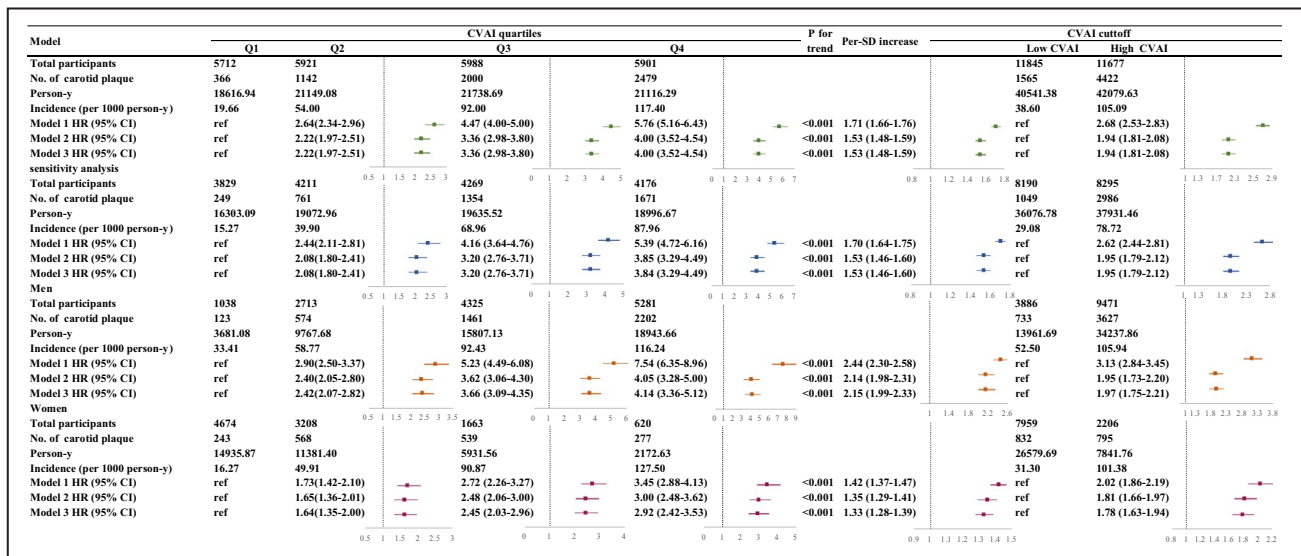
The mean age of the study population was  $42.66 \pm 10.92$  years, and 10 165 (43.21%) were women. During the 82 621 person-years of follow-up, a total of 5987 patients developed carotid plaque, with an incidence rate of 7.25 per 100 person-years. The baseline characteristics by quartiles of CVAI are shown in Table 1. With increasing CVAI quartiles (from quartile 1 to quartile 4), participants were older and had a higher level of BMI, hip circumference, WC, resting heart rate, uric acid, total cholesterol, triglycerides, low-density lipoprotein cholesterol, estimated glomerular filtration rate, alanine aminotransferase, aspartate aminotransferase, fasting plasma glucose, systolic blood pressure, diastolic blood pressure, and white blood cell count;

and a lower level of HDL-C. In addition, there was an increased proportion of participants who smoked cigarettes and drank alcohol; had hypertension, diabetes, or fatty liver disease; and revealed a medication history of hypolipidemic drugs and hypoglycemic drugs (all  $P_{trend} < 0.001$ ).

### Baseline CVAI and Its Dynamic Change With Risk of Carotid Plaque

Figure 1 showed that the risk of carotid plaque increased among the quartiles of CVAI. The risk of carotid plaque was increased with the increasing quartiles of CVAI in all 3 Cox regression models. In model 3, CVAI was significantly associated with carotid plaque risk comparing quartile 2 and quartile 3 and quartile 4 with quartile 1, with corresponding HRs and 95% CIs of 2.22 (1.97–2.51), 3.36 (2.98–3.80), and 4.00 (3.52–4.54), respectively (Figure 1). In the sensitivity analysis, by excluding participants who developed carotid intima-media thickness or carotid plaque in the first 2 years of follow-up, the associations remained significant (Figure 1). However, there was no significant association between  $\Delta$ CVAI and carotid plaque risk (Table 2).

Restricted cubic splines showed a nonlinear dose-response association between the baseline CVAI and carotid plaque risk ( $P_{nonlinearity} < 0.001$ ), and the risk of incident carotid plaque was  $>1.00$  when CVAI was  $>85.868$  (Figure 2). The risk of incident carotid plaque increased by 53% per 1-SD increase in baseline CVAI (HR, 1.53; 95% CI, 1.48–1.59) after adjusting for sex, fasting plasma glucose, systolic blood pressure,



**Figure 1. Forest plot of the association between baseline Chinese visceral adiposity index (CVAI) and carotid plaque risk.** Model 1 was the crude model; model 2 was adjusted for sex, fasting plasma glucose, systolic blood pressure, diastolic blood pressure, alanine aminotransferase, aspartate aminotransferase, uric acid, estimated glomerular filtration rate, resting heart rate, cigarette smoking, alcohol drinking, and medication history of hypolipidemic drugs and hypoglycemic drugs at baseline; and model 3 was further adjusted for white blood cell count at baseline. HR indicates hazard ratio.

**Table 2.** Association Between Dynamic ΔCVAI and Risk of Carotid Plaque

Model	ΔCVAI quintiles					P for trend	Per-SD increase	ΔCVAI cutoff	
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5			Low	High
Model 1 HR (95% CI)*	Reference	1.04 (0.95–1.14)	1.25 (1.14–1.36)	0.97 (0.88–1.06)	1.02 (0.93–1.12)	0.809	0.99 (0.98–0.99)	References	0.98 (0.97–1.00)
Model 2 HR (95% CI)†	Reference	0.97 (0.87–1.07)	0.92 (0.84–1.02)	0.95 (0.86–1.05)	0.94 (0.85–1.04)	0.201	1.00 (1.00–1.01)	References	0.99 (0.98–1.01)
Model 3 HR (95% CI)‡	Reference	1.03 (0.94–1.13)	1.08 (0.99–1.18)	1.01 (0.92–1.10)	0.99 (0.98–0.99)	0.658	1.00 (1.00–1.01)	References	0.99 (0.98–1.01)
<i>Sensitivity analysis</i>									
Model 1 HR (95% CI)*	Reference	1.11 (0.99–1.25)	1.27 (1.14–1.42)	0.96 (0.86–1.07)	0.96 (0.86–1.08)	0.077	0.98 (0.98–0.99)	References	0.97 (0.96–0.99)
Model 2 HR (95% CI)†	Reference	0.99 (0.87–1.12)	0.94 (0.83–1.06)	0.97 (0.86–1.09)	0.93 (0.82–1.05)	0.214	1.00 (0.99–1.00)	References	0.99 (0.98–1.00)
Model 3 HR (95% CI)‡	Reference	1.02 (0.91–1.14)	1.10 (0.98–1.23)	0.98 (0.88–1.09)	0.98 (0.98–0.98)	0.982	1.00 (0.99–1.00)	References	0.99 (0.98–1.00)

ΔCVAI indicates change in Chinese visceral adiposity index; and HR, hazard ratio.

\*Model 1 was the crude model.

†Model 2 was adjusted for sex, fasting plasma glucose, systolic blood pressure, diastolic blood pressure, alanine aminotransferase, aspartate aminotransferase, uric acid, estimated glomerular filtration rate, resting heart rate, cigarette smoking, alcohol drinking, and medication history of hypolipidemic drugs and hypoglycemic drugs at baseline.

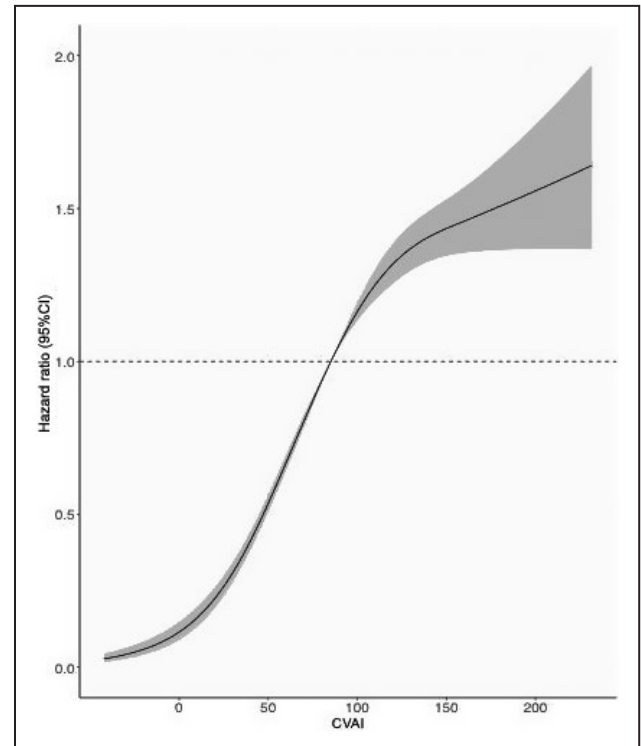
‡Model 3 was further adjusted for white blood cell count at baseline.

diastolic blood pressure, alanine aminotransferase, aspartate aminotransferase, uric acid, estimated glomerular filtration rate, resting heart rate, cigarette smoking, alcohol drinking, medication history of hypolipidemic drugs and hypoglycemic drugs, and white blood cell count in model 3 (Figure 1). In the sensitivity analysis, the associations between CVAI and carotid plaque risk remained significant in model 3 (Figure 1).

As shown in Figure 1, either in the overall analysis or in the sensitivity analysis of model 3, compared with CVAI ≤86.229, CVAI >86.229 could significantly increase carotid plaque risk (for overall analysis: HR, 1.94 [95% CI, 1.81–2.08]; for sensitivity analysis: HR, 1.95 [95% CI, 1.79–2.12]).

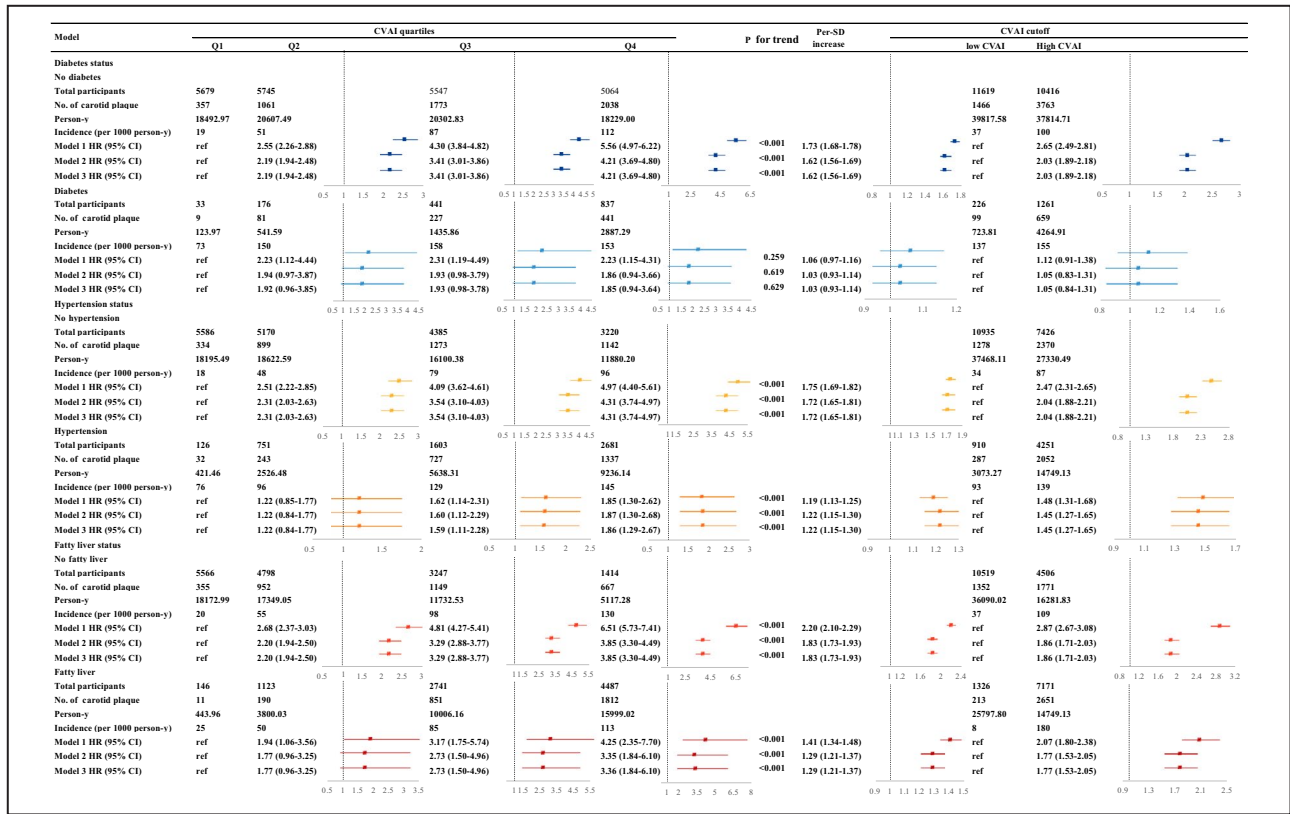
### Subgroup Analyses

In the subgroup analyses stratified by sex, the associations between CVAI and carotid plaque risk were both significant in men and women, and the HR was larger in men than in women (in model 3, for men: HR, 4.14 [95% CI, 3.36–5.12]; for women: HR, 2.92 [95% CI, 2.42–3.53]). For a 1-SD increase in CVAI, the



**Figure 2.** Nonlinear association between Chinese visceral adiposity index (CVAI) and the risk of carotid plaque.

Data are hazard ratios (HRs; solid line) and 95% CIs (gray area) from Cox proportional hazard regression analysis with restricted cubic splines. Adjusted for sex, fasting plasma glucose, systolic blood pressure, diastolic blood pressure, alanine aminotransferase, aspartate aminotransferase, uric acid, estimated glomerular filtration rate, resting heart rate, cigarette smoking, alcohol drinking, medication history of hypolipidemic drugs and hypoglycemic drugs, and white blood cell at baseline.



**Figure 3. Forest plot of the association between baseline Chinese visceral adiposity index (CVAI) and risk of carotid plaque stratified according to disease status.**

Model 1 was the crude model; model 2 was adjusted for sex, fasting plasma glucose, systolic blood pressure, diastolic blood pressure, alanine aminotransferase, aspartate aminotransferase, uric acid, estimated glomerular filtration rate resting heart rate, cigarette smoking, alcohol drinking, and medication history of hypolipidemic drugs and hypoglycemic drugs at baseline; and model 3 was further adjusted for white blood cell count at baseline. \**P* values <0.025 were considered statistically significant.

**Table 3. Interaction Between CVAI Level and Diabetes Status on Risk of Carotid Plaque**

CVAI level	Diabetes status		Interaction	
	No diabetes	Diabetes	HR <sub>i</sub> (95% CI)	<i>P</i> value
<b>Model 1*</b>				
Low CVAI	Reference	3.82 (3.11–4.68)	0.42 (0.34–0.53)	<0.001
High CVAI	2.65 (2.49–2.81)	4.26 (3.89–4.67)		
<b>Model 2†</b>				
Low CVAI	Reference	3.09 (2.51–3.80)	0.42 (0.38–0.47)	<0.001
High CVAI	2.07 (1.93–2.22)	2.99 (2.70–3.32)		
<b>Model 3‡</b>				
Low CVAI	Reference	3.09 (2.51–3.80)	0.42 (0.38–0.47)	<0.001
High CVAI	2.07 (1.93–2.22)	2.99 (2.70–3.32)		

CVAI indicates Chinese visceral adiposity index; HR<sub>eg</sub>, the combination effect of CVAI and diabetes on the risk of carotid plaque; and HR<sub>i</sub>, the interaction effect of CVAI and diabetes on the risk of carotid plaque.

\*Model 1 was the crude model.

†Model 2 was adjusted for sex, fasting plasma glucose, systolic blood pressure, diastolic blood pressure, alanine aminotransferase, aspartate aminotransferase, uric acid, estimated glomerular filtration rate, resting heart rate, cigarette smoking, alcohol drinking, and medication history of hypolipidemic drugs and hypoglycemic drugs at baseline.

‡Model 3 was further adjusted for white blood cell count at baseline.

**Table 4. Association Between Baseline CVAI Level and Risk of Carotid Plaque in Patients With Diabetes Stratified According to Medication History of Hypoglycemic Drugs**

Model	CVAI quartiles			P for trend	Per-SD increase	CVAI cutoff		
	Quartile 1	Quartile 2	Quartile 3			Quartile 4	Low CVAI	High CVAI
No hypoglycemic drugs								
Model 1 HR (95% CI)*	Reference	2.62 (1.21–5.71)	2.74 (1.29–5.83)	2.65 (1.26–5.61)	0.172	1.73 (1.68–1.78)	Reference	1.16 (0.92–1.45)
Model 2 HR (95% CI)†	Reference	2.32 (1.06–5.08)	2.30 (1.07–4.94)	2.30 (1.07–4.94)	0.314	1.62 (1.56–1.69)	Reference	1.08 (0.85–1.38)
Model 3 HR (95% CI)‡	Reference	2.31 (1.05–5.05)	2.30 (1.07–4.93)	2.29 (1.06–4.92)	0.319	1.62 (1.56–1.69)	Reference	1.09 (0.85–1.39)
Hypoglycemic drugs								
Model 1 HR (95% CI)*	Reference	0.57 (0.12–2.61)	0.66 (0.15–2.85)	0.63 (0.15–2.65)	0.910	1.06 (0.97–1.16)	Reference	1.03 (0.58–1.84)
Model 2 HR (95% CI)†	Reference	0.46 (0.09–2.29)	0.68 (0.14–3.29)	0.42 (0.08–2.15)	0.347	1.03 (0.93–1.14)	Reference	1.00 (0.51–1.97)
Model 3 HR (95% CI)‡	Reference	0.46 (0.09–2.30)	0.68 (0.14–3.30)	0.43 (0.08–2.17)	0.352	1.03 (0.93–1.14)	Reference	1.00 (0.51–1.96)

CVAI indicates Chinese visceral adiposity index; and HR, hazard ratio.

\*Model 1 was the crude model.

†Model 2 was adjusted for sex, fasting plasma glucose, systolic blood pressure, diastolic blood pressure, alanine aminotransferase, aspartate aminotransferase, uric acid, estimated glomerular filtration rate, resting heart rate, cigarette smoking, alcohol drinking, and medication history of hypolipidemic drugs.

‡Model 3 was further adjusted for white blood cell count at baseline.

HR of carotid plaque risk in men was also stronger than that in women (in model 3, for men: HR, 2.15 [95% CI, 1.99–2.33]; for women: HR, 1.33 [95% CI, 1.28–1.39]). A similar pattern was also observed when comparing CVAI >86.229 with CVAI ≤86.229 (Figure 1).

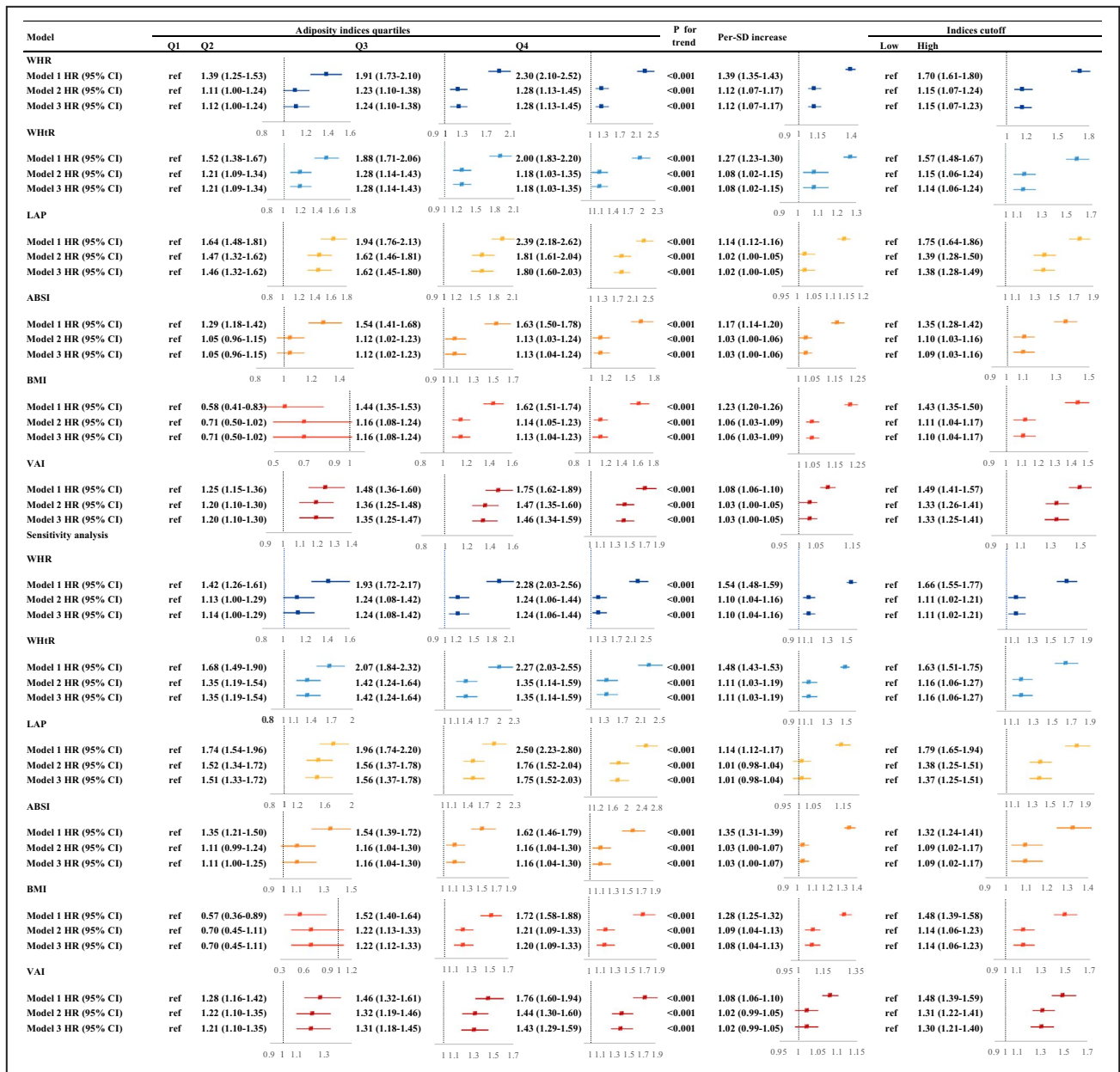
As shown in Figure 3, in the subgroup analyses stratified by hypertension and fatty liver disease, the association between CVAI and carotid plaque risk remained significant in all subgroups. In the subgroup analysis stratified by diabetes, the positive correlation between CVAI and carotid plaque risk was highly significant in the nondiabetes subgroup in all 3 models (in model 3, quartile 4 versus quartile 1: HR, 4.21 [95% CI, 3.69–4.80]; quartile 3 versus quartile 1: HR, 3.41 [95% CI, 3.01–3.86]; quartile 2 versus quartile 1: HR, 2.19 [95% CI, 1.94–2.48]). However, this association became nonsignificant in the diabetic population (Figure 3).

We also conducted a multiplicative interaction test and observed an antagonistic interaction effect between CVAI and diabetes status in all 3 models (in model 3: HR<sub>i</sub>, 0.42 [95% CI, 0.38–0.47]; *P*<0.001) (Table 3). We further conducted subgroup analysis by the medication history of hypoglycemic drugs in the diabetic group and found a significant positive correlation between CVAI and carotid plaque risk in the group without a medication history of hypoglycemic drugs, with no significant linear trend (in model 3, quartile 4 versus quartile 1: HR, 2.29 [95% CI, 1.06–4.92]; quartile 3 versus quartile 1: HR, 2.30 [95% CI, 1.07–4.93]; quartile 2 versus quartile 1: HR, 2.31 [95% CI, 1.05–5.05]) (Table 4). However, no significant correlation was observed in the subgroup of patients with a medication history of hypoglycemic drugs.

### Baseline Adiposity Indices and Risk of Carotid Plaque

Carotid plaque risk was significantly increased with the increasing quartiles of WHR, WHtR, LAP, ABSI, BMI, and VAI in all 3 Cox regression models, except for the nonsignificant association between ABSI and BMI and carotid plaque risk comparing quartile 2 with the reference. Carotid plaque risk was also increased with per-SD increase in WHR, WHtR, LAP, ABSI, BMI, and VAI, except that the association between VAI and LAP and risk of incident carotid plaque became weakly statistically significant in the sensitivity analyses. The corresponding HRs for carotid plaque with per-SD increase in model 3 were 1.12 (95% CI, 1.07–1.17) and 1.10 (95% CI, 1.04–1.16) for WHR, 1.08 (95% CI, 1.02–1.15) and 1.11 (95% CI, 1.03–1.19) for WHtR, 1.02 (95% CI, 1.00–1.05) and 1.01 (95% CI, 0.98–1.04) for LAP, 1.03 (95% CI, 1.00–1.06) and 1.03 (95% CI, 1.00–1.07) for ABSI, 1.06 (95% CI, 1.03–1.09) and 1.08 (95% CI, 1.04–1.13)





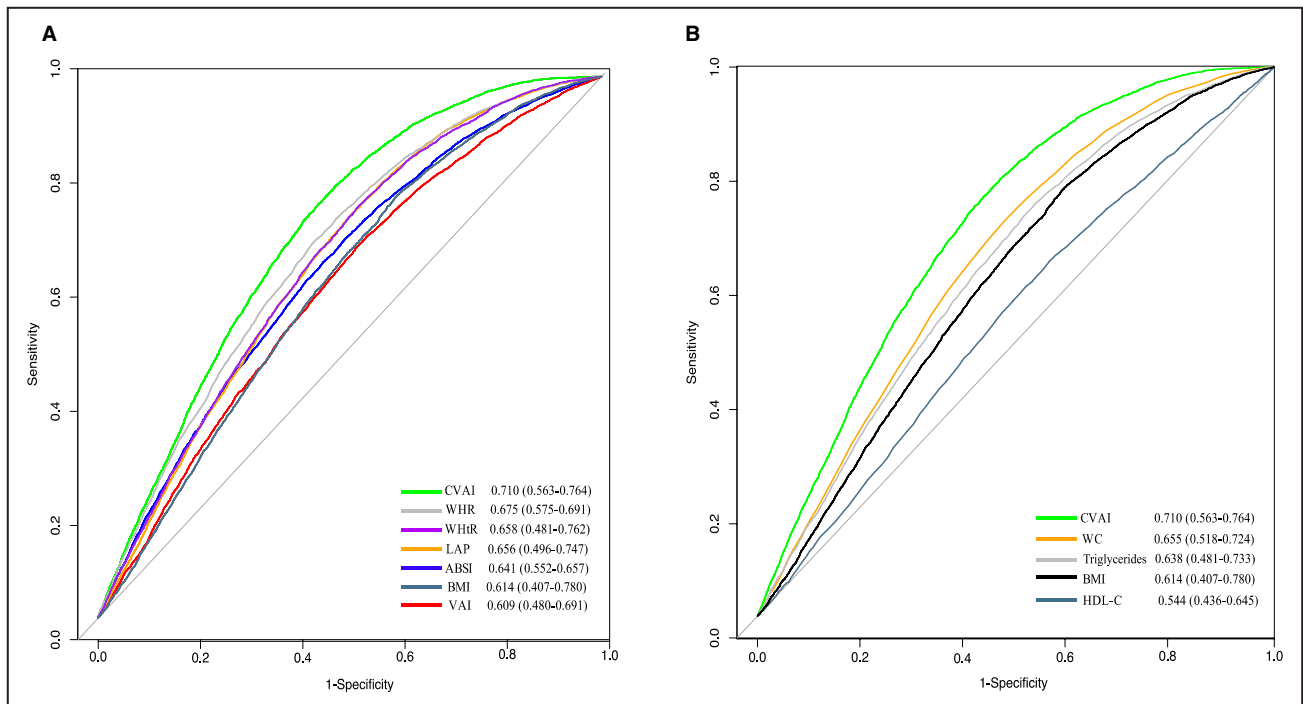
**Figure 4. Forest plot of the association between baseline adiposity indices level and risk of carotid plaque.**

Model 1 was the crude model; model 2 was adjusted for sex, fasting plasma glucose, systolic blood pressure, diastolic blood pressure, alanine aminotransferase, aspartate aminotransferase, uric acid, estimated glomerular filtration rate, resting heart rate, cigarette smoking, alcohol drinking, and medication history of hypolipidemic drugs and hypoglycemic drugs at baseline; and model 3 was further adjusted for white blood cell count at baseline. ABSI indicates a body shape index; BMI, body mass index; LAP, lipid accumulation product; VAI, visceral adiposity index; WHR, waist-to-hip ratio; and WHtR, waist-to-height ratio.

for BMI, and 1.03 (95% CI, 1.00–1.05) and 1.02 (95% CI, 0.99–1.05) for VAI in overall analyses and sensitivity analyses, respectively (Figure 4).

We constructed 2 receiver operating characteristic curves to compare the predictive efficacy of CVAI and other adiposity indices, and CVAI and its constituent indices on the risk of carotid plaque. The receiver operating characteristic curves and AUCs for CVAI, WHR, WHtR, LAP, ABSI, BMI, VAI, WC, triglycerides, and

HDL-C for predicting carotid plaque risk were shown in Figure 5. The corresponding AUCs were 0.710 (95% CI, 0.563–0.764) for CVAI, 0.675 (95% CI, 0.575–0.691) for WHR, 0.658 (95% CI, 0.481–0.762) for WHtR, 0.656 (95% CI, 0.496–0.747) for LAP, 0.641 (95% CI, 0.552–0.657) for ABSI, 0.614 (95% CI, 0.407–0.780) for BMI, and 0.609 (95% CI, 0.480–0.691) for VAI (Figure 5A). The corresponding AUCs were 0.655 (95% CI, 0.518–0.724) for WC, 0.638 (95% CI, 0.481–0.733)



**Figure 5. Receiver operating characteristic (ROC) curves of adiposity indices in predicting carotid plaque risk.**

**A**, The ROC curves and area under the curves (AUCs) (95% CIs) of different adiposity indices for predicting carotid plaque risk. **B**, The ROC curves and AUCs (95% CIs) of Chinese visceral adiposity index (CVAI) and its constituent indices for predicting carotid plaque risk. ABSI indicates a body shape index; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LAP, lipid accumulation product; VAI, visceral adiposity index; WC, waist circumference, WHR, waist-to-hip ratio; and WHtR, waist-to-height ratio.

for triglycerides, and 0.544 (95% CI, 0.436–0.645) for HDL-C, respectively (Figure 5B). The AUC of CVAI was the largest among all of the adiposity indices ( $P < 0.001$ ).

## DISCUSSION

In this cohort study, we observed a positive correlation between CVAI and carotid plaque risk in a nonlinear dose-response pattern. The association remained significant in all subgroup analyses stratified by sex, hypertension, and fatty liver disease except for in the diabetes subgroup. The association between CVAI and carotid plaque risk was much higher in men than in women. The sensitivity analysis excluding individuals who developed carotid plaque within the first 2 years further confirmed the robustness of the results.

Previous studies have shown that abdominal obesity and adipose tissue dysfunction were closely related to cardiovascular disease.<sup>38,39</sup> The accumulation of abdominal fat can independently increase the risk of cardiovascular disease, and fat cells may mechanically promote the increased vascular stiffness in obesity.<sup>40</sup> Furthermore, a retrospective study also found that CVAI was significantly higher in patients with carotid atherosclerosis and was associated with a 39% higher risk of carotid atherosclerosis.<sup>41</sup> Adipose tissue is an active endocrine and paracrine organ that releases a

large number of cytokines and bioactive mediators, such as leptin, adiponectin, interleukin 6, and tumor necrosis factor- $\alpha$ , which may influence blood flow and promote atherosclerosis.<sup>42</sup> Xia et al<sup>9</sup> promoted CVAI as a simple clinical index composed of age, WC, triglycerides, HDL-C, and BMI, which was easily available in clinical practice to reflect visceral fat mass. A Chinese prospective cohort study also found that the visceral obesity rate estimated by CVAI was more predictive of the occurrence of prediabetes and diabetes than the traditional estimates of obesity such as BMI and WC.<sup>43</sup> In addition, we also tried to analyze the impact of  $\Delta$ CVAI on carotid plaque risk during the observation period, but we did not find a significant correction between the dynamic change of CVAI and carotid plaque risk. In brief, our results supported CVAI as a reliable and promising marker of carotid plaque.

In the subgroup analyses stratified by sex, the association between CVAI and carotid plaque risk was stronger in men than in women. Male sex is an independent risk factor for atherosclerosis.<sup>21</sup> There are significant differences in body composition and fat distribution between men and women. Women are mainly composed of fat content and subcutaneous fat, while men have high muscle content and visceral fat.<sup>20</sup> With a given BMI, men with larger abdominal adipose tissue underlie more risk of coronary heart disease than

women.<sup>38</sup> Therefore, consistent with our results, the CVAI can reflect the degree of abdominal obesity and may more likely reflect the impact of visceral fat on the risk of carotid plaque.

In patients without diabetes, increased CVAI was strongly related to larger adverse risk of carotid plaque, but, in patients with diabetes, this association became weaker and not statistically significant. We also observed an antagonistic interaction between the abdominal adiposity index CVAI and diabetes, which may weaken the impact of CVAI on carotid plaque formation. Further stratified analyses according to the medication history of hypoglycemic drugs found that there was a significant positive correlation between CVAI and carotid plaque risk in the subgroup without hypoglycemic drug use. However, there were no significant results in the other subgroup. There are several possible explanations. First, the small sample size ( $n=1487$ ) in the diabetes subgroup may explain the nonsignificant results. Second, patients with diabetes may have blood glucose control (such as using hypoglycemic drugs) and changed their lifestyle and dietary habits during the follow-up period, which may affect the association between CVAI and carotid plaque risk. Third, as diabetes is accompanied by glucose regulation disorders, patients' risk of vascular disease may be more related to the variability in glycemic control,<sup>44</sup> which could explain our results in this subgroup.

Evidence supports that the risk of diabetes was affected by plasma concentrations of different adipokines, and the mechanism in the healthy population and patients with atherosclerosis was different.<sup>45</sup> Interestingly, our results also show that the risk of carotid plaque affected by the abdominal adiposity index CVAI was different in patients with diabetes and those without diabetes. Proinflammatory resistin was reported to be positively correlated with insulin sensitivity.<sup>46</sup> However, in patients with atherosclerosis, the plasma level of resistin was increased, and the positive correlation between resistin and insulin sensitivity was weakened.<sup>47,48</sup> Taken together, patients with diabetes may be able to reverse their carotid plaque risk caused by abdominal obesity by changing certain lifestyle or dietary habits or trying to keep their glucose levels steady.

Previous studies reported that CVAI was superior to BMI, WC, WHR, WHtR, VAI, ABSI, and LAP for diagnosing diabetic kidney disease, hypertension, diabetes, and prediabetes.<sup>9,24,43,49,50</sup> Similar results were also observed in our analyses that the AUC of CVAI was the largest among all of the adiposity indices in predicting the risk of incidence of carotid plaque. CVAI, as a comprehensive index, includes many well-known carotid plaque risk factors, such as BMI, WC, triglycerides, and HDL-C.<sup>9</sup> Compared with these single indicators, CVAI also presented the largest AUC.

BMI, WC, ABSI, WHR, and WHtR are typically recommended as indicators of general obesity or as measures of abdominal obesity but still have limitations in distinguishing subcutaneous adipose tissue from visceral fat.<sup>12,51,52</sup> VAI and LAP were also cardiometabolic risk indices, with similar correlations but with relatively less strength.<sup>13,14</sup> These results suggest that CVAI may be better than other adiposity indices at identifying carotid plaque risk.

This cohort study has many advantages, including the prospective design, large sample size, and adjustment for multiple potential confounding factors. Limitations should also be considered. First, we did not use imaging methods to quantitatively assess abdominal fat to further validate our results. Second, the CVAI values of 5901 participants were missing because of missing values of WC, triglycerides, or HDL-C. However, we used multiple imputation methods to fill in the missing data to reduce bias. Third, although we adjusted for many covariates, there is still the possibility of residual confounding, such as dietary intake and psychological factors. Finally, all of the participants in this study were selected from ongoing health checkups of highly educated employees, and, therefore, their education level may be higher than that of general Chinese citizens and their awareness of disease and prevention may also be stronger.<sup>53</sup> In addition, Beijing has better health care resources, and the diagnosis rate of diseases may be higher than that of other regions.<sup>54</sup> Moreover, with the rapid development of Beijing's economy, residents' diets and lifestyles are unique compared with other regions. All of the above may limit the generalizability of these findings.

## CONCLUSIONS

The CVAI was a useful and applicable indicator for predicting carotid plaque risk for both sexes, individuals with and without hypertension and fatty liver disease, and individuals without diabetes. The association between CVAI and risk of carotid plaque was in a nonlinear pattern. Individuals should keep their CVAI within a normal level to prevent carotid plaque.

## ARTICLE INFORMATION

Received June 2, 2021; accepted November 30, 2021.

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## Acknowledgments

The authors are grateful to the multidisciplinary team of the clinics of Xiaotangshan Hospital, the participants, and all of the research staff of this study.

## Sources of Funding

This study was supported by the Outstanding Talent Research Initiation Foundation of Xuzhou Medical University (No. D2019043), the 2021 Medical Research Project of Jiangsu Provincial Health Commission (No. Z2021012), and the Outstanding Youth Talent Support Program for Training Excellent Talents in Fangshan District, Beijing, China (No. 2016000000007B001).

## Disclosures

None.

## REFERENCES

- Grosse GM, Schulz-Schaeffer WJ, Teebken OE, Schuppner R, Dirks M, Worthmann H, Lichtinghagen R, Maye G, Limbourg FP, Weissenborn K. Monocyte subsets and related chemokines in carotid artery stenosis and ischemic stroke. *Int J Mol Sci*. 2016;17:433. doi: 10.3390/ijms17040433
- Tesfamariam B. Endothelial repair and regeneration following intimal injury. *J Cardiovasc Transl Res*. 2016;9:91–101. doi: 10.1007/s12265-016-9677-1
- Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. *Atherosclerosis*. 2012;220:128–133. doi: 10.1016/j.atherosclerosis.2011.06.044
- Clarke R, Du H, Kurmi OM, Parish S, Yang M, Arnold M, Guo YU, Bian Z, Wang L, Chen Y, et al. Burden of carotid artery atherosclerosis in Chinese adults: implications for future risk of cardiovascular diseases. *Eur J Prev Cardiol*. 2017;24:647–656. doi: 10.1177/2047487317689973
- Lear SA, Humphries KH, Kohli S, Frohlich JJ, Birmingham CL, Mancini GB. Visceral adipose tissue, a potential risk factor for carotid atherosclerosis: results of the Multicultural Community Health Assessment Trial (M-CHAT). *Stroke*. 2007;38:2422–2429. doi: 10.1161/STROKEAHA.107.484113
- Rallidis LS, Baroutsis K, Zolindaki M, Karagianni M, Varounis C, Dargès N, Lekakis J, Anastasiou-Nana M. Visceral adipose tissue is a better predictor of subclinical carotid atherosclerosis compared with waist circumference. *Ultrasound Med Biol*. 2014;40:1083–1088. doi: 10.1016/j.ultrasmedbio.2013.12.017
- Deurenberg P, Yap M, van Staveren WA. Body mass index and percent body fat: a meta analysis among different ethnic groups. *Int J Obes Relat Metab Disord*. 1998;22:1164–1171. doi: 10.1038/sj.ijo.0800741
- Camhi SM, Bray GA, Bouchard C, Greenway FL, Johnson WD, Newton RL, Ravussin E, Ryan DH, Smith SR, Katzmarzyk PT. The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: sex and race differences. *Obesity (Silver Spring)*. 2011;19:402–408. doi: 10.1038/oby.2010.248
- Xia MF, Chen Y, Lin HD, Ma H, Li XM, Aleteng Q, Li Q, Wang D, Hu YU, Pan BS, et al. A indicator of visceral adipose dysfunction to evaluate metabolic health in adult Chinese. *Sci Rep*. 2016;6:38214. doi: 10.1038/srep38214
- Kralova Lesna I, Petras M, Cejkova S, Kralova A, Fronck J, Janousek L, Thieme F, Tyl T, Poledne R. Cardiovascular disease predictors and adipose tissue macrophage polarization: is there a link? *Eur J Prev Cardiol*. 2018;25:328–334. doi: 10.1177/2047487317743355
- Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS, American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the society for vascular medicine. *J Am Soc Echocardiogr*. 2008;21:93–111. doi: 10.1016/j.echo.2007.11.011
- Krakauer NY, Krakauer JC. A new body shape index predicts mortality hazard independently of body mass index. *PLoS One*. 2012;7:e39504. doi: 10.1371/journal.pone.0039504
- Kahn HS. The, "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. *BMC Cardiovasc Disord*. 2005;5:26. doi: 10.1186/1471-2261-5-26
- Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, Galluzzo A, AlkaMeSy Study G. Visceral adiposity index: a reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes Care*. 2010;33:920–922. doi: 10.2337/dc09-1825
- Ma YC, Zuo LI, Chen JH, Luo Q, Yu XQ, Li Y, Xu JS, Huang SM, Wang LN, Huang W, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol*. 2006;17:2937–2944. doi: 10.1681/ASN.2006040368
- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37:S81–S90.
- Perloff D, Grim C, Flack J, Frohlich ED, Hill M, McDonald M, Morgenstern BZ. Human blood pressure determination by sphygmomanometry. *Circulation*. 1993;88:2460–2470. doi: 10.1161/01.CIR.88.5.2460
- Farrell GC, Chitturi S, Lau GK, Sollano JD. Asia-Pacific Working Party on N. Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia-Pacific region: executive summary. *J Gastroenterol Hepatol*. 2007;22:775–777. doi: 10.1111/j.1440-1746.2007.05002.x
- Ng'andu NH. An empirical comparison of statistical tests for assessing the proportional hazards assumption of Cox's model. *Stat Med*. 1997;16:611–626. doi: 10.1002/(SICI)1097-0258(19970330)16:6<611::AID-SIM437>3.0.CO;2-T
- Palmer BF, Clegg DJ. The sexual dimorphism of obesity. *Mol Cell Endocrinol*. 2015;402:113–119. doi: 10.1016/j.mce.2014.11.029
- Hou Q, Li S, Gao Y, Tian H. Relations of lipid parameters, other variables with carotid intima-media thickness and plaque in the general Chinese adults: an observational study. *Lipids Health Dis*. 2018;17:107. doi: 10.1186/s12944-018-0758-9
- Salari-Moghaddam A, Keshteli AH, Haghighatdoost F, Esmailzadeh A, Adibi P. Dietary glycaemic index and glycaemic load in relation to general obesity and central adiposity among adults. *Clin Nutr*. 2019;38:2936–2942. doi: 10.1016/j.clnu.2018.12.036
- Mostaza JM, Lahoz C, Salinero-Fort MA, de Burgos-Lunar C, Laguna F, Estirado E, García-Iglesias F, González-Alegre T, Cornejo-Del-Río V, Sabin C, et al. Carotid atherosclerosis severity in relation to glycaemic status: a cross-sectional population study. *Atherosclerosis*. 2015;242:377–382. doi: 10.1016/j.atherosclerosis.2015.07.028
- Han M, Qie R, Li Q, Liu L, Huang S, Wu X, Zhang D, Cheng C, Zhao Y, Liu D, et al. Chinese visceral adiposity index, a novel indicator of visceral obesity for assessing the risk of incident hypertension in a prospective cohort study. *Br J Nutr*. 2021;126:612–620. doi: 10.1017/S0007114520004298
- Ferreira JP, Girerd N, Bozec E, Machu JL, Boivin JM, London GM, Zannad F, Rossignol P. Intima-media thickness is linearly and continuously associated with Systolic Blood Pressure in a Population-Based Cohort (STANISLAS Cohort Study). *J Am Heart Assoc*. 2016;5:e003529. doi: 10.1161/JAHA.116.003529
- Ali N, Sumon AH, Fariha KA, Asaduzzaman MD, Kathak RR, Molla NH, Mou AD, Barman Z, Hasan M, Miah R, et al. Assessment of the relationship of serum liver enzymes activity with general and abdominal obesity in an urban Bangladeshi population. *Sci Rep*. 2021;11:6640. doi: 10.1038/s41598-021-86216-z
- Qu BG, Wang H, Jia YG, Su JL, Wang ZD, Wang YF, Han XH, Liu YX, Pan JD, Ren GY. The correlation and risk factors between carotid intima-media thickening and alcoholic liver disease coupled with helicobacter pylori infection. *Sci Rep*. 2017;7:43059. doi: 10.1038/srep43059
- Mele C, Tagliaferri MA, Saraceno G, Mai S, Vietti R, Zavattaro M, Aimaretti G, Scacchi M, Marzullo P. Serum uric acid potentially links metabolic health to measures of fuel use in lean and obese individuals. *Nutr Metab Cardiovasc Dis*. 2018;28:1029–1035. doi: 10.1016/j.numecd.2018.06.010
- Ishizaka N, Ishizaka Y, Toda E, Nagai R, Yamakado M. Association between serum uric acid, metabolic syndrome, and carotid atherosclerosis in Japanese individuals. *Arterioscler Thromb Vasc Biol*. 2005;25:1038–1044. doi: 10.1161/01.ATV.0000161274.87407.26
- Shahali A, Tasdighi E, Barzin M, Mahdavi M, Valizadeh M, Niroomand M, Azizi F, Hosseini-panah F. Abdominal obesity phenotypes and risk of kidney function decline: Tehran Lipid and Glucose Study. *Obes Res Clin Pract*. 2020;14:168–175. doi: 10.1016/j.orcp.2020.03.006
- Kawamoto R, Ohtsuka N, Kusunoki T, Yorimitsu N. An association between the estimated glomerular filtration rate and carotid

- atherosclerosis. *Intern Med*. 2008;47:391. doi: 10.2169/internalmed.47.0552
32. Farah BQ, Christofaro DG, Balagopal PB, Cavalcante BR, de Barros MV, Ritti-Dias RM. Association between resting heart rate and cardiovascular risk factors in adolescents. *Eur J Pediatr*. 2015;174:1621–1628. doi: 10.1007/s00431-015-2580-y
  33. Whelton SP, Blankstein R, Al-Mallah MH, Lima JA, Bluemke DA, Hundley WG, Polak JF, Blumenthal RS, Nasir K, Blaha MJ. Association of resting heart rate with carotid and aortic arterial stiffness: multi-ethnic study of atherosclerosis. *Hypertension*. 2013;62:477–484. doi: 10.1161/HYPERTENSIONAHA.113.01605
  34. Luo WS, Chen F, Ji JM, Guo ZR. Interaction of tobacco smoking and alcohol consumption with obesity on cardiovascular disease in a Chinese cohort. *Coron Artery Dis*. 2020;31:372–377. doi: 10.1097/MCA.0000000000000837
  35. Farhangi MA, Keshavarz SA, Eshraghian M, Ostadrahimi A, Saboor-Yaraghi AA. White blood cell count in women: relation to inflammatory biomarkers, haematological profiles, visceral adiposity, and other cardiovascular risk factors. *J Health Popul Nutr*. 2013;31:58–64. doi: 10.3329/jhpn.v31i1.14749
  36. Liu Y, Zhu Y, Jia W, Sun D, Zhao Li, Zhang C, Wang C, Lyu Q, Chen Y, Chen G, et al. Association of the total white blood cell, neutrophils, and monocytes count with the presence, severity, and types of carotid atherosclerotic plaque. *Front Med*. 2020;7:313. doi: 10.3389/fmed.2020.00313
  37. Li P, Stuart EA, Allison DB. Multiple imputation: a flexible tool for handling missing data. *JAMA*. 2015;314:1966–1967. doi: 10.1001/jama.2015.15281
  38. Emdin CA, Khera AV, Natarajan P, Klarin D, Zekavat SM, Hsiao AJ, Kathiresan S. Genetic association of waist-to-hip ratio with cardiometabolic traits, type 2 diabetes, and coronary heart disease. *JAMA*. 2017;317:626–634. doi: 10.1001/jama.2016.21042
  39. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, Vasan RS, Murabito JM, Meigs JB, Cupples LA, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation*. 2007;116:39–48. doi: 10.1161/CIRCULATIONAHA.106.675355
  40. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006;444:875–880. doi: 10.1038/nature05487
  41. Li B, Lai X, Yan C, Jia X, Li Y. The associations between neutrophil-to-lymphocyte ratio and the Chinese Visceral Adiposity Index, and carotid atherosclerosis and atherosclerotic cardiovascular disease risk. *Exp Gerontol*. 2020;139:111019. doi: 10.1016/j.exger.2020.111019
  42. Lau DC, Dhillon B, Yan H, Szmítko PE, Verma S. Adipokines: molecular links between obesity and atherosclerosis. *Am J Physiol Heart Circ Physiol*. 2005;288:H2031–H2041. doi: 10.1152/ajpheart.01058.2004
  43. Xia MF, Lin HD, Chen LY, Wu LI, Ma H, Li Q, Aleteng Q, Chen Y, Sun YX, Hu YU, et al. Association of visceral adiposity and its longitudinal increase with the risk of diabetes in Chinese adults: a prospective cohort study. *Diabetes Metab Res Rev*. 2018;34:e3048. doi: 10.1002/dmrr.3048
  44. Risso A, Mercuri F, Quagliaro L, Damante G, Ceriello A. Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture. *Am J Physiol Endocrinol Metab*. 2001;281:E924–E930. doi: 10.1152/ajpendo.2001.281.5.E924
  45. Schrover IM, van der Graaf Y, Spiering W, Visseren FL, SMART study group. The relation between body fat distribution, plasma concentrations of adipokines and the metabolic syndrome in patients with clinically manifest vascular disease. *Eur J Prev Cardiol*. 2018;25:1548–1557. doi: 10.1177/2047487318790722
  46. Domínguez Coello S, Cabrera de León A, Almeida González D, González Hernández A, Rodríguez Pérez MC, Fernández Ramos N, Brito Díaz B, Castro Fuentes R, Aguirre JA. Inverse association between serum resistin and insulin resistance in humans. *Diabetes Res Clin Pract*. 2008;82:256–261. doi: 10.1016/j.diabres.2008.08.001
  47. Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, Rader DJ. Resistin is an inflammatory marker of atherosclerosis in humans. *Circulation*. 2005;111:932–939. doi: 10.1161/01.CIR.0000155620.10387.43
  48. Gencer B, Auer R, de Rekeneire N, Butler J, Kalogeropoulos A, Bauer DC, Kritchevsky SB, Miljkovic I, Vittinghoff E, et al. Association between resistin levels and cardiovascular disease events in older adults: the health, aging and body composition study. *Atherosclerosis*. 2016;245:181–186. doi: 10.1016/j.atherosclerosis.2015.12.004
  49. Wan H, Wang Y, Xiang Q, Fang S, Chen YI, Chen C, Zhang W, Zhang H, Xia F, Wang N, et al. Associations between abdominal obesity indices and diabetic complications: Chinese visceral adiposity index and neck circumference. *Cardiovasc Diabetol*. 2020;19:118. doi: 10.1186/s12933-020-01095-4
  50. Han M, Qin P, Li Q, Qie R, Liu L, Zhao Y, Liu D, Zhang D, Guo C, Zhou Q, et al. Chinese visceral adiposity index: a reliable indicator of visceral fat function associated with risk of type 2 diabetes. *Diabetes Metab Res Rev*. 2021;37:e3370. doi: 10.1002/dmrr.3370
  51. Després JP. Body fat distribution and risk of cardiovascular disease: an update. *Circulation*. 2012;126:1301–1313. doi: 10.1161/CIRCULATIONAHA.111.067264
  52. Pou KM, Massaro JM, Hoffmann U, Lieb K, Vasan RS, O'Donnell CJ, Fox CS. Patterns of abdominal fat distribution: the Framingham Heart Study. *Diabetes Care*. 2009;32:481–485. doi: 10.2337/dc08-1359
  53. Chen S, Chao S, Konerman M, Zhang W, Rao H, Wu E, Lin A, Wei L, Lok AS. Survey of nonalcoholic fatty liver disease knowledge, nutrition, and physical activity patterns among the general public in Beijing, China. *Dig Dis Sci*. 2019;64:3480–3488. doi: 10.1007/s10620-019-05709-0
  54. Yang Y, Nicholas S, Li S, Huang Z, Chen X, Ma Y, Shi X. Health care utilization for patients with stroke: a 3-year cross-sectional study of China's two urban health insurance schemes across four cities. *BMC Public Health*. 2021;21:531. doi: 10.1186/s12889-021-10456-x