

## ORIGINAL ARTICLE

## Contribution of visceral fat accumulation to carotid intima–media thickness in a Chinese population

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**OBJECTIVE:** Recent observational studies have reported that body fat distribution might be differentially associated with subclinical atherosclerosis. We previously reported that visceral fat area (VFA)  $\geq 80 \text{ cm}^2$  is the optimal cutoff for identifying abdominal obesity in Chinese subjects. We examined whether VFA  $\geq 80 \text{ cm}^2$  reflects the association between abdominal obesity and subclinical atherosclerosis, and if determination of the visceral fat quantity is useful for assessing subclinical atherosclerosis in asymptomatic individuals.

**METHODS AND RESULTS:** Participants ( $N = 1005$ , men 515, women 490, 34–66 years) free of cardiovascular disease underwent magnetic resonance imaging and carotid ultrasound assessment to quantify VFA and carotid intima–media thickness (C-IMT). Overweight/obese subjects (body mass index (BMI)  $\geq 25.0 \text{ kg m}^{-2}$ ) had a higher C-IMT than lean subjects (BMI  $< 25.0 \text{ kg m}^{-2}$ ) ( $P < 0.01$ ). Subjects with VFA  $\geq 80 \text{ cm}^2$  had significantly higher C-IMT than those without abdominal obesity regardless of BMI ( $P < 0.01$ ). By multivariate regression analysis adjusted for anthropometric measurements and cardiovascular risk factors, waist circumference but not BMI was independently correlated with C-IMT in men ( $P < 0.001$ ). Similar findings were observed with an accurate obesity indices adjusted model, which showed that VFA was an independent risk factor for increased C-IMT in men but not in women.

**CONCLUSIONS:** VFA  $\geq 80 \text{ cm}^2$  effectively identified carotid atherosclerosis for both lean and obese individuals in middle-aged Chinese men.

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## INTRODUCTION

Obesity is a global epidemic and is strongly associated with metabolic disorders and cardiovascular disease (CVD).<sup>1</sup> The relationship between obesity and CVD depends not only on the amount of total body fat but also on its distribution.<sup>2–4</sup> In recent years, increasing evidence has shown that, compared with total body fat, visceral fat accumulation is more important for the development of insulin resistance, metabolic syndrome (Mets), type 2 diabetes and CVD.<sup>5–8</sup> Abdominal obesity is considered a fundamental pathology for Mets development, which is associated with increased risk of cardiovascular morbidity and mortality.<sup>9,10</sup>

Most studies use waist circumference or waist-to-hip ratio to define abdominal obesity.<sup>2–4,7,8</sup> However, measurement of these circumferences cannot distinguish between visceral and subcutaneous adipose tissue. The standard methods for quantifying visceral fat amount recommended by the International Diabetes Federation (IDF) are magnetic resonance imaging (MRI) and computed tomography.<sup>11</sup> We previously reported that for a Chinese population, visceral fat area (VFA)  $\geq 80 \text{ cm}^2$  is optimal for detecting two or more metabolic abnormalities. These include hyperglycemia, hypertension and dyslipidemia, using the IDF definition or the 2004 Chinese Diabetes Society definition.<sup>12</sup> Whether VFA  $\geq 80 \text{ cm}^2$  reflects an association between abdominal obesity and subclinical atherosclerosis is still unknown. Moreover,

to our knowledge, no study has focused on the association between visceral fat amount and the extent of subclinical atherosclerosis in various body mass index (BMI) categories in a Chinese population.

Quantitative assessment of carotid intima–media thickness (C-IMT) is accepted as an indicator of preclinical atherosclerosis and may be used as a marker for cardiovascular morbidity and mortality.<sup>13,14</sup> Therefore, the aims of this study were to: (1) determine if visceral fat accumulation was a stronger risk factor of subclinical atherosclerosis than general obesity in a Chinese population; (2) evaluate whether VFA  $\geq 80 \text{ cm}^2$  was the optimal value to reflect the association between abdominal obesity and subclinical atherosclerosis in both lean and overweight/obese subjects and (3) investigate if visceral fat quantity is useful for assessing subclinical atherosclerosis in asymptomatic individuals.

## SUBJECTS AND METHODS

## Subjects

A total of 1217 subjects, aged 30 to 70 years, were recruited from December 2009 to June 2010 in Baoshan community, Shanghai, China. The exclusion criteria were: (1) current treatment with systemic corticosteroids; (2) cirrhosis with ascites; (3) known hyperthyroidism or hypothyroidism; (4) presence of cancer; (5) severe disability and psychiatric disturbance;

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(6) pregnancy and (7) known history of CVD. The excluded were 182 with no MRI data, 3 with no carotid artery scans, 16 with incomplete anthropometric indices and 11 with incomplete lab data or C-reactive protein (CRP)  $\geq 10 \text{ mg l}^{-1}$ . We finally analyzed data from 1005 subjects (men 515, women 490) aged 34–66 years in this study.

All participants were invited to complete a questionnaire about present and past illness and medical therapy. The study was approved by the Ethics Committee of Shanghai Jiaotong University affiliated Sixth People's Hospital. Written informed consent was obtained from all the participants.

#### Clinical and laboratory assessments of risk factors

A physical examination, including measurement of height, weight, waist circumference (*W*) and blood pressure (BP), was performed for each participant. BMI was calculated as weight in kilograms divided by the square of height in meters. *W* was measured at the horizontal plane between the inferior costal margin and the iliac crest on mid-axillary line. Body fat percentage (%fat) was estimated by the TBF-410 Tanita Body Composition Analyzer (Tanita, Tokyo, Japan). BP was the average of three time measurements using a sphygmomanometer at an interval of 3 min.

After a 10-h overnight fast, blood samples were collected to measure plasma glucose level and lipid profile. Subjects without a validated history of diabetes underwent a 75-g oral glucose tolerance test. The 100-g carbohydrate (steamed bread meal) test was performed in diabetic patients.<sup>15</sup> Fasting plasma glucose (FPG) and 2-h post-OGTT plasma glucose (2hPG) were assayed by the glucose oxidase method. Serum triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c) were measured by enzymatic procedures using an autoanalyzer (Hitachi 7600-020, automatic analyzer, Tokyo, Japan). Glycated hemoglobin A1c (HbA1c) was determined by high-pressure liquid chromatography (Bio-Rad Inc., Hercules, CA, USA). The serum concentration of CRP was measured by particle-enhanced immunonephelometry using CardioPhase hs-CRP reagent (Siemens Healthcare Diagnostic Inc., Newark, NJ, USA). The detection limit of the assay was  $0.175 \text{ mg l}^{-1}$ . The intra-assay coefficients of variation for hs-CRP levels were 2.3%, 4.6%, 2.6% and 2.1% at 0.69, 5.95, 9.23 and  $179 \text{ mg l}^{-1}$ , respectively; inter-assay coefficients of variation were 2.3%, 4.0%, 1.3% and 1.1% at 0.69, 5.95, 9.23 and  $179 \text{ mg l}^{-1}$ . Serum insulin concentration was measured by radioimmunoassay (Linco Research, St Charles, MO, USA). Insulin sensitivity was estimated by homeostasis model assessment-insulin resistance (HOMA-IR) based on fasting glucose and insulin measurements as follows:  $\text{HOMA-IR} = \text{fasting serum insulin (mU l}^{-1}) \times \text{FPG (mmol l}^{-1}) / 22.5$ .<sup>16</sup> BMI  $\geq 25.0 \text{ kg m}^{-2}$  was defined as overweight/obesity according to the World Health Organization criterion.<sup>15</sup> The diagnostic definition for Mets followed the 2007 Joint Committee for Developing Chinese Guidelines on prevention and treatment of dyslipidemia definition,<sup>17</sup> which is the presence of three or more of the following: (1) central obesity of *W*  $> 90 \text{ cm}$  in men or  $> 85 \text{ cm}$  in women; (2) TG level of  $\geq 1.7 \text{ mmol l}^{-1}$  or specific treatment for lipid abnormality; (3) HDL-c  $< 1.04 \text{ mmol l}^{-1}$  (4) systolic BP (SBP)  $\geq 130 \text{ mmHg}$  and/or diastolic BP (DBP)  $\geq 85 \text{ mmHg}$  or treatment of previously diagnosed hypertension and (5) hyperglycemia of FPG  $\geq 6.1 \text{ mmol l}^{-1}$  and/or 2hPG level  $\geq 7.8 \text{ mmol l}^{-1}$  or previously diagnosed type 2 diabetes.

#### Carotid artery measurement

Carotid artery scans were performed using a high-resolution B-mode scanner (Sequoia 512, Siemens, Bonn, Germany) and a 10-MHz probe as previously described.<sup>18</sup> A single sonographer who was blinded to clinical characteristics measured C-IMT. Both common carotid arteries were scanned from proximal to distal to the bifurcation. C-IMT was measured at the far wall of both common carotid arteries approximately 1 cm proximal to the carotid bulb. Carotid IMT was defined as the mean of the maximal IMT of each carotid artery.

#### Magnetic resonance imaging

Visceral and subcutaneous adipose tissue areas were assessed using a 3.0 T clinical MRI scanner (Archiva, Philips Medical System, Amsterdam,

The Netherlands), using the abdominal coil. MRI scans were obtained at the abdominal level between L4 and L5 vertebrae in the supine position. Segmentation of the images into VFA and subcutaneous fat area (SFA) were performed by two trained observers using SLICE-O-MATIC image analysis software (version 4.2; Tomovision Inc., Montreal, QC, Canada). If results differed by more than 10%, a third observer who did not know the results reanalyzed the images.

#### Statistical analysis

All statistical analysis was performed with Statistical Package for Social Sciences version 13.0. (SPSS, Chicago, IL, USA). Data are presented as mean  $\pm$  standard deviation (s.d.) except for skewed variables, which are presented as median (interquartile range 25–75%). Clinical characteristics that followed a normal distribution were compared among the four groups using an unpaired Student's *t*-test, and those that were not normally distributed were compared with a Wilcoxon rank-sum test. For dichotomous or categorical variables, comparison between groups was performed using a  $\chi^2$  test. Partial correlation analysis was performed to investigate the association between C-IMT and other parameters adjusted for anti-hypertensive, anti-diabetic and lipid-lowering treatment. Multiple stepwise regression analysis was applied to assess associations between C-IMT, VFA and metabolic parameters after adjusting for potential confounders. All reported *P* values were two-tailed, and *P*-values  $< 0.05$  were considered statistically significant.

## RESULTS

#### Clinical characteristics of subjects

The final dataset included 1005 subjects (515 men, 240 premenopausal women and 250 postmenopausal women) aged 34–66 years ( $50.7 \pm 6.8$  years). The principle characteristics of the study subjects are in Table 1. Compared with men, both premenopausal and postmenopausal women had significantly lower *W*, VFA, C-IMT, TG and FPG, and higher %fat, HDL-c and SFA (all  $P < 0.05$ ). Postmenopausal women also had significantly higher age, TC, LDL-c and HbA1c than men and premenopausal women (all  $P < 0.01$ ). The frequency of Mets was significantly increased in men and the proportion of current smokers showed the same trend for both genders (all  $P < 0.05$ ).

#### Relationship between VFA and C-IMT by BMI category

Overweight/obese subjects (BMI  $\geq 25.0 \text{ kg m}^{-2}$ ) when compared with lean subjects had a higher *W*, %fat, SFA, VFA, BP, CRP and C-IMT (all  $P < 0.01$ ). They also had a worse glucose tolerance status (FPG, 2hPG, HbA1c, HOMA-IR) and lipid profile (all  $P < 0.05$ ). The prevalence of Mets and its components was higher in the BMI  $\geq 25.0 \text{ kg m}^{-2}$  category ( $P < 0.01$ ). However, no difference in age or smoking rate was observed between overweight/obese and lean subjects (Table 2).

To analyze the influence of visceral obesity on C-IMT by BMI category, subjects were divided into subgroups according to VFA (Table 2). In addition to increased CVD risk factors, C-IMT was elevated as VFA increased in both the BMI  $< 25.0 \text{ kg m}^{-2}$  group and the BMI  $\geq 25.0 \text{ kg m}^{-2}$  group (for BMI  $< 25.0 \text{ kg m}^{-2}$ , C-IMT was 0.60 mm (0.60–0.65) vs 0.60 mm (0.6–0.70),  $P < 0.01$  and for BMI  $\geq 25.0 \text{ kg m}^{-2}$ , C-IMT was 0.60 mm (0.60–0.65) vs 0.65 mm (0.60–0.70),  $P < 0.01$ ).

#### Association of C-IMT with anthropometric parameters, glucose, lipid profile and VFA

Table 3 shows partial correlation analysis adjusted for anti-hypertensive, anti-diabetic and lipid-lowering treatment for participants in different BMI categories. C-IMT showed significant positive correlation with age, *W*, VFA, SBP, LDL-c and 2hPG, and negative correlation with %fat in both the BMI  $< 25.0 \text{ kg m}^{-2}$  group and the BMI  $\geq 25.0 \text{ kg m}^{-2}$  group (all  $P < 0.05$ ). In addition,

**Table 1.** Demographic and clinical characteristics of study subjects

Parameters	Men	Premenopausal women	Postmenopausal women
N	515	240	250
Age (years)	51.4 ± 6.8	45.4 ± 4.5**	54.6 ± 5.3**††
BMI (kg m <sup>-2</sup> )	24.8 ± 3.2	24.0 ± 3.5**	24.4 ± 3.9
W (cm)	88.1 ± 9.1	80.9 ± 8.8**	82.1 ± 10.1**
%Fat (%)	25.4 (21.4–28.6)	32.8 (28.4–38.7)**	33.7 (28.9–38.1)**
SFA (cm <sup>2</sup> )	123.8 (93.4–159.5)	155.8 (117.7–194.8)**	170.5 (134.1–211.8)**††
VFA (cm <sup>2</sup> )	89.7 (56.3–128.6)	50.5 (30.1–77.3)**	69.1 (41.8–97.3)**††
C-IMT (mm)	0.65 (0.60–0.70)	0.60 (0.60–0.60)**	0.60 (0.60–0.65)**††
SBP (mm Hg)	128.0 (120.0–138.0)	121.0 (115.5–130.0)**	127.0 (120.0–134.3)††
DBP (mm Hg)	80.0 (78.0–89.0)	79.0 (74.0–81.0)**	80.0 (75.0–87.3)†
TC (mmol l <sup>-1</sup> )	4.9 (4.4–5.6)	4.7 (4.1–5.4)**	5.4 (4.7–6.1)**††
TG (mmol l <sup>-1</sup> )	1.5 (1.1–2.3)	1.0 (0.7–1.6)**	1.3 (0.9–1.9)**††
LDL-c (mmol l <sup>-1</sup> )	3.7 ± 1.0	3.4 ± 0.9**	3.9 ± 1.0**††
HDL-c (mmol l <sup>-1</sup> )	1.3 (1.1–1.5)	1.5 (1.3–1.8)**	1.6 (1.4–1.8)**
FPG (mmol l <sup>-1</sup> )	5.7 (5.2–6.3)	5.4 (5.1–5.9)**	5.5 (5.2–6.0)*†
2hPG (mmol l <sup>-1</sup> )	6.0 (4.7–8.0)	5.8 (4.9–7.0)	6.5 (5.2–8.1)*††
HbA1c (%)	5.7 (5.4–6.0)	5.6 (5.3–5.8)**	5.8 (5.5–6.1)**††
HOMA-IR	4.9 (3.5–6.6)	4.7 (3.5–6.3)	4.3 (3.2–6.1)*
CRP	0.8 (0.4–1.6)	0.5 (0.2–1.1)**	0.8 (0.4–1.7)††
Anti-hypertensive therapy, N(%)	103 (20.0)	32 (13.3)*	59 (23.6)††
Anti-diabetic therapy, N(%)	38 (7.4)	9 (3.8)	18 (7.2)
Lipid-lowering therapy, N(%)	6 (1.2)	0 (0.0)	7 (2.8)†
Current smoker, N(%)	342 (66.4)	10 (4.2)**	12 (4.8)**
Metabolic syndrome, N(%)	166 (32.2)	31 (12.9)**	61 (24.4)*††
Central obesity, N(%)	213 (41.4)	76 (31.7)*	87 (34.8)
Hyperglycemia, N(%)	190 (36.9)	48 (20.0)**	89 (35.6)††
Hypertriglyceridemia, N(%)	218 (42.3)	46 (19.2)**	75 (30.0)**††
Low HDL-c, N(%)	81 (15.7)	12 (5.0)**	5 (2.0)**
Hypertension, N(%)	282 (54.8)	96 (40.0)**	142 (56.8)††

Abbreviations: 2hPG, 2-h post-OGTT plasma glucose; BMI, body mass index; C-IMT, carotid intima-media thickness; CRP, C reactive protein; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SFA, subcutaneous fat area; TC, total cholesterol; TG, triglyceride; VFA, visceral fat area; W, waist circumference. \* $P < 0.05$ , \*\* $P < 0.01$  versus men. † $P < 0.05$ , †† $P < 0.01$  versus premenopausal women. Data are means ± s.d. or median (interquartile range).

C-IMT was positively correlated with DBP, TC, FPG, HbA1c and HOMA-IR in the BMI  $< 25.0 \text{ kg m}^{-2}$  group (all  $P < 0.05$ ). It was positively correlated with serum CRP and inversely correlated with SFA and HDL-c in the BMI  $\geq 25.0 \text{ kg m}^{-2}$  group (all  $P < 0.05$ ).

To further investigate the independent association between visceral obesity and C-IMT, multiple stepwise regression analysis was performed in men and women (Table 4). As independent variables, we used body fat parameters, the basic CVD risk factors identified in the univariate analysis of age, BP, HOMA-IR, 2hPG, LDL-c, HDL-c and CRP, as well as smoking status, anti-hypertensive therapy, anti-diabetic therapy and lipid-lowering therapy. The analysis adjusted for menopausal status in women. Three regression models were constructed according to the selected body fat parameters. The first model included all body fat parameters, including anthropometric variables ( $W$  and BMI) and accurate adiposity variables (%fat, VFA and SFA). We found that in addition to age, smoking, LDL-c, SBP and 2hPG,  $W$  (standardized  $\beta = 0.163$ ,  $P < 0.001$ ) was an independent factor for C-IMT in men. We next analyzed the strength of anthropometric obesity variables in model 2 and accurate adiposity variables in model 3.  $W$  (standardized  $\beta = 0.161$ ,  $P < 0.001$ ) and VFA (standardized  $\beta = 0.107$ ,  $P = 0.007$ ) were found to be two obesity-related factors significantly influencing C-IMT, respectively, in these two models in men. However, in women, no body fat parameters, except for age, HOMA-IR, SBP and anti-hypertensive therapy, affected the three models.

## DISCUSSION

Obesity is closely related to impaired glucose tolerance, dyslipidemia, hypertension and other cardiovascular risk factors, as well as cardiovascular events.<sup>19–21</sup> As abdominal obesity might

be more atherogenic than general obesity,<sup>22,23</sup> measurement of visceral abdominal tissue could be an early detection method for Mets and a strategic screening to prevent CVD. However, the optimal cutoff for VFA to identify early-stage atherosclerosis is still uncertain. Several groups proposed a cutoff of VFA  $100 \text{ cm}^2$  to define abdominal obesity and predict obesity-related disorders.<sup>24</sup> In our previous study, VFA  $\geq 80 \text{ cm}^2$  was found to be the discriminating value for predicting Mets in a Chinese population.<sup>12</sup> Here, we found that individuals with VFA  $\geq 80 \text{ cm}^2$  had a significantly higher incidence of Mets, in both the lean category (BMI  $< 25.0 \text{ kg m}^{-2}$ ) and the overweight/obesity category (BMI  $\geq 25.0 \text{ kg m}^{-2}$ ). This supports this VFA value as an optimal cutoff point for identifying individuals in a Chinese population with metabolic risk factors that are not solely dependent on BMI.

No study has focused on the relationship between VFA and C-IMT in different BMI categories in a Chinese population. In this study, we compared C-IMT between subjects with or without visceral obesity by BMI category. Subjects with VFA  $\geq 80 \text{ cm}^2$  had a higher C-IMT, independent of BMI. Furthermore, we found that VFA significantly positively correlated with C-IMT in correlation analysis. Regional fat distribution differs by gender. Women generally have more subcutaneous fat than men, whereas men have more visceral fat.<sup>25</sup> We also observed significantly higher VFA and lower %fat and SFA in men than in women, although the mean BMI in men and postmenopausal women were similar. As postmenopausal women have a higher risk of developing atherosclerosis because of loss of protection from estrogen,<sup>26</sup> we performed separate multiple stepwise regression analyses for men and women, adjusting for menopausal status in women. We found that obesity indices reflecting visceral rather than general obesity were associated with C-IMT, mainly in men. Although the

**Table 2.** Clinical characteristics according to BMI and VFA

Parameters	BMI < 25.0 kg m <sup>-2</sup>			BMI ≥ 25.0 kg m <sup>-2</sup>		
	Total	VFA < 80 cm <sup>2</sup>	VFA ≥ 80 cm <sup>2</sup>	Total	VFA < 80 cm <sup>2</sup>	VFA ≥ 80 cm <sup>2</sup>
N	594	457	137	411	92	319
Sex (men/women)	283/311	187/270	96/41	232/179	27/65	205/114
Age (years)	50.5 ± 6.7	50.0 ± 6.8	52.3 ± 6.1 <sup>‡</sup>	51.1 ± 7.0	49.0 ± 6.5	51.7 ± 7.0 <sup>††</sup>
BMI (kg m <sup>-2</sup> )	22.3 ± 1.9	21.9 ± 1.9	23.7 ± 1.0 <sup>‡</sup>	27.8 ± 2.4 <sup>##</sup>	26.8 ± 1.5	28.1 ± 2.6 <sup>††</sup>
W (cm)	79.5 ± 7.3	77.5 ± 6.6	85.8 ± 5.6 <sup>‡</sup>	92.7 ± 7.5 <sup>##</sup>	87.2 ± 5.6	94.3 ± 7.3 <sup>††</sup>
%Fat (%)	26.1 (21.9–30.4)	26.0 (21.2–30.3)	26.7 (22.8–30.5)	33.9 (27.7–39.9) <sup>##</sup>	36.4 (29.9–40.7)	32.7 (27.5–39.5)
SFA (cm <sup>2</sup> )	117.9 (89.8–151.1)	111.7 (83.8–145.3)	130.8 (109.1–160.0) <sup>‡</sup>	177.9 (144.0–225.0) <sup>##</sup>	184.7 (150.7–224.0)	176.3 (143.2–227.4)
VFA (cm <sup>2</sup> )	51.7 (32.2–77.0)	41.2 (26.1–59.9)	98.8 (87.5–116.2) <sup>‡</sup>	113.2 (83.6–141.0) <sup>##</sup>	63.3 (50.9–71.0)	122.9 (103.9–149.9) <sup>††</sup>
C-IMT (mm)	0.60 (0.60–0.65)	0.60 (0.60–0.65)	0.60 (0.60–0.70) <sup>‡</sup>	0.60 (0.60–0.70) <sup>##</sup>	0.60 (0.60–0.65)	0.65 (0.60–0.70) <sup>††</sup>
SBP (mmHg)	123.0 (120.0–130.0)	121.0 (118.0–130.0)	128.0 (120.0–138.0) <sup>‡</sup>	130.0 (120.0–140.0) <sup>##</sup>	123.0 (120.0–132.5)	130.0 (120.0–140.0) <sup>††</sup>
DBP (mmHg)	80.0 (74.0–81.0)	80.0 (73.0–80.0)	80.0 (77.5–86.5) <sup>‡</sup>	80.0 (79.0–90.0) <sup>##</sup>	80.0 (75.3–88.8)	80.0 (79.0–90.0) <sup>†</sup>
TC (mmol l <sup>-1</sup> )	4.9 (4.3–5.7)	4.8 (4.3–5.6)	5.3 (4.4–6.0) <sup>‡</sup>	5.1 (4.5–5.7) <sup>##</sup>	4.7 (4.2–5.5)	5.2 (4.6–5.8) <sup>††</sup>
TG (mmol l <sup>-1</sup> )	1.2 (0.8–1.8)	1.1 (0.8–1.6)	1.5 (1.1–2.4) <sup>‡</sup>	1.6 (1.1–2.4) <sup>##</sup>	1.2 (0.8–1.5)	1.8 (1.3–2.5) <sup>††</sup>
LDL-c (mmol l <sup>-1</sup> )	3.5 ± 1.0	3.5 ± 1.0	3.8 ± 1.0 <sup>‡</sup>	3.8 ± 1.0 <sup>##</sup>	3.7 ± 1.0	3.9 ± 1.0
HDL-c (mmol l <sup>-1</sup> )	1.5 (1.3–1.8)	1.5 (1.3–1.8)	1.3 (1.2–1.5) <sup>‡</sup>	1.3 (1.1–1.5) <sup>##</sup>	1.4 (1.3–1.6)	1.3 (1.1–1.4) <sup>††</sup>
FPG (mmol l <sup>-1</sup> )	5.4 (5.1–5.9)	5.4 (5.1–5.8)	5.7 (5.2–6.3) <sup>‡</sup>	5.8 (5.4–6.5) <sup>##</sup>	5.6 (5.3–6.2)	5.8 (5.4–6.5) <sup>†</sup>
2hPG (mmol l <sup>-1</sup> )	5.9 (4.8–7.2)	5.7 (4.8–6.8)	6.3 (5.1–8.1) <sup>‡</sup>	6.6 (5.3–8.7) <sup>##</sup>	6.3 (5.1–7.4)	6.8 (5.3–9.4) <sup>††</sup>
HbA1c (%)	5.6 (5.30–5.9)	5.6 (5.3–5.8)	5.6 (5.4–6.1) <sup>‡</sup>	5.8 (5.6–6.2) <sup>##</sup>	5.7 (5.5–6.0)	5.8 (5.6–6.3) <sup>†</sup>
HOMA-IR	3.9 (3.1–5.4)	3.8 (3.0–5.1)	4.7 (3.6–6.2) <sup>‡</sup>	5.8 (4.4–7.7) <sup>##</sup>	5.0 (3.5–6.7)	5.9 (4.6–8.2) <sup>††</sup>
CRP (mg dl <sup>-1</sup> )	0.5 (0.2–1.0)	0.5 (0.2–0.9)	0.9 (0.5–1.5) <sup>‡</sup>	1.1 (0.6–2.2) <sup>##</sup>	0.7 (0.4–1.2)	1.3 (0.7–2.5) <sup>††</sup>
Current smoker, N(%)	204 (34.3)	136 (29.8)	68 (49.6) <sup>‡</sup>	160 (38.9)	20 (21.7)	140 (43.9) <sup>††</sup>
Metabolic syndrome, N(%)	63 (10.6)	29 (6.3)	34 (24.8) <sup>‡</sup>	195 (47.4) <sup>##</sup>	21 (22.8)	174 (54.5) <sup>††</sup>
Central obesity, N(%)	66 (11.1)	27 (5.9)	39 (28.5) <sup>‡</sup>	310 (75.4) <sup>##</sup>	49 (53.3)	261 (81.8) <sup>††</sup>
Hyperglycemia, N(%)	146 (24.6)	91 (19.9)	55 (40.1) <sup>‡</sup>	181 (44.0) <sup>##</sup>	32 (34.8)	149 (46.7) <sup>†</sup>
Hypertriglyceridemia, N(%)	156 (26.3)	100 (21.9)	56 (40.9) <sup>‡</sup>	183 (44.5) <sup>##</sup>	16 (17.4)	167 (52.4) <sup>††</sup>
Low HDL-c, N(%)	41 (6.9)	25 (5.5)	16 (11.7) <sup>‡</sup>	57 (13.9) <sup>##</sup>	6 (6.5)	51 (16.0) <sup>†</sup>
Hypertension, N(%)	257 (43.3)	183 (40.0)	74 (54.0) <sup>‡</sup>	263 (64.0) <sup>##</sup>	45 (48.9)	218 (68.3) <sup>††</sup>

Abbreviations: 2hPG, 2-h post-OGTT plasma glucose; BMI, body mass index; C-IMT, carotid intima media thickness; CRP, C reactive protein; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SFA, subcutaneous fat area; TC, total cholesterol; TG, triglyceride; VFA, visceral fat area; W, waist circumference. <sup>#</sup>*P* < 0.05 versus BMI < 25.0 kg m<sup>-2</sup>, <sup>##</sup>*P* < 0.01 versus BMI < 25.0 kg m<sup>-2</sup>, <sup>†</sup>*P* < 0.05 versus BMI < 25.0 kg m<sup>-2</sup>, VFA < 80 cm<sup>2</sup>, <sup>‡</sup>*P* < 0.01 versus BMI < 25.0 kg m<sup>-2</sup>, VFA < 80 cm<sup>2</sup>, <sup>††</sup>*P* < 0.05 versus BMI ≥ 25.0 kg m<sup>-2</sup>, VFA < 80 cm<sup>2</sup>, <sup>†††</sup>*P* < 0.01 versus BMI ≥ 25.0 kg m<sup>-2</sup>, VFA < 80 cm<sup>2</sup>. Data are means ± s.d. or median (interquartile range).

**Table 3.** Partial correlation with C-IMT in different BMI categories

Variable	Total		BMI < 25.0 kg m <sup>-2</sup>		BMI ≥ 25.0 kg m <sup>-2</sup>	
	r	P	r	P	r	P
Age	0.319	<0.001	0.360	<0.001	0.276	<0.001
W	0.230	<0.001	0.210	<0.001	0.206	<0.001
%Fat	-0.108	0.001	-0.132	0.001	-0.246	<0.001
SFA	-0.032	0.305	-0.070	0.091	-0.135	0.006
VFA	0.205	<0.001	0.154	0.001	0.194	<0.001
SBP	0.205	<0.001	0.262	<0.001	0.120	0.016
DBP	0.122	<0.001	0.170	<0.001	0.037	0.461
TC	0.117	<0.001	0.130	0.002	0.096	0.052
TG	0.049	0.124	0.034	0.407	0.032	0.526
LDL-c	0.195	<0.001	0.192	<0.001	0.176	<0.001
HDL-c	-0.121	<0.001	-0.071	0.086	-0.135	0.006
FPG	0.152	<0.001	0.206	<0.001	0.062	0.212
2hPG	0.152	<0.001	0.172	<0.001	0.107	0.030
HbA1c	0.168	<0.001	0.219	<0.001	0.074	0.136
HOMA-IR	0.096	0.002	0.103	0.012	0.015	0.763
CRP	0.102	0.001	0.053	0.206	0.103	0.039

Abbreviations: CRP, C reactive protein; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; 2hPG, 2-h post-OGTT plasma glucose; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SFA, subcutaneous fat area; TC, total cholesterol; TG, triglyceride; VFA, visceral fat area; W, waist circumference. Partial correlation analysis adjusted anti-hypertensive, anti-diabetic and lipid-lowering treatment.

correlation weakened after adjustment for other traditional cardiovascular risk factors and other obesity indices, W and VFA were still independent risk factors for increased C-IMT in men. These results might be explained by an association between adiposity and subclinical atherosclerosis mediated by CVD risk factors that are likely to be in a causal pathway from visceral fat accumulation to CVD.<sup>22,27</sup> As all the obesity measures of BMI, W, %fat, VFA and SFA were highly correlated with each other, the attenuation of associations by multivariate adjustment is understandable.<sup>28</sup> Our findings are consistent with several studies that also reported a positive correlation of C-IMT to visceral fat accumulation.<sup>29,30</sup>

Previous publications describe a possible role for visceral fat accumulation in atherosclerosis development. Ryuichi *et al.*<sup>31</sup> found a graded and independent association between visceral obesity evaluated by B-mode ultrasonography and C-IMT in subjects aged ≥ 50 years with a BMI ≥ 23.0 kg m<sup>-2</sup>. Kim *et al.*,<sup>32</sup> found that visceral fat amount was associated with carotid atherosclerosis in type 2 diabetic men with a normal W. However, we could not compare these findings directly with ours because of the indirect measurement of visceral fat and differences in study subjects. Our investigation suggested that subjects defined as not obese by BMI had increased C-IMT because some individuals were prone to visceral fat accumulation for a given BMI. Some people with higher BMI but a lower quantity of visceral fat might be categorized as high-risk obese subjects, even though they actually have a lower C-IMT and are at a low risk for metabolic complications.

**Table 4.** Multiple stepwise regression analysis showing variables independently associated with C-IMT (mm) in men and women

Independent variables	Men				Women				
	$\beta$	SEM	Standardized $\beta$	P	Independent variables	$\beta$	SEM	Standardized $\beta$	P
<b>Model 1</b>									
Age	0.003	0.001	0.325	<0.001	Age	0.002	0.001	0.312	<0.001
Smoking status	0.019	0.004	0.164	<0.001	HOMA-IR	0.001	0.001	0.102	0.017
W	0.001	0.001	0.163	<0.001	SBP	0.001	0.001	0.104	0.023
LDL-c	0.011	0.002	0.203	<0.001	Anti-hypertensive therapy	0.011	0.005	0.107	0.018
SBP	0.001	0.001	0.102	0.010					
2hPG	0.001	0.001	0.106	0.007					
<b>Model 2</b>									
Age	0.003	0.001	0.325	<0.001	Age	0.002	0.001	0.311	<0.001
Smoking status	0.019	0.004	0.164	<0.001	HOMA-IR	0.001	0.001	0.108	0.011
W	0.001	0.001	0.161	<0.001	SBP	0.001	0.001	0.104	0.022
LDL-c	0.011	0.002	0.207	<0.001	Anti-hypertensive therapy	0.011	0.005	0.104	0.020
SBP	0.001	0.001	0.102	0.010					
2hPG	0.001	0.001	0.108	0.006					
<b>Model 3</b>									
Age	0.003	0.001	0.324	<0.001	Age	0.002	0.001	0.312	<0.001
Smoking status	0.019	0.004	0.165	<0.001	HOMA-IR	0.001	0.001	0.102	0.017
VFA	0.001	0.001	0.107	0.007	SBP	0.001	0.001	0.104	0.023
LDL-c	0.011	0.002	0.205	<0.001	Anti-hypertensive therapy	0.011	0.005	0.107	0.018
SBP	0.001	0.001	0.107	0.009					
2hPG	0.001	0.001	0.116	0.003					

Abbreviations: 2hPG, 2-h post-OGTT plasma glucose; BMI, body mass index; CRP, C reactive protein; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SFA, subcutaneous fat area; VFA, visceral fat area; W, waist circumference. Variables included in the original models are obesity indices (Model 1: BMI, W, % fat, VFA and SFA; Model 2: BMI and W; Model 3: % fat, VFA and SFA) and basic CVD risk factors, including age, smoking status, SBP, DBP, HOMA-IR, 2hPG, LDL-c, HDL-c, CRP, anti-hypertensive therapy, anti-diabetic therapy and lipid-lowering therapy. For women we also adjusted the menopausal status.

Although a cause-effect relationship has not been established, possible mechanisms responsible for the relationship between visceral fat accumulation and subclinical atherosclerosis are as follows. Obesity is considered to be a chronic inflammation state, in which the excess accumulation of visceral adipose tissue has a central role.<sup>33</sup> In this study, we also observed that CRP, a plasma marker of chronic low-grade inflammation, was significantly increased in subjects with abdominal obesity and correlated with C-IMT. However, this association was abolished in multivariable regression analysis after adjustment for parameters related to adiposity, insulin resistance, glucose and lipid metabolism. A possible explanation is that traditional cardiovascular risk factors display stronger pro-atherosclerotic effects than CRP. It is also possible that the relationship between CRP and atherosclerosis is mediated by abdominal obesity. In addition, visceral fat accumulation may be related to insulin resistance of the liver.<sup>34</sup> East Asians are prone to have more visceral fat than people of European descent with the same BMI.<sup>35</sup> Our results further demonstrate that the Chinese men show a greater propensity to develop CVD at a relatively low BMI.

The limitations of this study included the study population of primarily middle-aged Chinese, limiting the generalizability of our findings to other ethnic and age groups. The sample size of women, especially postmenopausal women, might not have been large enough for us to detect the contribution of visceral obesity to carotid atherosclerosis. Large population-based studies are required to confirm this association. Furthermore, the cross-sectional design precluded any inference of a casual relation between VFA, BMI and C-IMT. Future cardiovascular events and mortality should be recorded in well-controlled, prospective studies.

In conclusion, we investigated the association between VFA and C-IMT stratified by BMI. VFA positively correlated with C-IMT in a

middle-aged Chinese population. VFA  $\geq 80 \text{ cm}^2$  was effective for identifying carotid atherosclerosis for both lean and generally obese men.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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#### AUTHOR CONTRIBUTIONS

Y Bao and W Jia conceived and designed the study. X Ma, Y Wang, M Zhou, W Zong and Y Hao recruited the samples. X Ma, Y Wang and M Zhou did the statistical analyses. J Zhu and D Li performed the carotid artery ultrasound scans. Y Xiao performed the MRI scans. X Ma and Y Wang wrote the first draft of the paper. X Ma, Y Wang, M Zhou, Y Bao and W Jia revised the paper and contributed to the discussion. M Zhou, L Zhang and W Zong provided the technical support. Y Wang and X Ma contributed equally to this work and are the guarantors.

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