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Anthropometric Obesity Indices were Stronger than CT-Based Indices in Associations with Carotid Intima-Media Thickness in Japanese Men

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Aim: Computed tomography (CT) can directly provide information on body compositions and distributions, compared to anthropometric indices. It has been shown that various obesity indices are associated with carotid intima-media thickness (IMT). However, whether CT-based obesity indices are stronger than anthropometric indices in association with atherosclerosis remains to be determined in a general population.

Methods: We cross-sectionally assessed carotid IMT using ultrasound in 944 community-dwelling Japanese men free of stroke and myocardial infarction. CT image at the L4–L5 level was obtained to compute areas of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). Anthropometric measures assessed included body mass index (BMI), waist circumference, and waist-to-hip ratio. Using multivariable linear regression, slopes of IMT per 20th to 80th percentile of each index were compared. We also compared the slope of index with simultaneous adjustment for BMI in the same model.

Results: Areas of VAT and SAT were positively associated with IMT, but not stronger than those of anthropometric indices in point estimates. Among all obesity indices, BMI was strongest in association with IMT after adjusting for age and lifestyle factors or further adjusting for metabolic factors. In simultaneous adjustment models, BMI, but not CT-based indices, remained significant and showed the strongest association.

Conclusions: In community-dwelling Japanese men, anthropometric obesity indices, BMI in particular, were more strongly associated with carotid atherosclerosis than CT-based obesity indices. The association of general obesity with carotid atherosclerosis was strong and adding CT-based obesity measure did not considerably influence in the association.

Key words: Atherosclerosis, Carotid intima-media thickness, Abdominal adipose tissue, Computed tomography, Anthropometric obesity indices

Introduction

Abdominal adipose tissue, visceral adipose tissue (VAT) in particular, is considered to play a key role in the pathogenesis of insulin resistance and chronic inflammation[1, 2], in addition to being an important

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likely determinant of atherosclerosis[3, 4]. Although anthropometric obesity indices such as body mass index (BMI) and waist circumference (WC) have been commonly used, these indices do not provide precise information on abdominal adipose tissue. In contrast, computed tomography (CT) can directly assess not only VAT but also subcutaneous adipose tissue (SAT). Several studies have shown that CT-based obesity indices such as area/volume of VAT are associated with clustering of atherosclerosis risk factors[5-7], and some studies have reported that CT-based obesity indices are also associated with the measure of atherosclerosis[8-12]. However, it remains to be determined whether CT-based obesity indices have a stronger relationship with atherosclerosis than anthropometric indices such as BMI. In addition, it is not clear if the association of CT-based obesity indices with atherosclerosis is independent of an index of general obesity such as BMI. These questions are important because a stronger and/or independent association of CT-based index suggests the significant role of abdominal adipose tissue in atherosclerogenesis beyond general obesity.

Carotid intima-media thickness (IMT) assessed using ultrasound is a robust quantitative marker of atherosclerosis[13, 14]. IMT can be measured non-invasively, and its usefulness as a marker of generalized atherosclerosis has been shown in a Japanese population[13]. Furthermore, it has been shown in a Japanese population that the mean carotid IMT was positively associated with the estimated 10-year absolute risk of coronary artery disease death[15]. The aim of this study was to examine the associations of carotid IMT with various obesity indices (both CT-based and anthropometric), and to compare strengths of the association for each index among community-dwelling Japanese men.

Methods

Study Design and Participants

This cross-sectional study used the baseline assessment of the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA), which is a prospective population-based cohort study constructed on a random sample from general Japanese residents. Details of the enrollment methods have been reported previously[16, 17]. In brief, from 2006 to 2008, we randomly selected and invited 2379 Japanese men aged between 40 and 79 years who were residents of Kusatsu City, Shiga, based on the Basic Residents' Register of the city. A total of 1094 men agreed to participate.

For this study, men who did not undergo carotid artery ultrasound examination ($n=33$), who did not undergo abdominal CT ($n=9$), who had missing information for any of body weight, height, WC, or hip circumference ($n=46$), and who had a history of myocardial infarction or stroke ($n=69$) were excluded. Therefore, 944 men were included for the final analyses (**Fig. 1**). This study was approved by the institutional review board of Shiga University of Medical Science and written informed consent was obtained from all participants.

Anthropometric Obesity Indices

Body weight and height were measured while the participant was wearing light clothing without shoes. BMI was calculated as weight (in kilograms) divided by the square of the height (in meters). WC (in centimeters) and hip circumference (in centimeters) were measured twice at the umbilical level and maximal protrusion of the hip in an upright standing position, respectively. All analyses used the mean of two measures. Waist-to-hip ratio (WHR) was calculated as WC divided by hip circumference. Waist-to-height ratio (WHtR) was calculated as WC divided by height (in centimeters)[17].

Abdominal Adipose Tissue

A single cross-sectional CT image at the level of the L4–L5 vertebral space was selected to estimate abdominal adipose tissue. We defined adipose tissue within the inside edge of the abdominal wall as VAT, and defined that outside the area of the abdominal wall not including muscular fascia as abdominal SAT. Adipose tissue on CT images was identified tissue showing CT attenuation between −190 and −30 Hounsfield units in the above-defined anatomical cross-sectional area[17]. Inner and outer areas of the abdominal wall were manually tracked, and respective cross-sectional areas were calculated using image analysis software (SliceOmatic; Tomovision, Montreal, Canada). Area of abdominal total adipose tissue (TAT) was calculated using the sum of areas of VAT and SAT. All CT images were analyzed at Shiga University Medical Science by a trained physician-researcher who was blinded to the characteristics of participants[17]. Two types of CT scanner were used during the examination period: a GE-Imatron C150 Electron Beam Tomography system (GE Medical Systems, South San Francisco, CA; slice thickness, 6 mm) for participants examined between May 2006 and August 2007, and a 16-detector-row CT system (Aquilion-16TM, Toshiba Medical Systems, Tochigi, Japan; slice thickness, 7 mm) for participants examined thereafter. We tested interaction by CT type by inserting a product term (CT type × obesity index) in linear regression models,

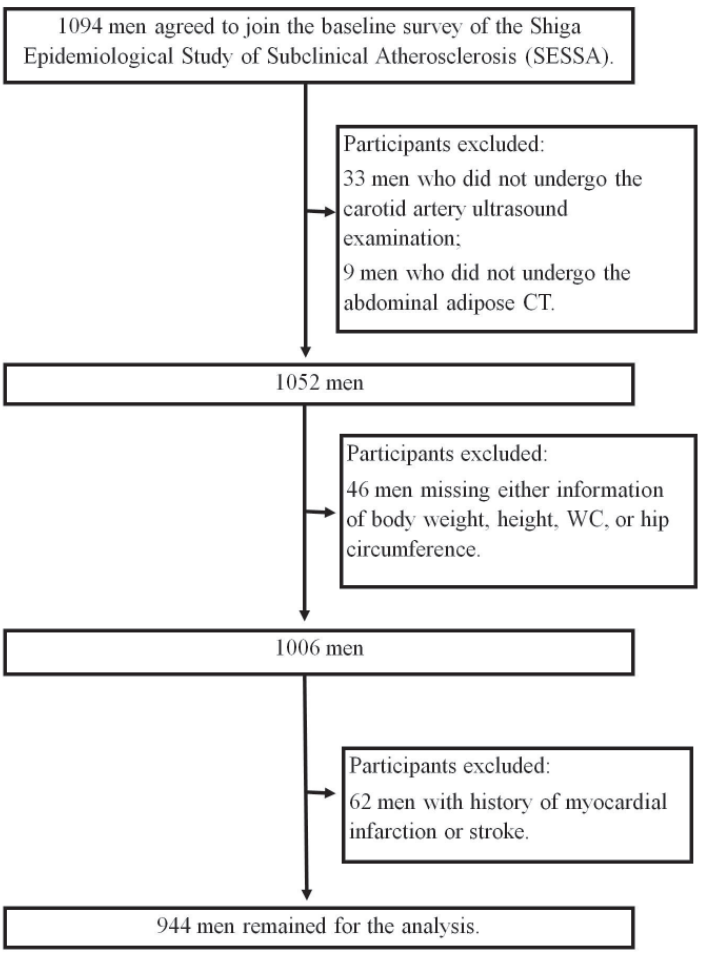

Fig. 1. Flow chart of the selection process of participants

and found no evidence of the interaction. Therefore, we have presented combined results with adjustment for CT type.

Blood Tests

Blood specimens were obtained early in the clinic visit after a 12-hour fast. Serum was separated by centrifugation (3000 revolutions/min, for 15 min) at 4℃ within 90 min of blood withdrawal. Glucose concentration was measured using a hexokinase glucose-6-phosphate dehydrogenase enzymatic assay from sodium fluoride-treated plasma, and glycated hemoglobin (HbA1c) was measured using a latex agglutination assay according to the standardized method of the Japanese Diabetes Society (JDS). We then converted JDS values to those of the National Glycohemoglobin Standardization Program (NGSP) using the following formula recommended by the JDS: HbA1c (NGSP) = 1.02 × HbA1c (JDS) + 0.25 (%)[18]. Diabetes was defined as fasting plasma glucose ≥ 126 mg/dL, HbA1c (NGSP) ≥ 6.5%, or the use of diabetic medication. Serum triglycerides (TG) and total cholesterol (TC) were measured using enzymatic assays. High-density lipoprotein cholesterol (HDL-C) was measured after heparin-calcium precipitation (Kyowa Medix, Tokyo, Japan)[19]. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula[20]: LDL-C (mg/dL) = TC (mg/dL) − HDL-C (mg/dL) − TG (mg/dL)/5. This formula is applicable only for participants with TG < 400 mg/dL[20]. Dyslipidemia was defined as LDL-C ≥ 140 mg/dL, HDL-C < 40 mg/dL, TG ≥ 150 mg/dL or the use of dyslipidemic medication in accordance with the diagnostic criteria for screening by the 2018 Japanese Atherosclerosis Society (JAS) Guidelines[21].

Other Risk Factors

Blood pressure was measured on the right arm

using an automated sphygmomanometer (BP-8800; Omron Health Care, Kyoto, Japan) with an appropriately sized cuff. Participants were asked to empty their bladders for urinalysis and sit quietly for at least 5 min before measuring the blood pressure. The average of two consecutive measures was used for analyses. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, or use of antihypertensive medication. Alcohol intake was categorized as current drinker, past drinker, or never. Amount of smoking was estimated as pack-years, defined as the product of the number of packs of cigarettes smoked per day with the number of years of smoking (one pack contains 20 cigarettes).

Carotid IMT

IMT of the common carotid artery, carotid bulb, and internal carotid artery on both right and left sides was measured using an ultrasound device equipped with a 7.5-MHz probe (Xario-660A; Toshiba Medical Systems, Japan), according to the protocol established by the Ultrasound Research Laboratory at the University of Pittsburgh[15, 22]. For the common carotid artery, both near and far walls were measured 1 cm proximal to the bulb. For the bulb and internal carotid artery segments, only far walls were measured. The IMT was traced using the automatic image reading program of the AMS (Chalmers University of Technology, Gotenburg, Sweden), and the average of the former 8 IMT values measured on both sides were eventually used as carotid IMT in this study. Sonographers received training for carotid scanning provided by the Ultrasound Research Laboratory at the University of Pittsburgh, and were blinded to the characteristics of participants at the time of the scan.

Statistical Analysis

Because several continuous variables did not follow a bell-shaped distribution and were strongly skewed, all continuous variables are presented as median and 20th and 80th percentile points. Categorical variables are presented as percentages.

We assessed the following 8 obesity indices: BMI, WC, WHR, WHtR, areas of VAT and SAT, VAT-to-SAT ratio (VSR), and VAT-to-TAT ratio (VTR). In single-index analyses, we inserted only one obesity index in a model and estimated crude and adjusted slopes of carotid IMT per 20th to 80th percentile of the index by using linear regression. In BMI-adjustment analyses, we simultaneously inserted BMI and other one obesity index in one model to test if the association of one of the other 7 indices was independent of BMI. Interpretation of a beta coefficient (i.e., a slope of "delta") of carotid IMT as per 20–80th percentile is that carotid IMT at the 80 percentile of an obesity index is thicker by "delta" than carotid IMT at the 20 percentile of the index. We chose such standardization because of strongly skewed distributions in some obesity indices. Similar approach to our method in standardization has been adopted in previous studies[23-26]. In addition, T-values by Student's *t* test for all slopes of carotid IMT in the regression models were shown (the null hypothesis: slope of delta = zero). BMI-adjustment analyses were conducted because BMI is the most frequently used obesity index for its simplicity and good precision[27]. Because some obesity indices were highly correlated with BMI, we computed variance inflation factor to consider potential problems from multicollinearity in the analyses. For the analysis of single adjustment and of BMI-adjustment, we constructed the following 4 models: unadjusted model; Model 1, adjusted for age and CT type; Model 2, Model 1 with further adjustments for lifestyle risk factors of alcohol intake (current vs. non-current) and smoking (pack-years); and Model 3, Model 2 with further adjustments for metabolic risk factors of hypertension (yes vs. no), diabetes (yes vs. no), and dyslipidemia (yes vs. no).

Japanese men tend to start losing weight, as reflected by a decline in BMI, at around 60–69 years old[28]. We therefore repeated the same analyses after age-stratification into 2 subgroups (< 65 vs. ≥ 65 years) to assess any differences in slope between the two age-groups. The interaction by age group was tested by adding a product term (age group × obesity index) in a model. All statistical analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC). A *P*-value of < 0.05 was considered statistically significant.

Results

Characteristics of the 944 male participants are presented in **Table 1**. Medians of age, BMI, WC, WHR, and WHtR were 64.4 years, 23.3 kg/m^2, 85.0 cm, 0.92, and 0.51, respectively. Medians of VAT area, SAT area, VSR, and VTR were 114 cm^2, 115 cm^2, 0.95, and 0.49, respectively. Prevalence of hypertension, diabetes, and dyslipidemia was 54.0%, 18.1%, and 55.5%, respectively. Median carotid IMT was 816 μm. All obesity indices except VSR and VTR correlated well with each other after adjusting for age (**Supplemental Table 1**).

In the single-index analyses (**Table 2**), obesity indices other than VSR and VTR showed significant positive associations with carotid IMT after adjusting for age, CT type, alcohol intake, and smoking (Models 1, 2). Further adjustment for hypertension, diabetes,

Table 1. Characteristics of participants (944 men, aged 40 to 79 years old, free of stroke and myocardial infarction in 2006-2008, Shiga, Japan)

Age (years)	64.4 (55.7, 73.4)
Weight (kg)	64.2 (57.1, 72.7)
Height (cm)	166 (161, 171)
BMI (kg/m^2)	23.3 (21.0, 25.9)
WC (cm)	85.0 (78.5, 91.6)
Hip circumference (cm)	92.0 (87.9, 96.7)
WHR	0.92 (0.88, 0.96)
WHtR	0.51 (0.47, 0.55)
VAT area (cm^2)	114 (71, 159)
SAT area (cm^2)	115 (80, 157)
TAT area (cm^2)	229 (151, 316)
VSR	0.95 (0.71, 1.30)
VTR	0.49 (0.42, 0.57)
Smoking (pack-years)	24.2 (1.0, 47.0)
Alcohol Intake (%)	
Current	77.1
Past	5.3
Never	17.6
SBP (mmHg)	135 (121, 152)
DBP (mmHg)	80 (71, 89)
Fasting glucose (mg/dL)	97 (89, 110)
HbA1c (NGSP) (%)	5.8 (5.5, 6.4)
TC (mg/dL)	207 (181, 235)
HDL-C (mg/dL)	57 (45, 71)
LDL-C (mg/dL)	122 (100, 150)
TG (mg/dL)	104 (72, 162)
Hypertension (%)	54.0
Diabetes (%)	18.1
Dyslipidemia (%)	55.5
CT type (%)	
Electron beam tomography	67.3
Multi-detector-row	32.7
Carotid IMT (μm)	816 (692, 985)

Values are presented as median (20th percentile, 80th percentile), or %. Abbreviations: BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; VAT: visceral adipose tissue; SAT: abdominal subcutaneous adipose tissue; TAT: abdominal total adipose tissue, defined as (VAT area + SAT area); VSR: VAT-to-SAT ratio; VTR: VAT-to-TAT ratio; IMT: intima-media thickness; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; HDL-C: high density lipid cholesterol; LDL-C: low density lipid cholesterol; TG: triglycerides.

and dyslipidemia (Model 3) attenuated the associations, but the slopes remained significant for all indices except VSR and VTR. Throughout the multivariable-adjusted models, associations of CT-based obesity indices were no stronger than those of anthropometric indices, and BMI showed the strongest association with carotid IMT. For example, adjusted slopes (in μm) per 20th–80th percentiles of BMI, WC, WHR, WHtR, VAT area, and SAT area were 38.3, 33.6, 29.7, 35.5, 29.0, and 22.8, respectively, in Model 3. In BMI-adjustment analyses (**Table 3**), none of the other 7 indices remained statistically significant in Models 2 and 3. In contrast, the association of BMI remained statistically significant even with simultaneous adjustment for any CT-based index in Models 2 and 3. All variance inflation factors for BMI and other indices were <5.2, less than a concerning level of 10[29], and none of the corresponding standard errors

Table 2. Crude and adjusted slope of carotid IMT per 20th to 80th percentile of a single obesity index (944 men, aged 40 to 79 years old, in 2006-2008, Shiga, Japan)

	Unadjusted				Model1			
	IMT (μm)	95% CI	T-value	*P*-value	IMT (μm)	95% CI	T-value	*P*-value
BMI	31.2	11.5, 50.8	3.1	0.002	49.8	32.7, 66.9	5.7	<0.001
WC	39.2	19.5, 59.0	3.9	<0.001	46.7	29.5, 63.8	5.3	<0.001
WHR	66.3	47.8, 84.8	7.0	<0.001	45.0	28.4, 61.5	5.3	<0.001
WHtR	70.8	51.0, 90.7	7.0	<0.001	49.1	31.3, 66.8	5.4	<0.001
VAT area	41.7	21.8, 61.7	4.1	<0.001	44.8	27.4, 62.2	5.0	<0.001
SAT area	15.7	-2.0, 33.4	1.7	0.082	32.5	16.8, 48.1	4.1	<0.001
VSR	26.7	7.2, 46.2	2.7	0.007	11.6	-5.5, 28.8	1.3	0.183
VTR	27.7	6.7, 48.9	2.6	0.010	11.9	-6.6, 30.4	1.3	0.208

	Model2				Model3			
	IMT (μm)	95% CI	T-value	*P*-value	IMT (μm)	95% CI	T-value	*P*-value
BMI	49.9	33.0, 66.8	5.8	<0.001	38.3	20.5, 56.2	4.2	<0.001
WC	46.2	29.1, 63.3	5.3	<0.001	33.6	15.6, 51.7	3.7	<0.001
WHR	42.5	25.9, 59.1	5.0	<0.001	29.7	12.1, 47.3	3.3	0.001
WHtR	48.6	31.0, 66.3	5.4	<0.001	35.5	16.7, 54.2	3.7	<0.001
VAT area	43.4	26.0, 60.8	4.9	<0.001	29.0	11.0, 48.1	3.1	0.002
SAT area	33.7	18.2, 49.2	4.3	<0.001	22.8	6.7, 38.9	2.8	0.006
VSR	8.6	-8.5, 25.7	1.0	0.326	2.7	-14.3, 19.7	0.3	0.756
VTR	8.3	-10.2, 26.9	0.9	0.377	2.3	-16.1, 20.7	0.3	0.804

Model1: adjusted for age and CT types (electron beam tomography vs multi-detector-row); Model2: further adjusted for alcohol intake, smoking; Model3: further adjusted for hypertension, diabetes, and dyslipidemia. T-value was the value by Student's *t* test for each slope of carotid IMT per 20th to 80th percentiles of obesity indices. Abbreviations: IMT: intima-media thickness; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; VAT: visceral adipose tissue; SAT: abdominal subcutaneous adipose tissue; VSR: VAT-to-SAT ratio; VTR: VAT-to-TAT ratio; TAT: abdominal total adipose tissue, defined as (VAT area + SAT area).

took extremely large values relative to the ones in single adjustment models, all of which suggest that multicollinearity is unlikely to be a concern in obtaining our estimates[30].

Age-stratified analyses showed that obesity indices in the <65-year-old subgroup were overall stronger in point estimates than those in the ≥ 65-year-old subgroup except for VSR and VTR (**Tables 4** and **5**). However, no statistical evidence of interaction by age group was observed in all the models for the association between carotid IMT and obesity indices.

Discussion

In this community-based cross-sectional study of Japanese men, areas of VAT and SAT were positively associated with carotid IMT independent of potential confounders, but their strengths of associations tended to be smaller than those of anthropometric indices. Among the obesity indices we studied, BMI was most strongly associated with carotid IMT.

VAT has been considered to play a key role in clustering of cardiovascular risk factors through the mechanisms of inflammation and insulin resistance, and has been proposed as an important determinant of obesity-related metabolic abnormalities[3, 4, 31, 32]. Studies have shown strong associations of CT-based obesity indices with insulin resistance and the metabolic syndrome[5-7]. However, it remained uncertain whether CT-based obesity indices were associated more strongly with atherosclerosis than anthropometric indices. Our results showed that their associations were not stronger, suggesting that CT-based abdominal obesity indices had a more limited role in atherosclerogenesis than previously thought[10], or at least, CT-based indices are not stronger markers of atherosclerosis relative to BMI.

Studies of asymptomatic individuals comparing the strengths of associations of CT-based obesity indices with carotid IMT to anthropometric indices are limited. Among the studies conducted in Japan, Takami and colleagues studied 849 Japanese men (mean age, 50.3 years; mean BMI, 23.5 kg/m^2) and found that correlation coefficients between CT-based obesity indices and carotid IMT were no larger than those of anthropometric indices including BMI[10]. A

Table 3. Adjusted slope of carotid IMT per 20th to 80th percentiles of BMI and another obesity index in one model (944 men, 40-79 years old, examined in 2006-2008, Shiga, Japan)

	Unadjusted				Model1 + BMI			
	IMT (μm)	95% CI	T-value	*P*-value	IMT (μm)	95% CI	T-value	*P*-value
WC	50.8	9.7, 91.9	2.4	0.016	12.8	-22.9, 48.5	0.7	0.483
BMI	-13.1	-53.9, 27.8	-0.6	0.53	38.6	2.9, 74.3	2.1	0.034
WHR	76.2	52.9, 99.4	6.4	<0.001	24.2	2.9, 45.5	2.2	0.026
BMI	-16.9	-41.2, 7.3	-1.4	0.170	33.9	11.9, 56.0	3.0	0.003
WHtR	164.2	126.1, 202.4	8.5	<0.001	15.2	-23.8, 54.1	0.8	0.445
BMI	-105.6	-142.6, -68.6	-5.6	<0.001	36.8	-0.8, 74.3	1.9	0.055
VAT area	39.0	10.5, 67.6	2.7	0.007	17.6	-7.3, 42.5	1.4	0.166
BMI	3.7	-24.3, 31.8	0.3	0.795	37.4	12.9, 61.9	3.0	0.003
SAT area	-22.3	-53.1, 8.6	-1.4	0.157	-14.0	-41.0, 13.1	-1.0	0.312
BMI	51.6	17.1, 86.0	2.9	0.003	62.4	32.5, 92.3	4.1	<0.001
VSR	29.5	10.0, 48.9	3.0	0.003	15.1	-1.8, 32.0	1.8	0.080
BMI	33.6	14.0, 53.3	3.4	<0.001	50.8	33.7, 67.9	5.8	<0.001
VTR	30.1	9.1, 51.2	2.8	0.005	14.8	-3.5, 33.0	1.6	0.113
BMI	33.0	13.4, 52.7	3.3	0.001	50.5	33.4, 67.6	5.8	<0.001

	Model2 + BMI				Model3 + BMI			
	IMT (μm)	95% CI	T-value	*P*-value	IMT (μm)	95% CI	T-value	*P*-value
WC	8.7	-27.2, 44.7	0.5	0.633	0.6	-35.3, 36.6	0.0	0.973
BMI	42.2	6.6, 77.9	2.3	0.020	37.8	2.23, 73.4	2.1	0.037
WHR	19.2	-2.2, 40.6	1.8	0.079	11.5	-10.3, 33.2	1.0	0.301
BMI	37.4	15.4, 59.3	3.3	<0.001	31.5	9.4, 53.6	2.8	0.005
WHtR	11.5	-27.4, 50.4	0.6	0.562	0.8	-38.3, 39.9	0.0	0.968
BMI	40.0	2.6, 77.4	2.1	0.036	37.7	0.4, 74.9	2.0	0.047
VAT area	13.6	-11.4, 38.6	1.1	0.287	4.5	-20.8, 29.8	0.4	0.727
BMI	40.3	15.9, 64.7	3.2	0.001	35.4	10.9, 59.8	2.8	0.005
SAT area	-10.9	-37.9, 16.0	-0.8	0.426	-13.5	-40.3, 13.4	-1.0	0.325
BMI	59.8	30.1, 89.4	4.0	<0.001	50.4	20.5, 80.2	3.3	0.001
VSR	12.1	-4.8, 29.0	1.4	0.159	7.0	-9.9, 24.0	0.8	0.416
BMI	50.7	33.8, 67.7	5.9	<0.001	39.2	21.2, 57.2	4.3	<0.001
VTR	11.3	-6.9, 29.5	1.2	0.224	6.3	-12.0, 24.6	0.7	0.501
BMI	50.5	33.5, 67.4	5.8	<0.001	39.0	21.0, 56.9	4.3	<0.001

Model1: adjusted for age and CT types (electron beam tomography vs multi-detector-row); Model2: further adjusted for alcohol intake, smoking; Model3: further adjusted for hypertension, diabetes, and dyslipidemia. T-value was the value by Student's *t* test for each slope of carotid IMT per 20th to 80th percentiles of obesity indices. Abbreviations: IMT: intima-media thickness; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; VAT: visceral adipose tissue; SAT: abdominal subcutaneous adipose tissue; VSR: VAT-to-SAT ratio; VTR: VAT-to-TAT ratio; TAT: abdominal total adipose tissue, defined as (VAT area + SAT area).

health check-up-based study of 158 Japanese men showed that the association of carotid IMT was stronger in the highest BMI category (≥ 27.6 kg/m^2) than the highest category of CT-based indices[33]. Those studies conducted in Japan seem consistent with our results. However, considering their use of measure of association being either correlation coefficients[10] or regression coefficients of dichotomized category[33], rather than standardized multivariable-adjusted regression coefficients per continuous exposure variables as

Table 4. Crude and Adjusted Slope of Carotid IMT per 20th to 80th Percentile of Obesity Indices (485 men, <65 years old, examined in 2006-2008, Shiga, Japan)

	Unadjusted		Model 1		Model 2		Model 3	
	IMT (μm)	95% CI	IMT (μm)	95% CI	IMT (μm)	95% CI	IMT (μm)	95% CI
BMI	49.7**	27.7, 71.7	63.6**	43.8, 83.3	63.0**	43.3, 82.8	50.9**	30.1, 71.6
WC	50.8**	27.6, 73.9	61.0**	40.3, 81.7	60.6**	39.7, 81.4	47.8**	26.0, 69.6
WHR	56.8**	34.0, 79.9	49.5**	28.8, 70.3	46.8**	25.8, 67.8	31.8*	9.6, 54.0
WHtR	73.6**	49.4, 97.9	66.9**	44.9, 88.9	65.7**	43.6, 87.8	51.4**	28.0, 74.7
VAT area	38.3*	14.5, 62.1	48.7**	27.3, 70.1	46.8**	25.3, 68.3	30.5*	7.5, 53.5
SAT area	18.9	-1.2, 39.0	48.2**	29.7, 66.7	48.4**	29.9, 66.9	37.2**	18.2, 56.2
VSR	19.0	-3.2, 41.2	-3.1	-23.8, 17.6	-6.5	-27.3, 14.4	-14.3	-34.9, 6.2
VTR	20.5	-3.7, 44.6	-2.6	-25.0, 19.9	-6.2	-28.8, 16.3	-14.3	-36.5, 8.0

*: p-value <0.05; **: p-value <0.001; Model1: adjusted for age and CT types (electron beam tomography vs multi-detector-row); Model2: further adjusted for alcohol intake, smoking; Model3: further adjusted for hypertension, diabetes, and dyslipidemia. Abbreviations: IMT: intima-media thickness; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; VAT: visceral adipose tissue; SAT: abdominal subcutaneous adipose tissue; VSR: VAT-to-SAT ratio; VTR: VAT-to-TAT ratio; TAT: abdominal total adipose tissue, defined as (VAT area + SAT area).

Table 5. Crude and Adjusted Slope of Carotid IMT per 20th to 80th Percentile of Obesity Indices (459 men, ≥ 65 years old, examined in 2006-2008, Shiga, Japan)

	Unadjusted		Model 1		Model 2		Model 3	
	IMT (μm)	95% CI	IMT (μm)	95% CI	IMT (μm)	95% CI	IMT (μm)	95% CI
BMI	33.6*	4.2, 63.0	33.9*	5.4, 62.4	35.6*	7.5, 63.7	24.6	-5.1, 54.3
WC	35.2*	7.1, 63.3	32.9*	5.5, 60.2	32.9*	5.6, 60.1	20.2	-8.8, 49.3
WHR	48.0**	22.0, 74.1	40.8*	15.1, 66.4	38.2*	12.4, 64.1	27.5*	0.1, 54.9
WHtR	41.4*	13.3, 69.5	33.3*	5.7, 60.9	33.8*	6.4, 61.3	21.9	-7.4, 51.1
VAT area	43.6*	15.6, 71.6	42.1*	14.5, 69.6	40.0*	13.4, 68.6	30.2*	0.9, 59.5
SAT area	20.2	-5.8, 46.3	14.5	-11.1, 40.0	16.7	-8.6, 42.1	4.2	-22.5, 30.9
VSR	28.2	-0.7, 57.2	31.4*	3.3, 59.6	30.0*	2.1, 57.9	27.0	-0.7, 54.7
VTR	26.7	-4.4, 57.9	31.6*	1.3, 61.9	29.4	-0.6, 59.4	26.6	-3.2, 56.4

*: p-value <0.05; **: p-value <0.001; Model1: adjusted for age and CT types (electron beam tomography vs multi-detector-row); Model2: further adjusted for alcohol intake, smoking; Model3: further adjusted for hypertension, diabetes, and dyslipidemia. Abbreviations: IMT: intima-media thickness; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; VAT: visceral adipose tissue; SAT: abdominal subcutaneous adipose tissue; VSR: VAT-to-SAT ratio; VTR: VAT-to-TAT ratio; TAT: abdominal total adipose tissue, defined as (VAT area + SAT area).

in our analyses, comparison of strength of association was difficult to judge from those studies. Some community-based studies outside Japan have compared the strength of association using standardized measures in assessing relationships between atherosclerosis and obesity indices, but the results were inconsistent. For example, in the Rancho Bernardo Study of Caucasian adults aged 55–88 years in the United States, none of the obesity indices (including CT-based indices) were significantly associated with coronary atherosclerosis (as measured by coronary artery calcium) with or without adjustment for risk factors[34]. On the contrary, a study of asymptomatic Korean adults who were examined at check-up showed a slightly stronger association in BMI than visceral fat area with coronary atherosclerosis (as measured by coronary artery calcium). However, those results are difficult to interpret because they were presented only as gender-combined estimates with no comments on the absence or presence of interaction by gender[35]. Our study was the first community-based study to clearly show a stronger association of BMI with carotid atherosclerosis as compared to CT-based obesity indices, including VAT area. Furthermore, the association between BMI and carotid IMT remained independent of a CT-based obesity index, whereas the opposite was not the case (**Table 3**). This finding implies that the association of general obesity with carotid atherosclerosis is strong and adding CT-based obesity measure does not significantly influence the association. We acknowledge that

the importance of anthropometric measures of abdominal obesity such as WC independent of BMI should not be ignored, as previously shown in multiple large-scale cohort studies[36-38]. It is noteworthy, however, that considerably little evidence supports the usefulness of CT-based abdominal obesity indices such as VAT area beyond anthropometric measures in relating to atherosclerosis/cardiovascular disease risk. For example, some Japanese studies showed the association of VAT with (clustering of) metabolic syndrome[39, 40], but those studies did not compare the strength of the association between VAT and anthropometric measures as we did. Furthermore, their outcomes were not a direct measure of atherosclerosis.

In BMI-adjustment analyses (**Table 3**), the negative slopes of BMI were observed in the unadjusted model, likely because of the simultaneous adjustment for other obesity index that was well correlated with BMI. However, it is noteworthy that all the negative slopes of BMI were observed only in combination with an anthropometric index, and only in the unadjusted model. The weaker association of BMI (even inverse in some cases) with carotid IMT in unadjusted model was in part because of confounding by age because adjustment for age (and CT type) in Model 1 resulted in a positive and stronger association of BMI in both single-index adjustment analyses (**Table 2**) and BMI-adjustment analyses (**Table 3**).

Although not significant, slopes of obesity indices tended to be smaller in the older group (≥ 65 years) than in the younger group (**Tables 4** and **5**). Similar findings have been reported from other populations[28, 41]. This may be because as men age, the body tends to become leaner, but the risk of atherosclerosis increases. However, additional studies are needed to further explore this possibility.

Our findings should be interpreted with caution. First, as a cross-sectional study, the temporal relationship between obesity indices and carotid IMT cannot be shown. Second, only male residents recruited from a single area of Japan were studied. Our results thus may not be applicable to women or other male populations with characteristics differing from those of our sample. Third, we only assessed one marker of atherosclerosis (carotid IMT) in association with obesity indices. The relationship with other markers may differ from the current study. Fourth, our measure of VAT was area, not volume, based on a single cross-sectional CT image. However, the technique for the ascertainment is widely used, and its values were highly correlated with volume[42, 43]. Therefore, it is less likely that our conclusion is sensitive to difference in the measure of adipose tissue (i.e., area vs. volume). One strength of our study was that we randomly selected a community-based sample with a broad age range, which increases the generalizability of our results to general Japanese men. Use of standardized protocols in assessing exposures (obesity indices) and outcomes (carotid IMT) is another strength of our study.

Conclusions

In community-dwelling Japanese men, anthropometric obesity indices, BMI in particular, were more strongly associated with carotid atherosclerosis than CT-based obesity indices. The association of general obesity with carotid atherosclerosis was strong and adding CT-based obesity measure did not considerably influence the association.

Acknowledgments

A complete listing of Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA) investigators is detailed in **Supplemental List 1**, and may be found at https://hs-web.shiga-med.ac.jp/sessa/research/. We thank SESSA investigators, staff, and participants for their important contribution to this work.

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Conflicts of Interest

All authors have no conflict of interest to disclose.

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Supplemental List 1

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Supplemental Table 1. Age-adjusted Spearman's Correlation Coefficients Among Obesity Indices (944 men, aged 40 to 79 years old, examined in 2006-2008, Shiga, Japan)

	BMI	WC	WHR	WHtR	VAT area	SAT area	VSR
WC	0.867	-	-	-	-	-	-
WHR	0.645	0.825	-	-	-	-	-
WHtR	0.882	0.930	0.844	-	-	-	-
VAT area	0.710	0.794	0.700	0.766	-	-	-
SAT area	0.799	0.833	0.658	0.811	0.683	-	-
VSR	-0.049*	0.017*	0.104	0.010*	0.427	-0.291	-
VTR	-0.049*	0.017*	0.104	0.010*	0.427	-0.291	1.000

*: *p*-value >0.05, otherwise all *P*-values for coefficient were ≤ 0.001. Abbreviations: BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; VAT: visceral adipose tissue; SAT: abdominal subcutaneous adipose tissue; VSR: VAT-to-SAT ratio; VTR: VAT-to-TAT ratio; TAT: abdominal total adipose tissue, defined as (VAT area + SAT area).