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Associations between the Combined Fat Mass Index and Fat-Free Mass Index with Carotid Intima-Media Thickness in a Japanese Population: The Tohoku Medical Megabank Community-Based Cohort Study

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Aim: Although many epidemiological studies have shown that obesity assessed by body mass index is associated with carotid intima-media thickness (cIMT), few studies have evaluated fat-free mass, which is a component of body composition. We investigated the associations between the combined fat mass index (FMI) and fat-free mass index (FFMI) with cIMT.

Methods: We conducted a cross-sectional study of 3,873 men and 9,112 women aged 20 years or older who lived in Miyagi prefecture, Japan. The FMI and FFMI were calculated as fat mass and fat-free mass divided by height squared, respectively. The indices were classified into sex-specific quartiles and were combined into 16 groups. The maximum common carotid artery was measured using high-resolution B-mode ultrasound. An analysis of covariance was used to assess associations between the combined FMI and FFMI with cIMT adjusted for age and smoking status. The linear trend test was conducted by stratifying the FMI and FFMI, scoring the categories from 1 (lowest) to 4 (highest), and entering the number as a continuous term in the regression model.

Results: In multivariable models, a higher FMI was not related to higher cIMT in men and women in most FFMI subgroups. Conversely, a higher FFMI was related to higher cIMT in all FMI subgroups ($p<0.001$ for linear trend).

Conclusions: FMI was not associated with cIMT in most FFMI subgroups. Conversely, FFMI was positively associated with cIMT independently of FMI.

Key words: Atherosclerosis, Body composition, Carotid intima-media thickness, Epidemiology

Introduction

Carotid intima-media thickness (cIMT) is considered a marker for atherosclerosis[1]. Many epidemiological studies have reported that an increase in cIMT is related to well-established cardiovascular disease (CVD) risk factors (i.e., age, smoking, systolic blood pressure (SBP), blood glucose, and total serum cholesterol)[1-4] and the incidence of myocardial infarction and stroke[5-9].

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Obesity assessed by body mass index (BMI) is a well-known major risk factor for CVD[10, 11] and is associated with an increase in cIMT[12-14]. However, a recent study showed that high blood pressure and serum glucose were related to the risk of incident CVD regardless of obesity assessed by BMI[15]. Furthermore, previous epidemiological studies on the Japanese population have shown that over 60% of diabetic participants were not obese[16] and the prevalence of non-obese hypertension participants was higher than that of obese hypertension participants[17]. Although BMI is often used as a proxy measure for adiposity, the major shortcoming of BMI measurement is that it cannot consider body composition (i.e., fat and fat-free mass)[18]. Therefore, BMI may not be a good indicator for screening high-risk individuals with CVD. It is well-known that fat mass (FM) worsens plasma lipids, blood pressure, and glucose/insulin resistance[11]. Metabolically active fat-free mass (FFM) has been shown to be positively associated with stroke volume and cardiac output[19, 20]. These findings suggest that both FM and FFM might affect the increase in cIMT.

To clarify the association between body composition and cIMT, two different body compositions should be considered. Many previous studies have mutually adjusted FM and FFM to consider body composition[21-25]. However, there is a correlation between FM and FFM because higher FFM is required to carry excess body fat. Therefore, it may be inappropriate to adopt FM and FFM simultaneously in the same statistical model.

Fat mass index (FMI) and fat-free mass index (FFMI) are indicators of body composition[26]. The FMI and FFMI are calculated as the FM and FFM in kilograms divided by the height in meters squared, respectively[18, 26-28]. Both indicators are useful for comparing individuals with different height measurements[18, 26-28]. In addition, combining FMI and FFMI not only avoids multicollinearity but also investigates the association between the FMI and cIMT in each FFMI subgroup and the association between FFMI and cIMT in each FMI subgroup. However, to the best of our knowledge, no study has examined the association between combined FMI and FFMI with cIMT.

Aim

We examined the association between combined FMI and FFMI with cIMT in a Japanese population.

Materials

Study Design and Population

We conducted a cross-sectional study using data from the Tohoku Medical Megabank Community-Based Cohort Study (TMM CommCohort Study). The design of the TMM CommCohort Study has been described in detail in a previous study[29]. Briefly, the source population for the survey comprised men and women aged ≥ 20 years living in Miyagi prefecture, northeastern Japan. All participants were recruited between May 2013 and March 2016 using the following three approaches. The type 1 survey (40,433 participants) was performed at a specific municipal health check-up site. The type 1 additional survey (664 participants) was conducted on different dates from specific municipal health check-ups. The type 2 survey (13,855 participants) was conducted in an assessment center. All surveys collected basic information from blood and urine, a questionnaire, and municipal health check-ups. In the type 2 survey, several physiological measurements (carotid echography, body composition, calcaneal ultrasound bone mineral density, etc.)[29]. Informed consent was obtained from a total of 54,952 participants. This study was approved by the Institutional Review Board of the Tohoku Medical Megabank Organization (approval number: 2021-4-028, approval date: May 31, 2021).

To be included in the analysis, participants were required to undergo several physiological measurements. Thus, 13,855 participants who underwent several physiological measurements in the type 2 survey were included. From the 13,855 participants, we excluded 870 participants for the following reasons: (1) those who withdrew from the study by July 13, 2021, failed to return the self-reported questionnaire or did not undergo physiological measurements (n=699); (2) data on body fat percentage (BF%), height or weight, and cIMT were missing (n=125); and (3) data on SBP, diastolic blood pressure (DBP), glucose, glycated hemoglobin A1c (HbA1c), total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) were missing (n=46). Therefore, 12,985 participants were analyzed for this study.

Anthropometry

Height was measured to the nearest 0.1 cm using a stadiometer (AD-6400; A&D Co, Ltd, Tokyo, Japan). Weight and BF% were measured using a body composition analyzer (InBody720; Biospace Co, Ltd, Seoul, Korea). Weight was measured in increments of 0.1 kg, and 1.0 kg was subtracted to account for the weight of the participant's clothing. BMI was calculated as weight (kg) divided by height squared

(m^2). FM was calculated by multiplying the weight (kg) by BF%. FMI was calculated as FM (kg) divided by the height squared (m^2). To calculate the FFMI, the FFM% was calculated by subtracting the BF% from 100%. The FFM was then calculated by multiplying the weight by the FFM%. Subsequently, FFMI was calculated as FFM (kg) divided by height squared (m^2)[18, 26-28, 30].

Carotid Intima-Media Thickness

Ultrasound imaging equipment (GM-72P00A; Panasonic Healthcare, Co, Ltd, Japan) was used to measure right and left cIMT at the common carotid artery. The UK Biobank study has shown an excellent reproducibility and validity of this automated device, and it has also been used in a previous study of the Japanese population[31, 32]. The left and right cIMT were measured at a plaque-free site 10 mm proximal to the carotid bifurcation. The Cardiovascular Health Study used maximum cIMT as a parameter since it is more closely associated with cardiovascular risk factors than the mean cIMT[5]. Furthermore, the Shiga Epidemiological Study of Subclinical Atherosclerosis showed that the mean cIMT of maximum values had stronger associations with coronary artery calcification, which can predict CVD events than internal carotid artery and bifurcation[33]. Thus, we measured the left and right maximum common carotid arteries. The analysis used the average of the maximum IMT values of the left and right IMT.

Potential Confounders

We obtained information on the participants' demographic characteristics, smoking status, and history of CVD using a self-reported questionnaire. Age was determined at the time of visiting the community support center. Smoking status was classified into the following three categories: never smoker, ex-smoker, and current smoker. Never smokers were defined as participants who had smoked $<$100 cigarettes during their lifetime. Ex-smokers were defined as participants who had smoked ≥ 100 cigarettes during their lifetime and indicated on the questionnaire that they no longer smoked. Current smokers were defined as participants who had smoked ≥ 100 cigarettes during their lifetime and indicated on the questionnaire that they currently smoke. FM has been associated with worsening blood pressure, glucose, and lipids[12]. Obesity, the state of excessive fat accumulation, can cause hypertension, type 2 diabetes, and hyperlipidemia[34]. Thus, we considered blood pressure, blood glucose, and lipids to be intermediate factors in the association between combined FMI and FFMI with cIMT. Hence, we did not adjust for blood pressure, blood glucose, and lipid levels.

Measurement of other Variables

After resting in a sitting position for ≥ 2 min, blood pressure was measured twice in the upper right arm using a digital automatic blood pressure monitor (HEM-9000AI; Omron Healthcare Co, Ltd, Kyoto, Japan). The mean values of the two recorded measurements were used. Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, and/or self-reported treatment for hypertension. Before the survey, we did not restrict diet or drinking. Thus, we collected non-fasting blood samples. Non-fasting glucose levels were measured using the hexokinase method. HbA1c levels were measured using the latex agglutination turbidimetry method. Diabetes was defined as non-fasting glucose ≥ 200 mg/dL, HbA1c ≥ 6.5%, and/or self-reported treatment for diabetes. TC was measured using the Ultra-Violet-End method using cholesterol dehydrogenase. TG was measured using an enzymatic method. HDL-C levels were measured using the direct method. We did not obtain low-density lipoprotein cholesterol (LDL-C) levels. Although the Friedewald formula can be used to calculate LDL-C, this formula only holds for fasting blood samples[35]. Since we obtained a non-fasting blood sample, we did not calculate the LDL-C. Dyslipidemia was defined as TG ≥ 150 mg/dL or HDL-C $<$40 mg/dL and/or self-reported treatment for dyslipidemia. Information regarding hypertension, diabetes, and dyslipidemia was obtained using a self-reported questionnaire. Furthermore, participants answered whether they have a history of each disease (stroke and myocardial infarction).

Statistical Analyses

Data are presented as the mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables and as the number (%) for categorical variables. Since the distributions of the FMI and FFMI differed between men and women, all analyses were performed separately for men and women. FMI was categorized into the following quartile groups using the whole population: Q1 (lowest group), Q2, Q3, and Q4 (highest group). FFMI was also categorized into the following quartile groups using the whole population: Q1 (lowest group), Q2, Q3, and Q4 (highest group). We examined the association between FMI and FFMI using Pearson's correlation coefficients.

Regarding the baseline characteristics of the FMI quartile, a trend test was performed to evaluate the linear relationships among FMI and age, height, BMI, BF%, FM, FFM, FFMI, cIMT, SBP, DBP, glucose, HbA1c, TC, TG, and HDL-C. During the trend test, a simple linear model was used to analyze age, height, BMI, BF%, FM, FFM, FFMI, cIMT, SBP, DBP, glucose, HbA1c, TC, TG, and HDL-C as continuous variables. The chi-square test was used to compare the treatment for hypertension, diabetes, dyslipidemia, the prevalence of hypertension, diabetes, dyslipidemia, smoking status, and history of CVD among the quartile groups for the FMI. A similar analysis was performed for the baseline characteristics of the FFMI quartile.

An analysis of covariance (ANCOVA) was used to test for associations between the FMI and least squares (LS) means of cIMT. The LS means and corresponding 95% confidence intervals (CIs) are presented. The multivariable-adjusted models included age (continuous) and smoking status (never smoker, ex-smoker, and current smoker). Similarly, we analyzed the association between FFMI and LS means of cIMT; p values for the analysis of linear trends were calculated by scoring the categories from 1 (the lowest category) to 4 (the highest category) and entering the number as a continuous term in the regression model.

The FMI and FFMI were combined and categorized into 16 groups. We also used ANCOVA to assess the association between the combined FMI and FFMI and LS means of cIMT. The p values for the analysis of linear trends were calculated by stratifying the FMI and FFMI, scoring the categories from 1 (the lowest category) to 4 (the highest category), and entering the number as a continuous term in the regression model.

We also conducted several sensitivity analyses to test the robustness of our findings. First, because age affects body composition and cIMT, we conducted a stratified analysis according to the following three age categories (20–39 years, 40–74 years, and 75 years or older). Second, several studies have shown that treatment for dyslipidemia, hypertension, and diabetes reduces cIMT[1, 36-38]. Furthermore, participants with cardiovascular disease have higher cIMT[39]. Therefore, to eliminate the effect of treatment for hypertension, diabetes, dyslipidemia, and history of CVD, we selected only individuals who did not undergo any treatment for hypertension, diabetes, dyslipidemia, and no history of CVD.

Statistical significance was set at $p<0.05$. All analyses were performed using SAS version 9.4 for Windows (SAS Inc, Cary, NC, USA).

Results

Characteristics of the Study Population

A total of 3,873 men and 9,112 women fulfilled all the inclusion criteria, and their data were included in the analyses. The mean age (±SD) of the study participants was 59.9 years (±14.1 years) for men and 56.0 years (±13.5 years) for women. The median FMI (IQR) was higher for women (6.7 [5.1–8.6] kg/m^2) than for men (5.5 [4.3–7.0] kg/m^2). Conversely, the median FFMI was higher for men (18.0 [17.0–18.9] kg/m^2) than for women (15.2 [14.5–16.0] kg/m^2). The cIMT (SD) was higher in men (0.65 [0.14] mm) than in women (0.60 [0.12] mm). The percentages of treatment for hypertension, diabetes, dyslipidemia, and the percentage of current smokers were higher in men than in women. The correlations of the FMI and FFMI were r=0.39 for men and r=0.52 for women.

The FMI was categorized into the following sex-specific quartiles for men: Q1, <4.3 kg/m^2; Q2, 4.3–5.5 kg/m^2; Q3, 5.6–7.0 kg/m^2; Q4, ≥ 7.0 kg/m^2. For women, they were as follows: Q1, <5.1 kg/m^2; Q2, 5.1–6.7 kg/m^2; Q3, 6.8–8.6 kg/m^2; and Q4, ≥ 8.6 kg/m^2 **(Supplemental Table 1)**. For both men and women, height and HDL-C were inversely associated with FMI ($p<0.001$ for linear trend), and other variables were positively associated with FMI ($p<0.001$ for linear trend). For both men and women, the prevalence of hypertension, diabetes, dyslipidemia, and smoking status were statistically different among the quartile groups ($p<0.05$ for difference).

The FFMI was categorized into the following sex-specific quartiles for men: Q1, <17.0 kg/m^2; Q2, 17.0–18.0 kg/m^2; Q3, 18.1–18.9 kg/m^2; and Q4, ≥ 18.9 kg/m^2. For women, they were as follows: Q1, < 14.5 kg/m^2; Q2, 14.5–15.1 kg/m^2; Q3, 15.2–16.0 kg/m^2; and Q4, ≥ 16.0 kg/m^2 **(Supplemental Table 2)**. For both men and women, BMI, BF%, FM, FFM, DBP, and TG were positively associated with the FFMI ($p<0.001$ for linear trend), and HDL-C was inversely associated with FFMI ($p<0.001$ for linear trend). For men only, height was positively associated with FFMI, and age was inversely associated with FFMI ($p<0.001$ for linear trend). For women only, IMT, SBP, glucose, and HbA1c were positively associated with FFMI ($p<0.001$ for linear trend), and TC was inversely associated with FFMI ($p<0.001$ for linear trend). For women only, the prevalence of hypertension and diabetes were statistically different among the quartile groups ($p<0.001$ for difference). For both men and women, the prevalence of dyslipidemia and smoking status were statistically different among the quartile groups ($p<0.001$ for difference).

The characteristics of the participants according to the combined FMI and FFMI are shown in **Table 1** for men and **Table 2** for women. Participants with higher FMI and higher FFMI were more likely to have a higher BMI in both men and women. Men categorized as FMI Q1 and FFMI Q4 (the lowest FMI quartile and the highest FFMI quartile) had younger age, taller height, lower cIMT, lower SBP, and lower glucose and had a lower prevalence of hypertension, diabetes, and more current smokers. Men categorized as FMI Q4 and FFMI Q1 (the highest FMI quartile and the lowest FFMI quartile) had older age, shorter height, higher cIMT, higher SBP, higher glucose, higher HbA1c, and higher prevalence of hypertension and diabetes and were fewer current smokers. Women categorized as FMI Q1 and FFMI Q4 had a taller height, lower TC, and lower TG and were more current smokers. Women categorized as FMI Q4 and FFMI Q1 had older age, shorter height, higher SBP, higher glucose, and higher TC and were fewer current smokers.

Associations between FMI and cIMT

FMI was associated with cIMT, even after adjusting for potential confounders for both men and women ($p<0.001$ for linear trend). For men, the cIMT LS means (95% CI) were 0.628 (0.609–0.647) for Q1, 0.641 (0.622–0.659) for Q2, 0.649 (0.631–0.668) for Q3, and 0.655 (0.637–0.674) for Q4. For women, the cIMT LS means (95% CI) were 0.584 (0.575–0.592) for Q1, 0.590 (0.581–0.599) for Q2, 0.593 (0.585–0.602) for Q3, and 0.600 (0.591–0.609) for Q4 **(Supplemental Table 3)**.

Associations between FFMI and cIMT

A higher FFMI was associated with a higher cIMT in both men and women adjusting for potential confounder ($p<0.001$ for linear trend). For men, the cIMT LS means (95% CIs) were 0.626 (0.607–0.644) for Q1, 0.637 (0.618–0.655) for Q2, 0.651 (0.632–0.669) for Q3, and 0.667 (0.648–0.685) for Q4. For women, the cIMT LS means (95% CI) were 0.579 (0.570–0.588) for Q1, 0.586 (0.577–0.595) for Q2, 0.593 (0.584–0.602) for Q3, and 0.606 (0.597–0.615) for Q4 **(Supplemental Table 4)**.

Associations between Combined FMI and FFMI with cIMT

For both men and women, the combined FMI and FFMI were associated with cIMT, even after adjusting for potential confounders **(Table 3)**. Higher FMI did not tend to be associated with higher cIMT in most FFMI subgroups, except for men categorized as FMI Q4 ($p=0.008$ for linear trend) and women categorized as FMI Q2 ($p<0.030$ for linear trend). Conversely, higher FFMI tended to be associated with higher cIMT in all FMI subgroups for both men and women ($p<0.05$ for linear trend).

We conducted a stratified analysis according to the three age categories (20–39 years, 40–74 years, and 75 years or older). Although FFMI was not statistically significantly associated with cIMT among 75 years or older, the results were substantially unchanged compared with those using all participants **(Supplemental Tables 5, 6, 7)**. Furthermore, the results of excluding participants' treatment for hypertension, diabetes, and dyslipidemia and participants with a history of CVD were also substantially unchanged compared with those using all participants **(Supplemental Table 8)**.

Discussion

In this cross-sectional study, we analyzed 12,985 Japanese participants aged ≥ 20 years to investigate the association between combined FMI and FFMI with cIMT. When the FMI and FFMI were combined, a higher FMI was not related to higher cIMT in men and women in most FFMI subgroups. Conversely, a higher FFMI was related to a higher cIMT in all FMI subgroups.

Several previous studies have shown an association between body composition (i.e., fat and fat-free mass) and cIMT. In a study of 421 obese middle-aged European men and women, FFM contributed to the increased cIMT independent of FM and other atherosclerotic risk factors[22]. The China Kadoorie Biobank study showed that FFM was more strongly associated with cIMT than FM[24]. The findings of the Southampton Women's Survey showed that when FMI and FFMI were mutually adjusted, FFMI was associated with cIMT, and FMI was not significantly associated with cIMT[40]. Furthermore, the Avon Longitudinal Study of Parents and Children study showed that elevated levels of FFM were associated with increases in cIMT independent of FM[25]. Several previous studies used absolute FM and BF% as an index of body fat[21-25]. However, the absolute FM is correlated with height. Because the weight is equal to the sum of FM and FFM, the BF% is affected by FFM[18]. Thus, we used the FMI and FFMI, which are not affected by FM or FFM and allowed for comparisons of individuals with different height measurements. Additionally, to clarify the association between body composition and cIMT, two different body compositions should be considered. Since a higher BMI resulted in not only a higher FMI but also a higher FFMI, the correlation between FMI and FFMI was observed (r=0.39 for men; r=0.52 for women). Therefore, it may be inappropriate to use FMI and FFMI simultaneously in the same statistical

Table 1. Characteristics of male participants according to the combined FMI and FFMI

FMI		Q1				Q2				Q3				Q4			
FFMI		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Number	3,873	395	253	193	128	246	299	255	167	208	224	281	255	120	191	240	418
Age, years	59.9 (14.1)	59.3 (16.0)	57.2 (15.2)	54.2 (14.7)	49.5 (15.2)	64.9 (13.4)	61.2 (12.8)	59.0 (12.9)	54.7 (13.2)	66.6 (11.2)	63.6 (12.0)	61.0 (12.5)	56.4 (12.6)	70.7 (10.6)	66.3 (11.1)	63.1 (12.4)	55.2 (13.6)
Height, cm	167.5 (6.3)	167.8 (6.8)	168.1 (6.1)	169.7 (6.6)	171.1 (6.6)	165.8 (6.2)	168.0 (6.3)	167.6 (5.9)	169.6 (5.8)	165.4 (5.9)	166.1 (5.9)	167.5 (5.9)	169.2 (5.8)	162.9 (5.9)	164.6 (6.0)	166.1 (5.7)	169.2 (5.9)
BMI, kg/m²	23.8 (3.1)	19.1 (1.2)	20.8 (0.8)	21.8 (0.7)	23.0 (1.1)	21.1 (0.8)	22.4 (0.5)	23.3 (0.5)	24.6 (0.7)	22.5 (0.8)	23.7 (0.5)	24.7 (0.5)	26.1 (0.9)	24.6 (1.1)	25.7 (1.2)	26.7 (1.2)	29.4 (2.7)
BF%, %	23.7 (6.3)	16.1 (3.5)	16.0 (2.9)	15.6 (2.5)	14.5 (3.0)	23.2 (1.5)	22.0 (1.4)	21.1 (1.3)	20.1 (1.3)	27.7 (1.6)	26.2 (1.4)	25.3 (1.3)	24.1 (1.4)	33.9 (2.8)	31.9 (2.8)	31.0 (2.9)	30.9 (4.1)
FM, kg	16.2 (6.2)	8.7 (2.2)	9.4 (2.0)	9.8 (1.9)	9.8 (2.3)	13.5 (1.3)	13.9 (1.4)	13.9 (1.5)	14.2 (1.4)	17.1 (1.7)	17.1 (1.6)	17.5 (1.7)	18.0 (1.8)	22.1 (2.6)	22.3 (3.2)	22.9 (3.4)	26.3 (6.4)
FFM, kg	50.6 (6.4)	45.1 (4.2)	49.4 (3.7)	53.0 (4.3)	57.5 (5.3)	44.5 (3.9)	49.4 (3.8)	51.7 (3.8)	56.8 (4.7)	44.5 (3.8)	48.3 (3.5)	51.7 (3.7)	56.9 (5.0)	43.1 (3.8)	47.5 (3.5)	50.9 (3.7)	58.0 (5.7)
FMI, kg/m²	5.5 (4.3-7.0)	3.2 (2.6-3.8)	3.5 (2.9-3.9)	3.5 (3.0-3.9)	3.6 (2.9-3.9)	4.9 (4.6-5.2)	5.0 (4.6-5.3)	4.9 (4.6-5.2)	4.9 (4.6-5.2)	6.2 (5.9-6.6)	6.2 (5.8-6.6)	6.2 (5.9-6.6)	6.3 (5.9-6.7)	8.2 (7.7-8.9)	7.8 (7.4-8.8)	8.0 (7.5-8.8)	8.6 (7.7-10.0)
FFMI, kg/m²	18.0 (17.0-18.9)	16.1 (15.6-16.6)	17.5 (17.2-17.7)	18.3 (18.1-18.6)	19.4 (19.1-19.9)	16.3 (15.9-16.7)	17.5 (17.2-17.7)	18.4 (18.1-18.6)	19.5 (19.2-20.0)	16.4 (16.0-16.8)	17.5 (17.2-17.7)	18.4 (18.2-18.6)	19.6 (19.3-20.2)	16.4 (15.8-16.8)	17.5 (17.3-17.7)	18.4 (18.2-18.6)	20.0 (19.4-20.8)
cIMT, mm	0.65 (0.14)	0.62 (0.14)	0.63 (0.14)	0.61 (0.13)	0.59 (0.11)	0.67 (0.15)	0.64 (0.14)	0.64 (0.15)	0.64 (0.13)	0.67 (0.14)	0.67 (0.14)	0.67 (0.15)	0.65 (0.14)	0.69 (0.15)	0.67 (0.13)	0.68 (0.15)	0.65 (0.14)
SBP, mmHg	133.8 (16.1)	130.0 (18.1)	130.3 (16.3)	129.0 (15.3)	127.1 (13.2)	133.4 (16.4)	134.8 (17.3)	132.7 (14.4)	132.1 (14.1)	137.9 (16.8)	137.7 (16.3)	133.3 (14.6)	133.3 (15.0)	138.9 (16.2)	137.4 (15.6)	137.8 (15.6)	136.2 (14.4)
DBP, mmHg	80.9 (10.9)	77.2 (10.5)	79.0 (10.6)	78.8 (11.7)	77.7 (9.5)	78.6 (11.3)	81.4 (11.0)	80.9 (10.2)	82.0 (10.6)	81.0 (10.4)	82.6 (10.6)	81.3 (9.7)	82.3 (10.5)	79.1 (12.1)	81.4 (9.8)	82.9 (10.8)	85.2 (11.1)
Treatment for hypertension, %	1,109 (28.6)	56 (14.2)	44 (17.4)	29 (15.0)	14 (10.9)	58 (23.6)	73 (24.4)	68 (26.7)	44 (26.4)	72 (34.6)	67 (29.9)	91 (32.4)	81 (31.8)	61 (50.8)	91 (47.6)	107 (44.6)	153 (36.6)
Hypertension, %	2,059 (53.2)	143 (36.2)	98 (38.7)	71 (36.8)	32 (25.0)	125 (50.8)	152 (50.8)	123 (48.2)	81 (48.5)	134 (64.4)	134 (59.8)	154 (54.8)	145 (56.9)	88 (73.3)	132 (69.1)	170 (70.8)	277 (66.3)
Glucose, mg/dL	92.6 (21.0)	88.7 (17.5)	88.6 (18.8)	87.4 (11.6)	86.1 (13.1)	92.5 (24.0)	91.2 (19.0)	93.4 (19.8)	90.8 (14.0)	94.0 (19.2)	93.8 (19.9)	94.1 (22.8)	92.4 (19.1)	100.7 (32.8)	95.8 (18.5)	96.9 (24.7)	96.1 (25.9)
HbA1c, %	5.6 (0.6)	5.5 (0.5)	5.4 (0.4)	5.4 (0.4)	5.4 (0.3)	5.6 (0.7)	5.5 (0.4)	5.6 (0.6)	5.5 (0.6)	5.6 (0.6)	5.7 (0.8)	5.6 (0.5)	5.6 (0.6)	5.9 (1.2)	5.7 (0.5)	5.7 (0.6)	5.8 (0.7)
Treatment for diabetes, %	307 (7.9)	31 (7.9)	16 (6.3)	10 (5.2)	2 (1.6)	23 (9.4)	9 (3.0)	20 (7.8)	7 (4.2)	20 (9.6)	21 (9.4)	26 (9.3)	19 (7.5)	20 (16.7)	16 (8.4)	27 (11.3)	40 (9.6)
Diabetes, %	405 (10.5)	33 (8.4)	18 (7.1)	11 (5.7)	4 (3.1)	26 (10.6)	12 (4.0)	25 (9.8)	10 (6.0)	26 (12.5)	28 (12.5)	35 (12.5)	35 (13.7)	26 (21.7)	22 (11.5)	34 (14.2)	60 (14.4)
TC, mg/dL	201.2 (35.0)	195.8 (35.5)	194.5 (32.5)	196.7 (34.1)	196.1 (34.4)	201.5 (33.3)	201.7 (33.5)	200.9 (34.5)	201.1 (33.6)	205.7 (32.5)	201.5 (34.4)	202.9 (32.4)	201.9 (34.8)	199.4 (35.7)	205.9 (37.7)	206.3 (36.5)	205.1 (39.0)
TG, mg/dL	101.0 (72.0-149.0)	73.0 (56.0-102.0)	73.0 (55.0-97.0)	82.0 (57.0-117.0)	77.0 (56.5-103.0)	94.0 (68.0-143.0)	100.0 (74.0-137.0)	94.0 (70.0-136.0)	100.0 (69.9-152.0)	110.0 (78.5-159.0)	109.5 (84.0-163.0)	104.0 (81.0-149.0)	117.0 (83.0-176.0)	110.5 (89.0-150.0)	125.0 (93.0-160.0)	127.0 (94.0-185.0)	138.5 (98.0-198.0)
HDL-C, mg/dL	57.1 (15.1)	66.1 (15.8)	64.3 (14.9)	63.8 (15.6)	64.6 (18.2)	58.9 (16.0)	58.9 (14.7)	57.5 (15.1)	56.0 (15.3)	55.2 (12.7)	54.7 (13.1)	54.6 (13.3)	51.7 (12.2)	55.7 (14.3)	53.3 (13.1)	51.7 (11.9)	49.3 (11.6)
Treatment for dyslipidemia, %	413 (10.7)	23 (5.8)	17 (6.7)	4 (2.1)	5 (3.9)	27 (11.0)	26 (8.7)	28 (11.0)	19 (11.4)	19 (9.1)	26 (11.6)	32 (11.4)	28 (11.0)	20 (16.7)	22 (11.5)	38 (15.8)	79 (18.9)
Dyslipidemia, %	1,360 (35.1)	56 (14.2)	43 (17.0)	37 (19.2)	19 (14.8)	83 (33.7)	83 (27.8)	90 (35.3)	68 (40.7)	79 (38.0)	91 (40.6)	107 (38.1)	113 (44.3)	45 (37.5)	81 (42.4)	121 (50.4)	244 (58.4)
History of cardiovascular disease, %	3.7 (7.9)	20 (5.1)	11 (4.4)	9 (4.7)	2 (1.6)	10 (4.1)	16 (5.4)	18 (7.1)	10 (5.9)	23 (11.1)	26 (11.6)	23 (8.2)	21 (8.2)	20 (16.7)	28 (14.7)	32 (13.3)	38 (9.1)

(Cont. Table 1)

FMI		Q1				Q2				Q3				Q4			
	FFMI	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Smoking status, %																	
Never smoker	1,107 (28.6)	118 (29.9)	79 (31.2)	58 (30.1)	36 (28.1)	81 (32.9)	96 (32.1)	78 (30.6)	43 (25.8)	59 (28.4)	66 (29.5)	68 (24.2)	64 (25.1)	41 (34.2)	52 (27.2)	67 (27.9)	101 (24.2)
Ex-smoker	1,944 (59.2)	191 (48.4)	117 (46.3)	89 (46.1)	54 (42.2)	117 (47.6)	143 (47.8)	127 (49.8)	86 (51.5)	109 (52.4)	114 (50.9)	159 (56.6)	119 (46.7)	68 (56.7)	109 (57.1)	136 (56.7)	206 (49.3)
Current smoker	811 (20.9)	86 (21.8)	57 (22.5)	46 (23.8)	38 (29.7)	47 (19.1)	59 (19.7)	50 (19.6)	37 (22.2)	38 (18.3)	44 (19.6)	53 (18.9)	72 (28.2)	10 (8.3)	29 (15.2)	37 (15.4)	108 (25.8)
Unknown	11 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.3)	0 (0.0)	1 (0.6)	2 (1.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.8)	1 (0.5)	0 (0.0	3 (0.7)

Values are expressed as mean (standard deviation) or median (interquartile range) for continuous variables or as number (%) for categorical variables.
BF%, body fat percentage; BMI, body mass index; cIMT, carotid intima-media thickness; DBP, diastolic blood pressure; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; Q, quartile; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride
Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or receiving treatment for hypertension.
Diabetes was defined as non-fasting glucose ≥ 200 mg/dL and/or HbA1c ≥ 6.5% or receiving treatment for diabetes.
Dyslipidemia was defined as TG ≥ 150 mg/dL or HDL-C <40 mg/dL and/or receiving treatment for dyslipidemia.

model. To consider both FMI and FFMI, we examined the association between combined FMI and FFMI with cIMT. Our findings support previous studies[22, 25, 40].

In this study, a higher FFMI was related to a higher cIMT in all FMI subgroups. A potential mechanism may be that the high metabolic demands of FFM require an increase in blood flow[25]. A previous study has shown that stroke volume and cardiac output were more strongly associated with FFM than adipose mass, diabetes, and age[19]. Further study has reported that the increment of the FFM by exercise training was associated with an increment of the left ventricle mass and the wall thickness[41]. Similarly, the findings of our previous study investigating the association between combined FMI and FFMI with hypertension have shown that FFMI was associated with hypertension even when FMI was considered and the Assessment Prognostic Risk Observational Survey showed that left ventricular hypertrophy caused by hypertension was significantly associated with an increase in cIMT[30, 42]. Therefore, greater FFMI might lead to an increased cIMT via hypertension and left ventricle hypertrophy.

We observed that a higher FMI was not related to a higher cIMT in most FFMI subgroups. Several studies have shown that cIMT is associated with well-known cardiovascular risk factors such as blood pressure, glucose, and lipids[1, 4]. In addition, adipose tissue is known to affect elevated blood pressure, glucose, and lipids[10]. Therefore, greater FM may be associated with increased cIMT via diseases resulting in atherosclerosis, such as hypertension, diabetes, and dyslipidemia. However, our findings showed that harmful effects of FM were not observed in most FFMI subgroups. Conversely, we showed that a higher FMI was positively related to a higher cIMT in FFMI Q4. Participants classified under FFMI Q4 had a greater increase in FFMI with increasing FMI than in other FFMI subgroups. Therefore, these results may reflect the effect of FFMI on cIMT classified in FFMI Q4. Further studies are required to elucidate the underlying mechanism.

The strength of this study, to our knowledge, is that this study is the first to show the association between combined FMI and FFMI with cIMT. Since this study enrolled a large population of approximately 13,000 participants, we were able to classify 16 groups of combined FMI and FFMI sex-specific quartiles. Therefore, we were able to show a relationship with cIMT due to differences in body composition. However, our study has several limitations. First, because we used the bioelectric impedance analysis (BIA) method to measure BF%, a measurement error may have occurred. However, a high correlation between whole-body FM measured using the BIA method and whole-body FM measured using the dual-energy X-ray absorptiometry method has been verified (men: r=0.95, women: r=0.92)[43]. Second, although plaque is also considered a marker of atherosclerosis, it is known to be related to the risk of CVD[1, 7-9]. Our study did not measure plaque. Thus, we could not show the association between body composition and plaque. Third, our study enrolled only the Japanese population. It is well-known that body composition varies due to race. A study showed

Table 2. Characteristics of female participants according to the combined FMI and FFMI

	FMI	Q1				Q2				Q3				Q4			
	FFMI	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Number	9,112	931	666	449	231	691	668	563	357	516	605	656	501	140	339	610	1,189
Age, years	56.0 (13.5)	52.4 (14.1)	51.1 (13.8)	50.7 (13.8)	51.0 (12.3)	55.8 (14.3)	55.5 (13.7)	54.6 (13.5)	54.6 (14.0)	59.1 (12.2)	59.8 (11.8)	58.9 (12.6)	56.6 (13.2)	64.2 (12.1)	62.2 (11.2)	60.1 (12.0)	56.3 (13.0)
Height, cm	155.8 (5.8)	157.4 (5.4)	157.5 (5.6)	157.3 (5.6)	158.4 (5.5)	156.0 (5.5)	155.9 (5.7)	156.5 (5.7)	156.5 (5.9)	154.4 (5.5)	154.7 (5.7)	155.2 (5.5)	156.0 (5.9)	152.4 (5.4)	153.3 (5.9)	153.7 (5.4)	155.1 (5.9)
BMI, kg/m^2	22.3 (3.5)	17.7 (1.0)	18.9 (0.8)	19.7 (0.8)	20.7 (0.9)	19.8 (0.7)	20.7 (0.5)	21.5 (0.5)	22.5 (0.7)	21.4 (0.7)	22.4 (0.6)	23.2 (0.6)	24.3 (0.8)	23.5 (1.0)	24.8 (1.2)	25.9 (1.5)	28.4 (2.9)
BF%, %	30.7 (7.3)	22.0 (3.8)	21.5 (3.3)	21.0 (3.0)	20.4 (2.9)	29.8 (1.8)	28.3 (1.6)	27.6 (1.5)	26.4 (1.6)	35.0 (1.8)	33.8 (1.6)	32.9 (1.6)	31.6 (1.5)	40.5 (2.3)	39.9 (2.6)	39.5 (3.2)	39.6 (4.1)
FM, kg	17.1 (6.5)	9.7 (2.1)	10.1 (2.0)	10.3 (1.9)	10.7 (1.9)	14.3 (1.4)	14.3 (1.4)	14.6 (1.6)	14.6 (1.6)	17.8 (1.7)	18.1 (1.8)	18.4 (1.8)	18.7 (1.9)	22.1 (2.4)	23.3 (3.2)	24.2 (3.7)	27.4 (5.9)
FFM, kg	37.1 (4.0)	34.2 (2.7)	36.8 (2.7)	38.5 (2.8)	41.4 (3.0)	33.8 (2.6)	36.1 (2.7)	38.1 (2.8)	40.6 (3.4)	33.1 (2.8)	35.5 (2.7)	37.5 (2.7)	40.5 (3.6)	32.4 (2.5)	35.0 (2.8)	36.9 (2.6)	41.2 (4.1)
FMI, kg/m^2	6.7 (5.1-8.6)	4.1 (3.4-4.6)	4.2 (3.6-4.7)	4.3 (3.7-4.8)	4.4 (3.9-4.8)	5.9 (5.5-6.3)	5.8 (5.5-6.3)	6.0 (5.6-6.3)	5.9 (5.5-6.4)	7.4 (7.0-7.9)	7.5 (7.1-8.0)	7.6 (7.1-8.1)	7.7 (7.2-8.1)	9.2 (8.8-9.9)	9.6 (9.1-10.5)	9.9 (9.1-11.0)	10.7 (9.6-12.4)
FFMI, kg/m^2	15.2 (14.5-16.0)	13.9 (13.5-14.2)	14.8 (14.6-15.0)	15.5 (15.3-15.7)	16.3 (16.1-16.7)	14.0 (13.6-14.2)	14.8 (14.6-15.0)	15.5 (15.3-15.7)	16.4 (16.2-16.8)	14.0 (13.6-14.2)	14.8 (14.6-15.0)	15.5 (15.4-15.7)	16.5 (16.2-16.8)	14.0 (13.8-14.3)	14.9 (14.7-15.1)	15.6 (15.4-15.8)	16.8 (16.4-17.5)
cIMT, mm	0.60 (0.12)	0.56 (0.11)	0.56 (0.10)	0.56 (0.11)	0.57 (0.12)	0.58 (0.13)	0.59 (0.11)	0.59 (0.12)	0.60 (0.11)	0.60 (0.12)	0.61 (0.12)	0.62 (0.13)	0.61 (0.13)	0.62 (0.13)	0.63 (0.12)	0.62 (0.12)	0.62 (0.13)
SBP, mmHg	125.9 (17.8)	119.1 (16.9)	118.8 (16.7)	119.6 (16.6)	122.2 (17.5)	124.2 (17.3)	124.6 (17.3)	125.5 (18.1)	123.8 (16.9)	125.7 (17.7)	128.5 (17.7)	128.5 (17.3)	128.6 (18.0)	132.0 (17.6)	132.0 (17.6)	132.0 (17.6)	131.5 (16.4)
DBP, mmHg	76.5 (10.5)	73.0 (9.9)	73.0 (10.0)	73.5 (10.5)	74.8 (11.8)	75.4 (9.9)	75.5 (9.7)	75.7 (11.0)	74.9 (10.4)	75.5 (9.8)	77.2 (9.7)	77.4 (10.1)	77.6 (10.9)	77.4 (9.9)	79.5 (10.5)	79.8 (10.0)	81.1 (10.1)
Treatment for hypertension, %	1,567 (17.2)	71 (7.6)	54 (8.1)	31 (6.9)	20 (8.7)	80 (11.6)	73 (10.9)	71 (12.6)	54 (15.1)	75 (14.5)	106 (17.5)	128 (19.5)	89 (17.8)	46 (32.9)	95 (28.0)	192 (31.5)	382 (32.1)
Hypertension, %	3,076 (33.8)	179 (19.2)	128 (19.2)	82 (18.3)	56 (24.2)	185 (26.8)	172 (25.8)	172 (30.6)	105 (29.4)	159 (30.8)	223 (36.9)	251 (38.3)	185 (36.9)	75 (53.6)	168 (49.6)	307 (50.3)	629 (52.9)
Glucose, mg/dL	86.6 (14.7)	82.9 (9.9)	82.9 (10.2)	83.7 (13.4)	84.2 (10.7)	84.8 (12.4)	85.4 (12.6)	85.6 (12.7)	85.5 (11.3)	87.2 (19.1)	87.2 (14.3)	87.5 (14.6)	88.6 (15.7)	91.3 (15.0)	89.1 (15.0)	90.0 (16.8)	91.0 (18.8)
HbA1c, %	5.5 (0.5)	5.4 (0.4)	5.3 (0.3)	5.4 (0.4)	5.4 (0.3)	5.4 (0.5)	5.4 (0.4)	5.4 (0.4)	5.4 (0.3)	5.5 (0.5)	5.5 (0.5)	5.5 (0.4)	5.5 (0.5)	5.6 (0.5)	5.6 (0.5)	5.6 (0.5)	5.7 (0.7)
Treatment for diabetes, %	320 (3.5)	21 (2.3)	10 (1.5)	10 (2.2)	4 (1.7)	12 (1.7)	11 (1.7)	13 (2.3)	7 (2.0)	18 (3.5)	15 (2.5)	20 (3.1)	17 (3.4)	11 (7.9)	20 (5.9)	34 (5.6)	97 (8.2)
Diabetes, %	422 (4.6)	24 (2.6)	12 (1.8)	11 (2.5)	6 (2.6)	18 (2.6)	21 (3.1)	15 (2.7)	7 (2.0)	29 (5.6)	21 (3.5)	24 (3.7)	24 (4.8)	14 (10.0)	24 (7.1)	41 (6.7)	131 (11.0)
TC, mg/dL	212.1 (35.5)	208.1 (35.8)	205.2 (34.0)	202.9 (35.4)	200.3 (34.6)	215.2 (36.0)	212.7 (34.0)	213.0 (36.6)	208.0 (31.7)	221.2 (35.9)	219.3 (36.6)	213.6 (34.1)	208.9 (34.3)	221.1 (34.4)	216.4 (34.3)	215.1 (34.3)	212.9 (36.5)
TG, mg/dL	79.0 (58.0-112.0)	62.0 (49.0-83.0)	60.5 (47.0-80.0)	60.0 (47.0-84.0)	59.0 (44.0-76.0)	74.0 (56.0-100.0)	73.0 (56.0-99.0)	71.0 (53.0-95.0)	73.0 (54.0-103.0)	65.0 (56.0-77.0)	85.0 (64.0-115.0)	89.0 (66.0-123.5)	91.0 (65.0-128.0)	95.5 (75.0-132.5)	98.0 (72.0-138.0)	100.0 (74.0-142.0)	108.0 (78.0-152.0)
HDL-C, mg/dL	67.6 (16.3)	75.7 (16.4)	75.6 (16.0)	75.0 (16.3)	75.3 (15.8)	70.9 (16.5)	69.5 (15.1)	70.8 (15.7)	69.5 (16.3)	67.0 (14.5)	66.2 (15.0)	64.9 (14.4)	62.1 (14.2)	63.8 (13.3)	62.1 (14.4)	60.8 (13.9)	58.0 (13.8)
Treatment for dyslipidemia, %	1,025 (11.3)	58 (6.2)	31 (4.7)	16 (3.6)	9 (3.9)	60 (8.7)	70 (10.5)	54 (9.6)	31 (8.7)	49 (9.5)	87 (14.4)	103 (15.7)	57 (11.4)	33 (23.6)	55 (16.2)	108 (17.7)	204 (17.2)
Dyslipidemia, %	1,988 (21.8)	87 (9.3)	59 (8.9)	31 (6.9)	14 (6.1)	104 (15.1)	122 (18.3)	83 (14.7)	61 (17.1)	109 (21.1)	158 (26.1)	170 (25.9)	139 (27.7)	54 (38.6)	114 (33.6)	218 (35.7)	465 (39.1)
History of cardiovascular disease, %		25 (2.7)	10 (1.5)	7 (1.6)	2 (0.9)	24 (3.5)	17 (2.5)	13 (2.3)	6 (1.7)	20 (3.9)	19 (3.1)	19 (2.9)	12 (2.4)	10 (7.1)	15 (4.4)	13 (2.1)	42 (3.5)

(Cont. Table 2)

	FMI	Q1				Q2				Q3				Q4			
	FFMI	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Smoking status, %																	
Never smoker	7,217 (78.7)	733 (78.7)	514 (77.2)	328 (73.1)	165 (71.4)	550 (79.6)	546 (81.7)	454 (80.6)	270 (75.6)	412 (79.8)	492 (81.3)	540 (82.3)	382 (76.3)	118 (84.3)	281 (82.9)	495 (81.2)	890 (74.9)
Ex-smoker	1,248 (13.6)	115 (12.4)	91 (13.7)	75 (16.7)	41 (17.8)	89 (12.9)	81 (12.1)	76 (13.5)	54 (15.1)	68 (13.2)	76 (12.6)	79 (12.0)	73 (14.6)	16 (11.4)	43 (12.7)	74 (12.1)	187 (15.7)
Current smoker	672 (7.3)	80 (8.6)	57 (8.6)	45 (10.0)	23 (10.0)	51 (7.4)	38 (5.7)	32 (5.7)	33 (9.2)	35 (6.8)	33 (5.5)	37 (5.6)	40 (8.0)	6 (4.3)	15 (4.4)	38 (6.2)	107 (9.0)
Unknown	34 (0.4)	3 (0.3)	4 (0.6)	1 (0.2)	2 (0.9)	1 (0.1)	3 (0.5)	1 (0.2)	0 (0.0)	1 (0.2)	4 (0.7)	0 (0.0)	6 (1.2)	0 (0.0)	0 (0.0)	3 (0.5)	5 (0.4)

Values are expressed as mean (standard deviation) or median (interquartile range) for continuous variables or as number (%) for categorical variables.
BF%, body fat percentage; BMI, body mass index; cIMT, carotid intima-media thickness; DBP, diastolic blood pressure; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; Q, quartile; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride
Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or receiving treatment for hypertension.
Diabetes was defined as non-fasting glucose ≥ 200 mg/dL and/or HbA1c ≥ 6.5% or receiving treatment for diabetes.
Dyslipidemia was defined as TG ≥ 150 mg/dL or HDL-C ＜40 mg/dL and/or receiving treatment for dyslipidemia.

Table 3. Adjusted least square means of cIMT associated with FMI and FFMI

Men	FMIQ1	FMIQ2	FMIQ3	FMIQ4	*p* for linear trend among FFMI subgroups[a]
	LS means cIMT (mm), 95%CI				
FFMIQ1	0.614 (0.593-0.634)	0.639 (0.617-0.661)	0.628 (0.605-0.651)	0.627 (0.600-0.653)	0.004
FFMIQ2	0.639 (0.616-0.661)	0.629 (0.607-0.650)	0.646 (0.623-0.669)	0.631 (0.608-0.655)	0.019
FFMIQ3	0.641 (0.617-0.664)	0.642 (0.620-0.664)	0.657 (0.636-0.679)	0.656 (0.633-0.679)	0.001
FFMIQ4	0.644 (0.618-0.671)	0.664 (0.640-0.688)	0.661 (0.639-0.683)	0.675 (0.655-0.695)	＜0.001
p for linear treand among FMI subgroups[b]	0.130	0.966	0.139	0.008	
Women	**FMIQ1**	**FMIQ2**	**FMIQ3**	**FMIQ4**	***p* for linear trend among FFMI subgroups[a]**
	LS means cIMT (mm), 95%CI				
FFMIQ1	0.579 (0.569-0.589)	0.580 (0.569-0.590)	0.582 (0.570-0.593)	0.567 (0.550-0.585)	0.004
FFMIQ2	0.583 (0.572-0.593)	0.585 (0.575-0.596)	0.588 (0.577-0.599)	0.591 (0.578-0.604)	＜0.001
FFMIQ3	0.585 (0.573-0.597)	0.598 (0.587-0.609)	0.597 (0.586-0.607)	0.591 (0.580-0.602)	＜0.001
FFMIQ4	0.597 (0.583-0.612)	0.604 (0.591-0.616)	0.603 (0.592-0.614)	0.610 (0.600-0.619)	＜0.001
p for linear trend among FMI subgroups[b]	0.568	0.030	0.837	0.067	

Adjusted for age (continuous), smoking status (never-smoker, ex-smoker, current smoker, and unknown).
[a] *p* values for the analysis of linear trends were calculated by stratifying FMI, scoring the FFMI categories, from 1 for the lowest category to 4 for the highest category, entering the number as a continuous term in the regression model.
[b] *p* values for the analysis of linear trends were calculated by stratifying FFMI, scoring the FMI categories, from 1 for the lowest category to 4 for the highest category, entering the number as a continuous term in the regression model.
ANCOVA, analysis of covariance; CI, confidence interval; cIMT, carotid intima-media thickness; FFMI, fat-free mass index; FMI, fat mass index; LS, least squares; Q, quartile

that the FFMI differed among the four ethnic groups (Caucasian, African American, Hispanic, and Asian), with African Americans having the highest FFMI and Asians having the lowest FFMI[44]. Furthermore, South Asians have more body fat and less skeletal muscle mass than Caucasians[45]. Therefore, similar investigations are required for other populations. Fourth, residual or unmeasured confounding factors may exist. Although we used combined FMI and FFMI to avoid collinearity, even in the same FMI subgroup, higher FMI tended to have higher FFMI. Therefore, we could not completely rule out the effects of FMI and FFMI. Fifth, participants who voluntarily underwent several physiological measurements may have higher health consciousness than those who did not, which could have caused a volunteer bias in our study. Finally, this study had a cross-sectional design and could not definitively establish a causal relationship between combined FMI and FFMI with cIMT. To clarify the causal relationship, prospective cohort studies are required.

Conclusion

When FFMI was not considered, a higher FMI was associated with higher cIMT. When FMI was not considered, a higher FFMI was associated with higher cIMT. When the FMI and FFMI were combined, the FMI did not tend to be associated with higher cIMT in most FFMI subgroups. However, FFMI tended to be associated with higher cIMT in all FMI subgroups. These findings suggest that because higher FFM could induce adaptive changes in systemic hemodynamics, cIMT might represent not only atherosclerosis but also physiological adaptations in hemodynamics such as thickening of the vascular wall with elevated blood pressure. Further studies are warranted to elucidate the association between body composition and the incidence of cardiovascular diseases, such as stroke and myocardial infarction, and the potential mechanisms of the relationship between body composition and cIMT.

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https://www.megabank.tohoku.ac.jp/english/a200601/.

Conflicts of Interest

None.

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Supplemental Table 1. Characteristics of participants according to FMI

	Men	FMI				*p* value[a]	Women	FMI				*p* value[a]
		Q1 (<4.3)	Q2 (4.3-5.5)	Q3 (5.6-7.0)	Q4 (≥ 7.0)			Q1 (<5.1)	Q2 (5.1-6.7)	Q3 (6.8-8.6)	Q4 (≥ 8.6)	
Number	3,873	969	967	968	969		9,112	2,277	2,279	2,293	2,278	
Age, years	59.9 (14.1)	56.4 (15.7)	60.4 (13.5)	61.6 (12.7)	61.3 (13.7)	<0.001	56.0 (13.5)	51.5 (13.8)	55.2 (13.9)	58.7 (12.5)	58.7 (12.7)	<0.001
Height, cm	167.5 (6.3)	168.7 (6.6)	167.6 (6.2)	167.2 (6.0)	166.7 (6.3)	<0.001	155.8 (5.8)	157.5 (5.5)	156.2 (5.7)	155.1 (5.7)	154.3 (5.8)	<0.001
BMI, kg/m^2	23.8 (3.1)	20.6 (1.7)	22.7 (1.3)	24.4 (1.5)	27.4 (2.7)	<0.001	22.3 (3.5)	18.8 (1.4)	20.9 (1.1)	22.8 (1.2)	26.9 (2.9)	<0.001
BF%, %	23.7 (6.3)	15.8 (3.1)	21.7 (1.7)	25.7 (1.9)	31.5 (3.6)	<0.001	30.7 (7.3)	21.5 (3.5)	28.3 (2.0)	33.3 (2.0)	39.7 (3.6)	<0.001
FM, kg	16.2 (6.2)	9.3 (2.2)	13.8 (1.4)	17.5 (1.7)	24.2 (5.2)	<0.001	17.1 (6.5)	10.1 (2.0)	14.4 (1.5)	18.3 (1.8)	25.6 (5.2)	<0.001
FFM, kg	50.6 (6.4)	49.4 (6.1)	50.0 (5.7)	50.7 (6.0)	52.3 (7.2)	<0.001	37.1 (4.0)	36.5 (3.6)	36.6 (3.7)	36.6 (3.9)	38.6 (4.5)	<0.001
FMI, kg/m^2	5.5 (4.3-7.0)	3.4 (2.8-3.8)	4.9 (4.6-5.2)	6.2 (5.9-6.6)	8.2 (7.5-9.2)	-	6.7 (5.1-8.6)	4.2 (3.5-4.7)	5.9 (5.5-6.3)	7.6 (7.1-8.0)	10.2 (9.3-11.5)	-
FFMI, (kg/m^2	18.0 (17.0-18.9)	17.3 (16.3-18.3)	17.8 (17.0-18.6)	18.1 (17.1-19.0)	18.6 (17.6-19.8)	-	15.2 (14.5-16.0)	14.7 (14.0-15.3)	14.9 (14.3-15.6)	15.2 (14.5-15.9)	16.1 (15.3-16.9)	-
cIMT, mm	0.65 (0.14)	0.61 (0.13)	0.65 (0.14)	0.66 (0.14)	0.67 (0.14)	<0.001	0.60 (0.12)	0.56 (0.11)	0.59 (0.12)	0.61 (0.12)	0.62 (0.13)	<0.001
SBP, mmHg	133.8 (16.1)	129.5 (16.5)	133.4 (15.8)	135.3 (15.7)	137.2 (15.2)	<0.001	125.9 (17.8)	119.4 (16.9)	124.6 (17.4)	127.9 (17.7)	131.7 (17.0)	<0.001
DBP, mmHg	80.9 (10.9)	78.1 (10.7)	80.7 (10.9)	81.8 (10.3)	83.1 (11.1)	<0.001	76.5 (10.5)	73.3 (10.3)	75.4 (10.2)	76.9 (10.1)	80.3 (10.2)	<0.001
Treatment for hypertension, %	1,109 (28.6)	143 (14.8)	243 (25.1)	311 (32.1)	412 (42.5)	<0.001	1,567 (17.2)	176 (7.7)	278 (12.2)	398 (17.5)	715 (31.4)	<0.001
Hypertension, %	2,059 (53.2)	344 (35.5)	481 (49.7)	567 (58.6)	667 (68.8)	<0.001	3,076 (33.8)	445 (19.5)	634 (27.8)	818 (35.9)	1,179 (51.8)	<0.001
Glucose, mg/dL	92.6 (21.0)	88.1 (16.3)	92.0 (19.9)	93.6 (20.4)	96.8 (25.3)	<0.001	86.6 (14.7)	83.2 (10.9)	85.3 (12.4)	87.6 (15.9)	90.5 (17.5)	<0.001
HbA1c, %	5.6 (0.6)	5.4 (0.4)	5.5 (0.6)	5.6 (0.6)	5.8 (0.7)	<0.001	5.5 (0.5)	5.4 (0.3)	5.4 (0.4)	5.5 (0.5)	5.7 (0.6)	<0.001
Treatment for diabetes, %	307 (7.9)	59 (6.1)	59 (6.1)	86 (8.9)	103 (10.6)	<0.001	320 (3.5)	45 (2.0)	43 (1.9)	70 (3.1)	162 (7.1)	<0.001
Diabetes, %	405 (10.5)	66 (6.8)	73 (7.6)	124 (12.8)	142 (14.7)	<0.001	422 (4.6)	53 (2.3)	61 (2.7)	98 (4.3)	210 (9.2)	<0.001
TC (mg/dL)	201.2 (35.0)	195.7 (34.3)	201.3 (33.7)	202.9 (33.5)	204.9 (37.7)	<0.001	212.1 (35.5)	205.4 (35.2)	212.8 (35.0)	215.8 (35.5)	214.5 (35.5)	<0.001
TG, mg/dL	101.0 (72.0-149.0)	75.0 (56.0-104.0)	97.0 (71.0-141.0)	110.5 (82.0-162.0)	129.0 (95.0-183.0)	<0.001	79.0 (58.0-112.0)	61.0 (48.0-82.0)	73.0 (55.0-100.0)	87.0 (64.0-120.0)	104.0 (75.0-148.0)	<0.001
HDL-C, mg/dL	57.1 (15.1)	65.0 (15.9)	58.0 (15.3)	54.0 (12.9)	51.5 (12.5)	<0.001	67.6 (16.3)	75.5 (16.2)	70.2 (15.9)	65.1 (14.6)	59.7 (14.0)	<0.001
Treatment for dyslipidemia, %	413 (10.7)	49 (5.1)	100 (10.3)	105 (10.9)	159 (16.4)	<0.001	1,025 (11.3)	114 (5.0)	215 (9.4)	296 (13.0)	400 (17.6)	<0.001
Dyslipidemia, %	1,360 (35.1)	155 (16.0)	324 (33.5)	390 (40.3)	491 (50.7)	<0.001	1,988 (21.8)	191 (8.4)	370 (16.2)	576 (25.3)	851 (37.4)	<0.001

(Cont. Supplemental Table 1)

	Men	FMI				*p* value[a]	Women	FMI				*p* value[a]
		Q1 (＜4.3)	Q2 (4.3-5.5)	Q3 (5.6-7.0)	Q4 (≥ 7.0)			Q1 (＜5.1)	Q2 (5.1-6.7)	Q3 (6.8-8.6)	Q4 (≥ 8.6)	
History of cardiovascular disease, %												
Smoking status, %												
Never smoker	1,107 (28.6)	291 (30.0)	298 (30.8)	257 (26.6)	261 (26.9)	0.018	7,170 (78.7)	1,740 (76.4)	1,820 (79.9)	1,826 (80.2)	1784 (78.3)	0.022
Ex-smoker	1,944 (59.2)	451 (46.5)	473 (48.9)	501 (51.8)	519 (53.6)		1,238 (13.6)	322 (14.1)	300 (13.2)	296 (13.0)	320 (14.1)	
Current smoker	811 (20.9)	227 (23.4)	193 (20.0)	207 (21.4)	184 (19.0)		670 (7.4)	205 (9.0)	154 (6.8)	145 (6.4)	166 (7.3)	
Unknown	11 (0.3)	0 (0.0)	3 (0.3)	3 (0.3)	5 (0.5)		34 (0.4)	10 (0.4)	5 (0.2)	11 (0.5)	8 (0.4)	

Values are expressed as mean (standard deviation) or median (interquartile range) for continuous variables or as number (%) for categorical variables.
BF%, body fat percentage; BMI, body mass index; cIMT, carotid intima-media thickness; DBP, diastolic blood pressure; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; Q, quartile; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride
Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or receiving treatment for hypertension.
Diabetes was defined as non-fasting glucose ≥ 200 mg/dL and/or HbA1c ≥ 6.5% or receiving treatment for diabetes.
Dyslipidemia was defined as TG ≥ 150 mg/dL or HDL-C ＜40 mg/dL, and/or receiving treatment for dyslipidemia.
[a] *p* value for trend test for continuous variables and chi-square test for categorical variables.

Supplemental Table 2. Characteristics of participants according to FFMI

	Men	FFMI				*p* value[a]	Women	FFMI				*p* value[a]
		Q1 (< 17.0)	Q2 (17.0-18.0)	Q3 (18.1-18.9)	Q4 (≥ 18.9)			Q1 (< 14.5)	Q2 (14.5-15.1)	Q3 (15.2-16.0)	Q4 (≥ 16.0)	
Number	3,873	969	967	969	968		9,112	2,278	2,278	2,278	2,278	
Age, years	59.9 (14.1)	63.7 (14.3)	61.7 (13.4)	59.6 (13.4)	54.7 (13.6)	< 0.001	56.0 (13.5)	55.7 (14.0)	56.4 (13.5)	56.5 (13.4)	55.6 (13.2)	0.974
Height, cm	167.5 (6.3)	166.1 (6.5)	166.9 (6.3)	167.6 (6.1)	169.5 (6.0)	< 0.001	155.8 (5.8)	156.0 (5.7)	155.7 (5.9)	155.5 (5.7)	155.9 (5.9)	0.370
BMI, kg/m^2	23.8 (3.1)	21.0 (2.1)	22.9 (1.9)	24.2 (1.9)	26.9 (3.1)	< 0.001	22.3 (3.5)	19.5 (2.0)	21.2 (2.1)	22.8 (2.4)	25.8 (3.6)	< 0.001
BF%, %	23.7 (6.3)	22.6 (6.7)	23.3 (6.0)	23.7 (5.7)	25.1 (6.6)	< 0.001	30.7 (7.3)	28.5 (6.6)	29.5 (6.8)	31.0 (7.0)	33.8 (7.5)	< 0.001
FM, kg	16.2 (6.2)	13.4 (5.0)	15.1 (4.9)	16.4 (5.1)	19.9 (7.6)	< 0.001	17.1 (6.5)	13.7 (4.3)	15.4 (4.9)	17.4 (5.5)	21.8 (7.7)	< 0.001
FFM, kg	50.6 (6.4)	44.6 (4.0)	48.8 (3.7)	51.8 (3.9)	57.4 (5.3)	< 0.001	37.1 (4.0)	33.7 (2.7)	36.0 (2.8)	37.7 (2.8)	40.9 (3.8)	< 0.001
FMI, kg/m^2	5.5 (4.3-7.0)	4.7 (3.5-6.1)	5.3 (4.2-6.6)	5.7 (4.5-7.0)	6.7 (5.1-8.3)	-	6.7 (5.1-8.6)	5.6 (4.3-6.9)	6.2 (4.9-7.7)	7.0 (5.5-8.7)	8.8 (6.7-10.8)	-
FFMI, kg/m^2	18.0 (17.0-18.9)	16.3 (15.8-16.7)	17.5 (17.2-17.7)	18.4 (18.2-18.6)	19.7 (19.3-20.3)	-	15.2 (14.5-16.0)	13.9 (13.6-14.2)	14.8 (14.6-15.0)	15.5 (15.4-15.7)	16.6 (16.3-17.2)	-
cIMT, mm	0.65 (0.14)	0.65 (0.14)	0.65 (0.14)	0.65 (0.15)	0.64 (0.14)	0.108	0.60 (0.12)	0.58 (0.12)	0.59 (0.12)	0.60 (0.12)	0.61 (0.13)	< 0.001
SBP, mmHg	133.8 (16.1)	133.7 (17.5)	134.8 (16.7)	133.4 (15.2)	133.5 (14.7)	0.411	125.9 (17.8)	122.9 (17.6)	125.0 (17.9)	126.9 (18.0)	128.8 (17.4)	< 0.001
DBP, mmHg	80.9 (10.9)	78.6 (11.0)	81.1 (10.6)	81.1 (10.6)	82.9 (10.9)	< 0.001	76.5 (10.5)	74.6 (10.0)	75.8 (10.2)	76.9 (10.6)	78.7 (10.8)	< 0.001
Treatment for hypertension, %	1,109 (28.6)	247 (25.5)	275 (28.4)	295 (30.4)	292 (30.2)	< 0.001	1,567 (17.2)	272 (11.9)	328 (14.0)	422 (18.5)	545 (23.9)	< 0.001
Hypertension, %	2,059 (53.2)	490 (50.6)	516 (53.4)	518 (53.5)	535 (55.3)	0.224	3,076 (33.8)	598 (26.3)	691 (30.3)	812 (35.7)	975 (42.8)	< 0.001
Glucose, mg/dL	92.6 (21.0)	92.3 (22.3)	92.0 (19.2)	93.3 (21.0)	92.9 (21.3)	0.289	86.6 (14.7)	85.0 (13.7)	85.7 (13.0)	87.0 (14.8)	88.9 (16.6)	< 0.001
HbA1c, %	5.6 (0.6)	5.6 (0.7)	5.6 (0.5)	5.6 (0.6)	5.6 (0.6)	0.08	5.5 (0.5)	5.4 (0.4)	5.5 (0.4)	5.5 (0.4)	5.6 (0.6)	< 0.001
Treatment for diabetes, %	307 (7.9)	94 (9.7)	62 (6.4)	83 (8.6)	68 (7.0)	< 0.001	320 (3.5)	62 (2.7)	56 (2.5)	77 (3.4)	125 (5.5)	< 0.001
Diabetes, %	405 (10.5)	111 (11.5)	80 (8.3)	105 (10.8)	109 (11.3)	0.079	422 (4.6)	85 (3.7)	78 (3.4)	91 (4.0)	168 (7.4)	< 0.001
TC, mg/dL	201.2 (35.0)	199.8 (34.5)	200.6 (34.5)	202.0 (34.4)	202.4 (36.5)	0.074	212.1 (35.5)	214.0 (36.2)	212.8 (35.2)	211.7 (35.3)	210.0 (35.3)	< 0.001
TG, mg/dL	101.0 (72.0-149.0)	90.0 (65.0-131.0)	99.0 (71.0-140.0)	101.0 (74.0-149.0)	115.5 (80.0-176.0)	< 0.001	79.0 (58.0-112.0)	72.0 (54.0-98.0)	74.0 (56.0-105.0)	81.0 (58.0-114.0)	92.0 (64.0-133.0)	< 0.001
HDL-C, mg/dL	57.1 (15.1)	60.6 (15.7)	58.3 (14.7)	56.5 (14.6)	53.1 (14.4)	< 0.001	67.6 (16.3)	71.5 (16.3)	69.3 (15.9)	67.2 (15.9)	62.4 (15.7)	< 0.001
Treatment for dyslipidemia, %	413 (10.7)	89 (9.2)	91 (9.4)	102 (10.5)	131 (13.5)	< 0.001	1,025 (11.3)	200 (8.8)	243 (10.7)	281 (12.3)	301 (13.2)	< 0.001
Dyslipidemia, %	1,360 (35.1)	263 (27.1)	298 (30.8)	355 (36.6)	444 (45.9)	< 0.001	1,988 (21.8)	354 (15.5)	453 (19.9)	502 (22.0)	679 (29.8)	< 0.001

(Cont. Supplemental Table 2)

	Men	FFMI				*p* value[a]	Women	FFMI				*p* value[a]
		Q1 (< 17.0)	Q2 (17.0-18.0)	Q3 (18.1-18.9)	Q4 (≥ 18.9)			Q1 (< 14.5)	Q2 (14.5-15.1)	Q3 (15.2-16.0)	Q4 (≥ 16.0)	
History of cardiovascular disease, %												
Smoking status, %												
Never smoker	1,107 (28.6)	299 (30.9)	293 (30.3)	271 (28.0)	244 (25.2)	< 0.001	7,217 (78.7)	1,813 (79.6)	1,833 (80.5)	1,817 (79.8)	1,707 (74.9)	< 0.001
Ex-smoker	1,944 (59.2)	485 (50.1)	483 (50.0)	511 (52.7)	465 (48.0)		1,248 (13.6)	288 (12.6)	291 (12.8)	304 (13.4)	355 (15.6)	
Current smoker	811 (20.9)	181 (18.7)	189 (19.5)	186 (19.2)	255 (26.3)		672 (7.3)	172 (7.6)	143 (6.3)	152 (6.7)	203 (8.9)	
Unknown	11 (0.3)	4 (0.4)	2 (0.2)	1 (0.1)	4 (0.4)		34 (0.4)	5 (0.2)	11 (0.5)	5 (0.2)	13 (0.6)	

Values are expressed as mean (standard deviation) or median (interquartile range) for continuous variables or as number (%) for categorical variables.
BF%, body fat percentage; BMI, body mass index; cIMT, carotid intima-media thickness; DBP, diastolic blood pressure; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; Q, quartile; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride
Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or receiving treatment for hypertension.
Diabetes was defined as non-fasting glucose ≥ 200 mg/dL and/or HbA1c ≥ 6.5% or receiving treatment for diabetes.
Dyslipidemia was defined as TG ≥ 150 mg/dL or HDL-C < 40 mg/dL and/or receiving treatment for dyslipidemia.
[a] *p* value for trend test for continuous variables and chi-square test for categorical variables.

Supplemental Table 3. Association between FMI and cIMT

Men	Multivariable model		
Quartiles of FMI	LS meansc IMT (mm)	95% CI	*p* for trend
Q1 (lowest)	0.628	(0.609-0.647)	<0.001
Q2	0.641	(0.622-0.659)	
Q3	0.649	(0.631-0.668)	
Q4 (highest)	0.655	(0.637-0.674)	
p for ANCOVA	<0.001		
Women			
Q1 (lowest)	0.584	(0.575-0.592)	<0.001
Q2	0.590	(0.581-0.599)	
Q3	0.593	(0.585-0.602)	
Q4 (highest)	0.600	(0.591-0.609)	
p for ANCOVA	<0.001		

Adjusted for age (continuous), smoking status (never-smoker, ex-smoker, current smoker, and unknown).
p-values for the analysis of linear trends were calculated by scoring the FMI categories, from 1 for the lowest category to 4 for the highest category, entering the number as a continuous term in the regression model.
ANCOVA, analysis of covariance; CI, confidence interval; cIMT carotid intima-media thickness; FMI fat mass index; LS, least squares; Q, quartile

Supplemental Table 4. Association between FFMI and cIMT

Men	Multivariable model		
Quartiles of FFMI	LS means cIMT (mm)	95% CI	*p* for trend
Q1(lowest)	0.626	(0.607-0.644)	<0.001
Q2	0.637	(0.618-0.655)	
Q3	0.651	(0.632-0.669)	
Q4(highest)	0.667	(0.648-0.685)	
p for ANCOVA	<0.001		
Women			
Q1(lowest)	0.579	(0.570-0.588)	<0.001
Q2	0.586	(0.577-0.595)	
Q3	0.593	(0.584-0.602)	
Q4(highest)	0.606	(0.597-0.615)	
p for ANCOVA	<0.001		

Adjusted for age (continuous), smoking status (never-smoker, ex-smoker, current smoker, and unknown).
p-values for the analysis of linear trends were calculated by scoring the FFMI categories, from 1 for the lowest category to 4 for the highest category, entering the number as a continuous term in the regression model.
ANCOVA, analysis of covariance; CI, confidence interval; cIMT, carotid intima-media thickness; FFMI, fat-free mass index; LS, least squares; Q, quartile

Supplemental Table 5. Adjusted least square means of cIMT associated with FMI and FFMI among 20-39 years old

Men	FMIQ1	FMIQ2	FMIQ3	FMIQ4	*p* for linear trend among FFMI subgroups[a]
			LS means cIMT (mm), 95%CI		
FFMIQ1	0.473 (0.446-0.500)	0.465 (0.433-0.497)	0.478 (0.448-0.508)	0.490 (0.436-0.544)	0.467
FFMIQ2	0.510 (0.477-0.543)	0.471 (0.442-0.501)	0.485 (0.455-0.515)	0.472 (0.438-0.506)	0.084
FFMIQ3	0.494 (0.461-0.527)	0.494 (0.466-0.523)	0.483 (0.452-0.514)	0.510 (0.479-0.542)	0.367
FFMIQ4	0.524 (0.478-0.570)	0.507 (0.474-0.541)	0.497 (0.464-0.530)	0.515 (0.488-0.542)	0.924
p for linear trend among FMI subgroups[b]	0.001	0.013	0.417	0.027	
Women	**FMIQ1**	**FMIQ2**	**FMIQ3**	**FMIQ4**	***p* for linear trend among FFMI subgroups[a]**
			LS means cIMT (mm), 95%CI		
FFMIQ1	0.453 (0.435-0.470)	0.452 (0.434-0.471)	0.463 (0.432-0.468)	0.440 (0.414-0.467)	0.252
FFMIQ2	0.461 (0.443-0.479)	0.457 (0.439-0.475)	0.469 (0.445-0.481)	0.470 (0.447-0.492)	0.376
FFMIQ3	0.457 (0.438-0.476)	0.469 (0.440-0.477)	0.463 (0.451-0.488)	0.459 (0.441-0.478)	0.492
FFMIQ4	0.467 (0.442-0.492)	0.450 (0.448-0.491)	0.469 (0.444-0.482)	0.483 (0.467-0.499)	0.006
p for linear trend among FMI subgroups[b]	0.191	0.041	0.072	0.002	

Adjusted for age (continuous), smoking status (never-smoker, ex-smoker, current smoker, and unknown).
[b] *p*-values for the analysis of linear trends were calculated by stratifying FFMI, scoring the FMI categories, from 1 for the lowest category to 4 for the highest category, entering the number as a continuous term in the regression model.
[b] *p* values for the analysis of linear trends were calculated by stratifying FFMI, scoring the FMI categories, from 1 for the lowest category to 4 for the highest category, entering the number as a continuous term in the regression model.
ANCOVA, analysis of covariance; CI, confidence interval; cIMT, carotid intima-media thickness; FFMI, fat-free mass index; FMI, fat mass index; LS, least squares; Q, quartile

Supplemental Table 6. Adjusted least square means of cIMT associated with FMI and FFMI among 40-74 years old

Men	FMIQ1	FMIQ2	FMIQ3	FMIQ4	*p* for linear trend among FFMI subgroups[a]
			LS means cIMT (mm), 95%CI		
FFMIQ1	0.619 (0.592-0.647)	0.642 (0.613-0.671)	0.634 (0.604-0.664)	0.648 (0.612-0.683)	0.066
FFMIQ2	0.638 (0.609-0.667)	0.641 (0.613-0.670)	0.660 (0.630-0.690)	0.632 (0.601-0.663)	0.777
FFMIQ3	0.645 (0.614-0.675)	0.652 (0.623-0.682)	0.66 (0.632-0.688)	0.662 (0.632-0.692)	0.158
FFMIQ4	0.633 (0.598-0.668)	0.673 (0.642-0.705)	0.674 (0.645-0.704)	0.685 (0.659-0.712)	0.001
p for linear trend among FMI subgroups[b]	0.038	0.025	0.005	<0.001	
Women	**FMIQ1**	**FMIQ2**	**FMIQ3**	**FMIQ4**	***p* for linear trend among FFMI subgroups[a]**
			LS means cIMT (mm), 95%CI		
FFMIQ1	0.593 (0.582-0.605)	0.590 (0.578-0.602)	0.596 (0.583-0.609)	0.575 (0.555-0.595)	0.359
FFMIQ2	0.595 (0.583-0.607)	0.599 (0.587-0.611)	0.606 (0.593-0.618)	0.602 (0.587-0.616)	0.061
FFMIQ3	0.600 (0.587-0.614)	0.613 (0.600-0.626)	0.609 (0.597-0.621)	0.606 (0.593-0.618)	0.923
FFMIQ4	0.613 (0.597-0.628)	0.617 (0.600-0.631)	0.620 (0.607-0.633)	0.624 (0.613-0.635)	0.104
p for linear trend among FMI subgroups[b]	0.008	<0.001	0.001	<0.001	

Adjusted for age (continuous), smoking status (never-smoker, ex-smoker, current smoker, and unknown).
[b] *p*-values for the analysis of linear trends were calculated by stratifying FFMI, scoring the FMI categories, from 1 for the lowest category to 4 for the highest category, entering the number as a continuous term in the regression model.
[b] *p* values for the analysis of linear trends were calculated by stratifying FFMI, scoring the FMI categories, from 1 for the lowest category to 4 for the highest category, entering the number as a continuous term in the regression model.
ANCOVA, analysis of covariance; CI, confidence interval; cIMT, carotid intima-media thickness; FFMI, fat-free mass index; FMI, fat mass index; LS, least squares; Q, quartile

Supplemental Table 7. Adjusted least square means of cIMT associated with FMI and FFMI among 75 years or older

Men	FMIQ1	FMIQ2	FMIQ3	FMIQ4	*p* for linear trend among FFMI subgroups[a]
	LS means cIMT (mm), 95%CI				
FFMIQ1	0.756 (0.700-0.811)	0.771 (0.699-0.844)	0.758 (0.692-0.824)	0.733 (0.660-0.806)	0.680
FFMIQ2	0.767 (0.701-0.834)	0.782 (0.724-0.840)	0.690 (0.631-0.749)	0.745 (0.675-0.815)	0.112
FFMIQ3	0.794 (0.728-0.860)	0.774 (0.711-0.837)	0.789 (0.729-0.850)	0.754 (0.688-0.819)	0.406
FFMIQ4	0.770 (0.689-0.851)	0.806 (0.738-0.875)	0.766 (0.702-0.830)	0.821 (0.764-0.879)	0.224
p for linear trend among FMI subgroups[b]	0.400	0.535	0.199	0.019	
Women	**FMIQ1**	**FMIQ2**	**FMIQ3**	**FMIQ4**	***p* for linear trend among FFMI subgroups[a]**
	LS means cIMT (mm), 95%CI				
FFMIQ1	0.744 (0.683-0.806)	0.759 (0.690-0.824)	0.725 (0.651-0.799)	0.707 (0.629-0.786)	0.258
FFMIQ2	0.768 (0.698-0.838)	0.737 (0.668-0.806)	0.754 (0.688-0.820)	0.760 (0.685-0.836)	0.938
FFMIQ3	0.779 (0.710-0.848)	0.763 (0.692-0.834)	0.750 (0.683-0.817)	0.734 (0.666-0.802)	0.253
FFMIQ4	0.791 (0.710-0.873)	0.777 (0.705-0.849)	0.748 (0.676-0.819)	0.757 (0.693-0.820)	0.275
p for linear trend among FMI subgroups[b]	0.126	0.461	0.745	0.247	

Adjusted for age (continuous), smoking status (never-smoker, ex-smoker, current smoker, and unknown).
[b]*p*-values for the analysis of linear trends were calculated by stratifying FFMI, scoring the FMI categories, from 1 for the lowest category to 4 for the highest category, entering the number as a continuous term in the regression model.
[b]*p* values for the analysis of linear trends were calculated by stratifying FFMI, scoring the FMI categories, from 1 for the lowest category to 4 for the highest category, entering the number as a continuous term in the regression model.
ANCOVA, analysis of covariance; CI, confidence interval; cIMT, carotid intima-media thickness; FFMI, fat-free mass index; FMI, fat mass index; LS, least squares; Q, quartile

Supplemental Table 8. Adjusted least square means of cIMT associated with FMI and FFMIT excluding treatment for hypertension, diabetes, dyslipidemia, and participants with history of cardiovascular disease

Men	FMIQ1	FMIQ2	FMIQ3	FMIQ4	*p* for linear trend among FFMI subgroups[a]
	LS means cIMT (mm), 95%CI				
FFMIQ1	0.594 (0.574-0.615)	0.602 (0.579-0.626)	0.598 (0.574-0.622)	0.602 (0.573-0.631)	0.610
FFMIQ2	0.613 (0.590-0.637)	0.610 (0.588-0.632)	0.624 (0.602-0.647)	0.609 (0.584-0.635)	0.768
FFMIQ3	0.622 (0.597-0.647)	0.621 (0.598-0.644)	0.628 (0.606-0.650)	0.645 (0.622-0.668)	0.102
FFMIQ4	0.618 (0.591-0.646)	0.638 (0.612-0.663)	0.630 (0.606-0.654)	0.655 (0.635-0.675)	0.002
p for linear trend among FMI subgroups[b]	0.011	0.007	0.023	$<$0.001	
Women	**FMIQ1**	**FMIQ2**	**FMIQ3**	**FMIQ4**	***p* for linear trend among FFMI subgroups[a]**
	LS means cIMT (mm), 95%CI				
FFMIQ1	0.560 (0.549-0.571)	0.557 (0.545-0.569)	0.556 (0.544-0.568)	0.557 (0.539-0.574)	0.436
FFMIQ2	0.562 (0.551-0.574)	0.567 (0.556-0.579)	0.572 (0.560-0.584)	0.570 (0.556-0.583)	0.052
FFMIQ3	0.565 (0.553-0.578)	0.574 (0.562-0.586)	0.575 (0.563-0.587)	0.575 (0.563-0.586)	0.291
FFMIQ4	0.570 (0.554-0.585)	0.576 (0.563-0.589)	0.583 (0.571-0.595)	0.588 (0.577-0.598)	0.004
p for linear trend among FMI subgroups[b]	0.104	$<$0.001	$<$0.001	$<$0.001	

Adjusted for age (continuous), smoking status (never-smoker, ex-smoker, current smoker, and unknown).
[b]*p*-values for the analysis of linear trends were calculated by stratifying FFMI, scoring the FMI categories, from 1 for the lowest category to 4 for the highest category, entering the number as a continuous term in the regression model.
[b]*p* values for the analysis of linear trends were calculated by stratifying FFMI, scoring the FMI categories, from 1 for the lowest category to 4 for the highest category, entering the number as a continuous term in the regression model.
ANCOVA, analysis of covariance; CI, confidence interval; cIMT, carotid intima-media thickness; FFMI, fat-free mass index; FMI, fat mass index; LS, least squares; Q, quartile