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The relationship between insulin resistance and vascular calcification in coronary arteries, and the thoracic and abdominal aorta: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—Insulin resistance may be related to vascular calcification as both are associated with abdominal obesity. We investigated the association of insulin resistance with abdominal aortic calcium (AAC), coronary artery calcium (CAC) and thoracic aortic calcium (TAC), and whether it differs according to different levels of subcutaneous fat area (SFA) and visceral fat area (VFA) in a cross-sectional study design.

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Disclosures
None.

Methods—We investigated 1632 participants without diabetes from the Multi-Ethnic Study of Atherosclerosis with valid data on homeostasis model assessment index (HOMA-IR), AAC, CAC, and TAC. Adipocytokines, SFA, and VFA were also determined.

Results—HOMA-IR was associated with the presence of CAC, but not AAC and TAC, and the association remained significant after adjusting for traditional risk factors, adipocytokines, abdominal muscle mass, SFA, and VFA (prevalence ratio=1.04 per one interquartile range [IQR] increase, *P*=0.01). As the strength of the association of HOMA-IR with vascular calcification may differ by abdominal fat composition, subgroup analysis was performed among participants with different tertiles of SFA and VFA. Significant interactions between HOMA-IR with SFA and VFA separately were observed for the presence of TAC, but not AAC and CAC, even after adjusting for confounding factors. The association of HOMA-IR with TAC tended to be stronger in participants with more SFA and VFA.

Conclusions—Atherosclerotic calcification, especially in the coronary arteries, is related to insulin resistance. Further studies are needed to delineate the mechanisms by which visceral obesity can lead to vascular calcification.

Keywords

adipocytokines; body composition; calcium; insulin resistance; vascular calcification

1. Introduction

Excess adipose tissue is a cardiovascular disease (CVD) risk factor and is one of the main driving forces for the metabolic syndrome. In addition to its role in lipid storage and mobilization, adipose tissue is an endocrine organ [1] and excess adiposity is associated with dysregulated secretion of adipocytokines including IL-6, adiponectin, resistin, and leptin [2], which may lead to insulin resistance [3]. Abdominal adiposity can be classified by computed tomography (CT) into two primary components, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). SAT and VAT produce and secrete different adipocytokines at different levels [4].

Previous studies show conflicting results on the association of insulin resistance associated with coronary artery calcification in asymptomatic individuals with both positive [5–8] and negative findings [9]. As adipose tissue and adipocytokines play an important role in insulin resistance, they may confound the association between insulin resistance and vascular calcification, and may explain the discrepancy of the previous reports. In addition to the coronary arteries, calcium can also deposit in arteries of other vascular beds during the chronic inflammatory process of atherosclerosis development [10–12]. As calcification in different vascular beds could be developed at similar extent and time frame in a systemic manner [13], insulin resistance may be more closely related to systemic calcification in several vascular beds than to calcification in different individual vascular beds. In this study, we investigated the association of insulin resistance with the prevalence and extent of calcified atherosclerosis in the coronary arteries, and thoracic and abdominal aorta as well as their combination, and whether this association was independent of adipocytokines, inflammation biomarkers, abdominal muscle mass, subcutaneous fat area (SFA) and visceral

fat area (VFA) in a cross-sectional study design. We also investigated whether the strength of such association would differ according to levels of SFA and VFA.

2. Methods

2.1. Participants

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal cohort, consisting of 6814 men and women in four major ethnic groups, non-Hispanic whites, African American, Hispanic American, and Chinese Americans. All participants were between 45 and 84 years of age and free of clinically apparent CVD at baseline. Participants were examined approximately 2, 4, 6, and 8 years after the baseline clinical visit. The study was approved by the institutional review boards at all participating centers and informed written consent was obtained from all participants. Details of the study objectives, design, and protocol have been described previously [14].

At either visit 2 or 3 (from 2002–2005), all the MESA participants underwent CT scans of the chest for coronary artery calcium (CAC) and thoracic aortic calcium (TAC), whereas a random subsample of 1974 participants underwent abdominal CT scanning for an ancillary study to determine the presence and extent of calcified atherosclerosis in the abdominal aorta. These CT scans were later interrogated for abdominal body composition [15–17] and these participants also had circulating levels of adipocytokines measured from stored blood samples. Among these 1974 participants, 1910 participants have valid data in all the markers of subclinical calcified atherosclerosis, i.e. CAC, TAC, and abdominal aortic calcium (AAC); 1635 of them did not have prevalent diabetes (defined as fasting glucose <7.0 mmol/l and not taking glucose-lowering medications). After excluding 3 participants with missing data on insulin resistance, a total of 1632 participants were included in this analysis.

2.2. Vascular calcification and body fat composition

The calcium measurements (i.e. CAC and TAC) were derived from CT scans as described previously [16–21]. Briefly, all the MESA participants underwent CT scans of the chest for CAC and TAC using either an electron-beam CT scanner at 3 field centers or a multidetector row helical CT scanner at the other 3 field centers. Participants were scanned twice consecutively at the same visit at one of the field centers, and these scans were read independently at a centralized reading center using a standard protocol. The average of the results of the two scans was used to provide a more accurate estimate of the amount of calcium present. For all calcium measurements, calcification was identified as a plaque of ≥1 mm^2 with a density of ≥130 Hounsfield units (HU) and quantified using the previously described Agatston scoring method [22].

Using the abdominal CT scans obtained for determining the presence and extent of calcified atherosclerosis in the abdominal aorta (AAC), body composition of the abdomen was assessed using Medical Imaging Processing Analysis and Visualization (MIPAV) software version 4.1.2, that produced areas of subcutaneous and visceral fat, measured in square centimeters [19]. For each participant, a transverse cross section slice at the L4/L5 vertebral

junction was analyzed. Fat tissue was identified as having a density between -190 and -30 HU. Lean muscle mass was identified as a density between 0 and 100 HU.

2.3. Laboratory assessment

At visits 2 and 3, venous blood was collected after a 12-hour fast, then shipped to the MESA central laboratory for the measurement of total cholesterol, high-density lipoprotein (HDL) cholesterol and glucose levels. Dyslipidemia was defined as a total cholesterol to HDL cholesterol ratio >5.0 or the use of any lipid-lowering medication. Fasting blood was also used for the measurement of insulin levels and the inflammation markers C-reactive protein (CRP), fibrinogen and IL-6 as described previously [15, 17]. Circulating levels of adiponectin, leptin, TNF-α, and resistin were measured in stored fasting blood samples from visits 2 and 3 using Bio-Rad Luminex flow cytometry (Millepore, Billerica, MA) [15].

2.4. Other variables of interest

Information on age, ethnicity, education, smoking, alcohol use, total gross family income, family history of CVD, physical activity, and medication use for hypertension, hypercholesterolemia and diabetes were obtained using standardized questionnaires from either visit 2 or 3, which was contemporaneous with the measurement of body composition and adipocytokines. However, data on education and family history of CVD were obtained from the baseline visit and visit 2 respectively. Participants wore light clothing and no shoes when measuring height and weight. Body mass index (BMI) was measured as the weight in kilograms divided by height in meters squared. A standard flexible tape measure was used to measure hip and waist circumferences. Resting blood pressure (BP) was measured three times in a seated position and the average of the last two BP readings was used in the analysis. Hypertension was defined as BP≥140/90 mmHg. Participants who had previous diagnosis of hypertension and took anti-hypertensive medications were defined as hypertensive. Physical activity was measured as the total number of hours of moderate and vigorous activities per week, multiplied by metabolic equivalent (MET) level as described elsewhere [18].

2.5. Statistical Analysis

Data analysis was performed using SPSS (version 21, IBM, Armonk, NY, USA) or STATA (version 12.1, StataCorp, College Station, TX, USA). Data were presented as mean (SD) or percentage. For variables with a skewed distribution, data were presented as median (interquartile range [IQR]). Insulin resistance was estimated using the homeostasis model assessment index (HOMA-IR), according to the updated computer model as described previously [23]. In a separate analysis, similar results were obtained using the traditional formula for HOMA-IR, i.e. fasting insulin (mU/l)×glucose (mmol/l) / 22.5) [24] (data not shown). Distributions of demographic data, cardiovascular risk factors, adipocytokine levels, inflammation biomarkers, body composition, AAC, CAC, and TAC were compared across insulin resistance groups (i.e. HOMA-IR quartiles) among all the participants using one-way ANOVA or chi-square tests, where appropriate. Variables that showed significant increasing or decreasing trend with insulin resistance were used as covariates in subsequent multiple regression analysis.

For the association of HOMA-IR with atherosclerotic calcification, AAC, CAC, and TAC were first assessed as categorical variables (zero score versus non-zero score). As there was a high prevalence of calcification in the cohort, odds ratios from logistic regression did not approximate the relative risk. Therefore, prevalence ratios (PR) were presented from the general linear regression model $y = \exp(X^{T\beta})$ [16, 18–21]. We assumed Gaussian error and used robust standard error estimates. In a separate analysis, the association of HOMA-IR with increasing increments of AAC, CAC, and TAC (categories: 0, first tertile, second tertile, and third tertile) was also assessed using ordinal logistic regression [16]. We also assessed the combination of AAC, CAC, and TAC to investigate whether HOMA-IR would be associated with more systemic disease. In all the regression analyses, similar results were obtained when BMI was replaced by height and waist-to-hip ratio in the adjusted models (data not shown). For the interaction test, the *P* values for interactions were estimated by including the multiplicative interaction term in the multivariable regression models in full sample after adjusting for the main effects of the covariates and the categorical subgroup variable.

3. Results

Table 1 shows participant characteristics according to the levels of insulin resistance as measured by HOMA-IR. Participants with higher HOMA-IR were more likely to be Hispanic American, hypertensive, users of lipid lowering medications, and have higher BMI, waist-to-hip ratio, BP, heart rate and triglycerides, but less likely to be non-Hispanic White, Chinese American or current alcohol user, as well as having lower education, gross family income and HDL cholesterol. Fibrinogen, CRP, resistin, leptin, IL-6, TNF-α, abdominal muscle mass, SFA, and VFA were all higher with increasing quartiles of HOMA-IR, while adiponectin was lower (Table 1).

As shown in Figure 1A and Supplemental Table 1, the percentage of participants with a non-zero score of AAC or CAC tended to be greater in participants with higher HOMA-IR (*P*=0.007 and 0.008 respectively), while TAC did not differ by HOMA-IR levels (*P*=0.67). In multivariable general linear model analysis (Table 2), the association of HOMA-IR with the presence of CAC remained significant after adjusting for traditional cardiovascular risk factors, adipocytokines, inflammation biomarkers, abdominal muscle mass, SFA, and VFA (PR=1.04, *P*=0.01). The association of HOMA-IR with the presence of AAC was of borderline significance in the full adjustment model (PR=1.03, *P*=0.07). No significant association was found with the presence of TAC (*P*=0.52). When assessing the association of HOMA-IR with the presence of AAC, CAC and TAC at the same time, no significant association was found (Fig. 1A and Supplementary Table S1).

Among participants with a non-zero calcium score in the coronaries, abdominal aorta or thoracic aorta, there was no significant trend in the extent of calcified atherosclerosis in these three vascular beds with HOMA-IR (Fig. 1B and Supplementary Table S1). There was also no significant association of HOMA-IR with increasing increments of AAC, CAC, TAC, and their sum scores in ordinal logistic regression (Supplementary Table S2).

As shown in Table 3, when subgroup analysis was performed according to the tertiles of SFA and VFA, the association of HOMA-IR with the presence of TAC was stronger in participants with more SFA and VFA, after adjustment for confounding factors (*P* for interaction <0.001 and =0.034 respectively). By contrast, there was no significant interaction of HOMA-IR with either SFA or VFA for the presence of AAC or CAC in the fully adjusted models (Table 3). When assessing the combination of AAC, CAC and TAC, similar trends to TAC were found, in which the association of HOMA-IR with the combination tended to be stronger in participants with more SFA even in the fully adjusted models (Supplementary Table S3). No significant interaction was found with sex (data not shown).

4. Discussion

Calcified atherosclerosis in several vascular beds, especially the coronary arteries, can predict incident cardiovascular events [25]. This study investigated the association of insulin resistance with the prevalence and extent of calcified atherosclerosis in the coronary, thoracic aortic and abdominal aortic beds. Insulin resistance was associated with the presence, but not extent of calcified atherosclerosis, especially in the coronary and abdominal aortic vascular beds. The association of insulin resistance with calcified atherosclerosis was modified by abdominal fat composition in some cases.

A previous study using MESA data at baseline showed that insulin resistance is associated with the presence of CAC, but the association was attenuated after adjusting for other traditional cardiovascular risk factors [9]. A similar result was obtained in the present study, where a modest association between insulin resistance and vascular calcification, was observed. Moreover, there was no relationship between insulin resistance and the severity of vascular calcification. Compared to this previous study, the present study has the advantage of having data on adipocytokines, inflammation biomarkers, and body fat composition at the visit 2 or 3 of the MESA study. Moreover, we also assessed AAC and TAC in addition to CAC, and their combination to investigate whether HOMA-IR would be associated with more systemic disease. Our analysis showed that the modest association between insulin resistance and CAC was independent of adipocytokines, inflammation biomarkers and abdominal fat composition. In fact, among several metabolic markers in the Study of Inherited Risk of Coronary Atherosclerosis, leptin and HOMA-IR showed the most robust association with CAC after adjusting for different traditional cardiovascular risk factors [8]. In our study, the association of HOMA-IR with vascular calcification tended to be attenuated after further adjusting for abdominal fat composition, suggesting that the association was confounded or mediated by abdominal obesity. Abdominal obesity is a risk factor for vascular calcification [26, 27]. In obesity, excess adipose tissue and macrophage infiltration in adipose tissue can cause dysregulated secretion of adipocytokines such as decreased adiponectin levels and increased IL-6 levels, leading to insulin resistance and chronic inflammation [1, 2], which is usually involved in the pathogenesis of atherosclerosis. Interestingly, the association of adipocytokines and related inflammatory biomarkers such as IL-6 and fibrinogen with CAC is stronger in individuals with abdominal obesity [28]. Beside altered adipocytokine secretion, obesity can also impair insulin signaling and glucose homeostasis by intracellular fat deposition and infiltration of fat into the pancreatic islet cells, leading to insulin resistance [29]. Moreover, abdominal obesity is

often associated with altered free fatty acid metabolism and deposition of ectopic fat such as epicardial fat, which can contribute to the pathogenesis of calcified atherosclerosis through a paracrine pathway [30]. Abdominal obesity is also associated with other CVD risk factors such as dyslipidemia, altered cardiac hemodynamics, endothelial dysfunction, and systemic oxidative stress which are involved in the pathogenesis of calcified coronary atherosclerosis [29].

Our findings on TAC among all participants are consistent with an earlier MESA study using data at baseline, which showed no significant association between HOMA-IR and extra-coronary calcification including TAC [31]. However, AAC was not studied in the previous study, nor was the impact of adjustment for adipocytokines and abdominal fat composition. In this study, the association of HOMA-IR with the presence of TAC tended to be stronger in participants with more subcutaneous or visceral fat. In a study of 650 asymptomatic subjects recruited from a university-affiliated disease prevention center, TAC may represent more advanced atherosclerotic disease as individuals with TAC are more likely to have calcification in other vascular beds, compared to individuals with CAC [13]. Therefore, the presence of TAC may represent a more systemic disease condition and hence is more likely to show significant results in subgroup analysis by abdominal fat composition. Individuals with more subcutaneous or visceral fat may have more severe dysregulation of different adipocytokines and other related inflammation biomarkers, leading to stronger association between insulin resistance and calcified atherosclerosis. In fact, previous studies have reported the association of abdominal fat with vascular calcification, especially for TAC [26]. However, in our study, the interaction with VFA and SFA was independent of circulating levels of adipocytokines, other inflammation biomarkers, and abdominal muscle mass. Therefore, the effect of abdominal fat composition on the strength of the association between insulin resistance and calcified atherosclerosis is likely driven by as yet unidentified factors that are distinct from adipocytokines and inflammation biomarkers. As insulin resistance is the central feature of the metabolic syndrome and is associated with other CVD risk factor [32], it may increase the risk of vascular calcification by exacerbating other traditional CVD risk factors. Moreover, individuals with more SFA and VFA are more likely to have more fat deposited in other tissues such as epicardial fat, which has also been shown to be associated with vascular calcification [33]. Further studies are needed to identify the underlying mechanism for the effect of abdominal fat composition on the strength of the association between insulin resistance and vascular calcification observed in this study.

Our study has the advantages of making use of data from the MESA cohort with a good study design and quality control, a large well-characterized sample, standardized assessments of vascular calcium and body composition, and availability of data on several important adipocytokines. However, there are also several limitations in our study. The cross-sectional study design limits inferences on causality. As all MESA participants were free of clinically apparent CVD at baseline, there may be some participants with undiagnosed CVD and the prevalence of AAC, CAC and TAC in this study may be lower than the general population. However, the use of screening for calcified atherosclerosis in those who have a history of clinical CVD is likely not indicated, as these individuals will be, by definition, at high risk and treated accordingly. The association of insulin resistance with

calcified atherosclerosis was modest, and we can not exclude residual confounding due to misclassification and imperfect ascertainment of risk factors. HOMA-IR is only an estimation of insulin resistance. The use of more direct measures of insulin resistance, such as hyperinsulinemic euglycemic clamp is better than the use of HOMA-IR.

5. Conclusion

We observed a modest association of insulin resistance with the presence but not extent of calcified atherosclerosis, especially in the coronary aortic beds. As the association was independent of adipocytokines, inflammation biomarkers and abdominal fat composition, it is possible that vascular calcification may not be the main mechanism for insulin resistance to promote atherosclerosis. For TAC, the association tended to be stronger in participants with abdominal obesity. Further studies using prospective study design are needed to clarify these associations and their causal relationship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Insulin resistance is associated with CAC, but not AAC and TAC.
- The association of insulin resistance with vascular calcification is modest.
- Association of insulin resistance with TAC varies according to body fat composition.

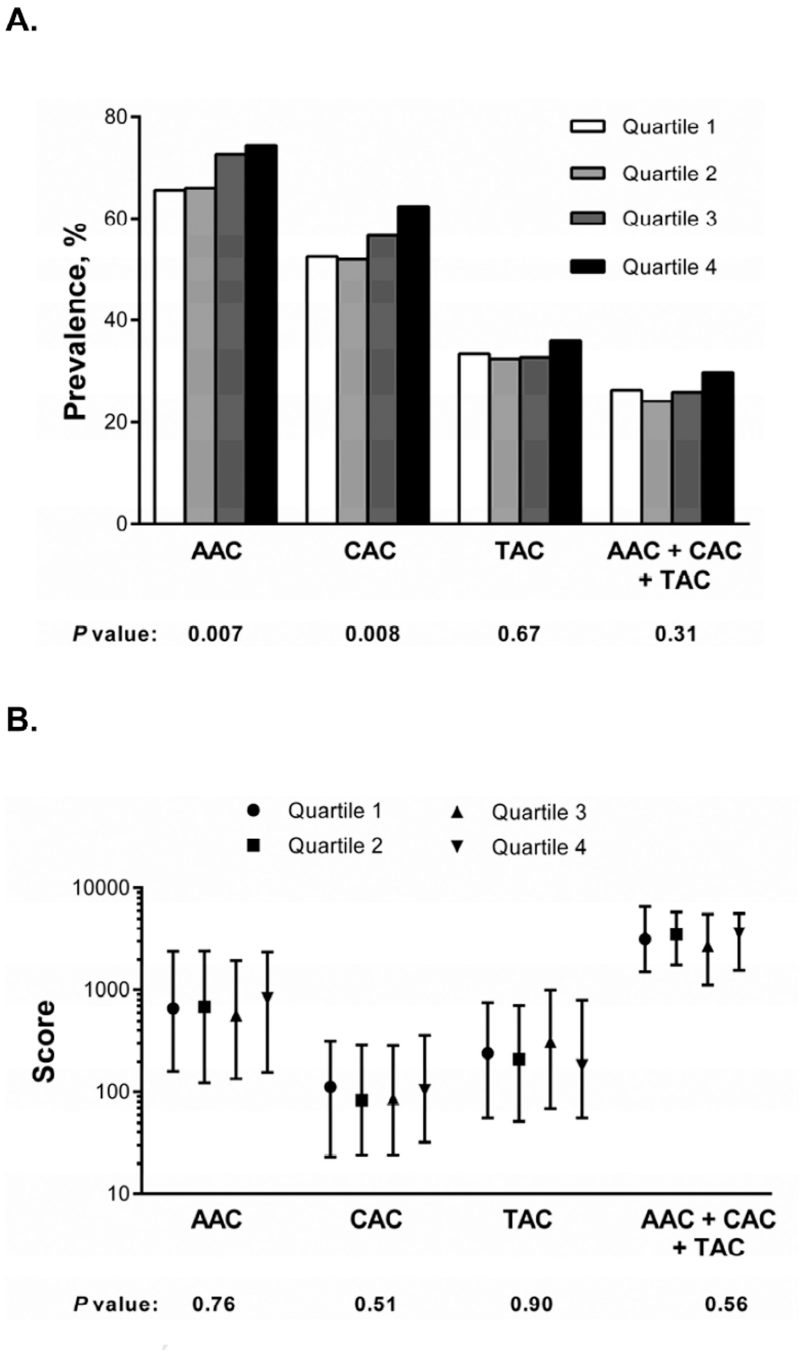

Fig. 1.

Association of calcium score with HOMA-IR. (A) Prevalence of AAC, CAC, and TAC according to quartiles of HOMA-IR. *P* values were estimated by chi-square test. (B) Median calcium score among participants with the indicated calcium score or the sum score >0 according to quartiles of HOMA-IR. Error bar indicates the interquartile range. *P* values were estimated by one-way ANOVA using log-transformed data.

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Table 1

Clinical characteristics of participants according to the levels of insulin resistance.

Characteristics	n	HOMA-IR				*P*
		Quartile 1 (n=414)	Quartile 2 (n=399)	Quartile 3 (n=402)	Quartile 4 (n=417)	
Age, years	1632	65.2 (10.2)	64.1 (9.8)	64.6 (9.8)	64.0 (9.0)	0.28
Women, %	1632	51.2 (212)	50.1 (200)	46.3 (186)	54.9 (229)	0.10
Ethnicity, %						<0.001
Caucasian	685	49.3 (204)	38.6 (154)	44.0 (177)	36.0 (150)	
Chinese-American	220	16.2 (67)	16.8 (67)	10.9 (44)	10.1 (42)	
African-American	335	20.8 (86)	18.5 (74)	20.6 (83)	22.1 (92)	
Hispanic	392	13.8 (57)	26.1 (104)	24.4 (98)	31.9 (133)	
Education[a], %						0.007
<High school	256	13.1 (54)	15.1 (60)	15.9 (64)	18.7 (78)	
High school	675	38.0 (157)	41.0 (163)	40.3 (162)	46.3 (193)	
>High school	699	48.9 (202)	44.0 (175)	43.8 (176)	35.0 (146)	
Smoking, %						0.11
Never	760	45.7 (188)	50.6 (200)	49.4 (198)	42.0 (174)	
Former	685	41.6 (171)	39.5 (156)	42.1 (169)	45.7 (189)	
Current	176	12.7 (52)	9.9 (39)	8.5 (34)	12.3 (51)	
Current alcohol use, %	1629	60.0 (248)	56.6 (226)	54.2 (218)	47.7 (198)	0.004
Total gross family income, %						0.04
<$50 000	894	52.7 (208)	56.8 (217)	58.7 (226)	61.1 (243)	
$50 000–$99999	402	25.8 (102)	24.6 (94)	105 (27.3)	101 (25.4)	
≥$100 000	264	21.5 (85)	18.6 (71)	14.0 (54)	13.6 (54)	
BMI, kg/m^2	1632	24.6 (3.6)	26.8 (4.4)	28.4 (4.4)	31.0 (5.1)	<0.001
Waist-to-hip ratio	1632	0.89 (0.07)	0.93 (0.07)	0.95 (0.07)	0.96 (0.07)	<0.001
Heart rate, beats per minute	1632	62.6 (9.6)	63.8 (9.7)	64.7 (9.5)	66.3 (10.1)	<0.001
Hypertension, %	1618	32.7 (134)	42.6 (169)	50.1 (200)	51.5 (212)	<0.001
Dyslipidemia, %	1593	20.0 (81)	33.0 (128)	44.0 (172)	48.2 (197)	<0.001
Family history of CVD[b], %	1622	11.7 (48)	13.4 (53)	16.2 (65)	18.4 (76)	0.04

Characteristics	n	HOMA-IR				*P*
		Quartile 1 (n=414)	**Quartile 2 (n=399)**	**Quartile 3 (n=402)**	**Quartile 4 (n=417)**	
Physical activity[c], MET-hours/weeks	1630	63.5 (35.5–118.5)	59.5 (33.3–97.6)	66.1 (36.8–114.7)	51.9 (27.4–97.2)	0.06
Fibrinogen[c], mg/dL	1632	404 (365–452)	419 (372–474)	431 (375–490)	437 (388–496)	<0.001
CRP[c], mg/L	1632	0.89 (0.47–2.00)	1.16 (0.61–2.63)	1.64 (0.85–3.61)	1.89 (0.98–4.28)	<0.001
Resistin[c], ng/mL	1632	14.3 (11.2–17.9)	14.6 (11.2–18.4)	15.3 (12.2–19.2)	15.2 (12.5–19.3)	0.002
Adiponectin[c], μg/mL	1632	23.5 (15.1–33.5)	19.5 (13.1–28.6)	16.5 (11.8–23.4)	14.5 (10.4–20.9)	<0.001
Leptin[c], ng/mL	1632	5.6 (2.4–12.6)	10.8 (4.7–22.6)	13.9 (7.0–28.2)	25.4 (13.5–42.5)	<0.001
IL-6[c], pg/mL	1599	1.5 (1.0–2.2)	1.7 (1.1–2.6)	1.9 (1.2–2.8)	2.2 (1.5–3.2)	<0.001
TNF-α[c], pg/mL	1631	4.0 (3.0–5.2)	4.4 (3.3–6.0)	4.8 (3.8–6.3)	5.0 (3.7–7.1)	<0.001
Abdominal muscle mass[c], cm^2	1586	130.0 (27.3)	137.7 (29.1)	144.0 (28.6)	148.5 (31.1)	<0.001
SFA[c], cm^2	1378	200.4 (89.4)	242.5 (107.9)	265.3 (116.1)	309.8 (125.0)	<0.001
VFA[c], cm^2	1601	99.5 (48.1)	132.0 (55.6)	159.4 (65.6)	178.5 (68.7)	<0.001

Data are expressed as mean (SD), percent (n), or median (IQR). For HOMA-IR, the cut-off values for quartile 1, 2, 3 and 4 are <0.50, 0.50–0.71, 0.71–1.00 and ≥1.01 respectively.

[a] self-reported at baseline.

[b] self-reported at visit 2.

[c] *P* values were estimated using log-transformed data.

Table 2

Association of HOMA-IR with the presence of AAC, CAC, and TAC in multivariable general linear model analysis.

	Model 1 PR (95% CI)	***P***	**Model 2 PR (95% CI)**	***P***	**Model 3 PR (95% CI)**	***P***	**Model 4 PR (95% CI)**	***P***
AAC	1.02 (1.01–1.02)	<0.001	1.01 (1.00–1.02)	0.008	1.04 (1.01–1.06)	0.006	1.03 (1.00–1.05)	0.07
CAC	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	<0.001	1.05 (1.02–1.08)	0.002	1.04 (1.01–1.08)	0.01
TAC	1.01 (1.00–1.03)	0.10	1.01 (0.99–1.03)	0.23	0.98 (0.91–1.07)	0.69	0.97 (0.90–1.05)	0.52
AAC + CAC + TAC	1.02 (1.00–1.04)	0.02	1.02 (1.00–1.04)	0.01	1.07 (1.02–1.13)	0.009	1.05 (0.98–1.14)	0.18

PR is expressed in terms of per IQR (i.e. 0.52 unit) increase in HOMA-IR.

Model 1: Adjusted for age, sex, and ethnicity.

Model 2: Further adjusted for BMI, education (<high school, high school, and >high school), current alcohol use, total gross family income (<$50 000, $50 000–99 999, and ≥$100 000), heart rate, hypertension, dyslipidemia, and family history of CVD.

Model 3: Further adjusted for fibrinogen, CRP, resistin, adiponectin, leptin, IL–6, and TNF-α.

Model 4: Further adjusted for abdominal muscle mass, SFA, and VFA.

Table 3

Association of HOMA-IR with of the presence of AAC, CAC, and TAC in multivariable general linear model analysis by tertiles of SFA and VFA.

	PR (95% CI)		
	AAC	**CAC**	**TAC**
SFA			
Tertile 1	1.01 (1.00–1.01)	1.02 (1.01–1.02)	1.00 (0.97–1.02)
Tertile 2	1.02 (0.97–1.07)	1.02 (0.96–1.09)	1.02 (0.94–1.10)
Tertile 3	1.00 (0.96–1.04)	1.04 (1.01–1.07)	1.11 (1.07–1.15)
P for interaction	0.86	0.13	<0.001
Adjusted *P* for interaction[a]	0.36	0.83	<0.001
VFA			
Tertile 1	0.98 (0.96–1.01)	1.02 (0.98–1.06)	1.01 (0.96–1.06)
Tertile 2	1.01 (1.01–1.02)	1.02 (1.01–1.02)	0.97 (0.90–1.06)
Tertile 3	1.04 (1.01–1.07)	1.04 (1.00–1.08)	1.09 (1.01–1.17)
P for interaction	0.10	0.05	0.21
Adjusted *P* for interaction[a]	0.92	0.51	0.03

PR is expressed in terms of per IQR (i.e. 0.52 unit) increase in HOMA-IR.

For SFA, the cut-off values for tertiles 1, 2, and 3 are <192.0, 192.0–278.9, and ≥279.0 cm^2 respectively.

For VFA, the cut-off values for tertiles 1, 2, and 3 are <105.4, 105.4–162.7, and ≥162.8 cm^2 respectively.

All data were adjusted for age, sex, ethnicity, BMI, education (<high school, high school, and >high school), current alcohol use, total gross family income (<$50 000, $50 000–99 999, and ≥$100 000), heart rate, hypertension, dyslipidemia, and family history of CVD.

P for interaction was further adjusted for the main effect of the subgroup categorical variable.

[a]Further adjusted for the main effects of fibrinogen, CRP, resistin, adiponectin, leptin, IL-6, TNF-α, and abdominal muscle mass (all as continuous variables in the adjustment model).