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Association Between Carotid Intima-Media Thickness and Pericardial Fat in the Multi-Ethnic Study of Atherosclerosis (MESA)

Elsayed Z. Soliman, MD, MSc, MS^a, Jingzhong Ding, MD, PhD^b, Fang-Chi Hsu, PhD^c, J. Jeffrey Carr, MD, MSCE^{a,d}, Joseph F. Polak, MD, MPH^e, and David C. Goff Jr, MD, PhD^{a,b}

^a Department of Epidemiology and Prevention, Wake Forest University School of Medicine

^b Department of Internal Medicine, Wake Forest University School of Medicine

^c Department of Biostatistical Sciences, Wake Forest University School of Medicine

^d Department of Radiologic Sciences, Wake Forest University School of Medicine

^e Department of Radiology, Tufts Medical Center, Tufts University

Abstract

Introduction—Carotid intima-media thickness (IMT) is a sub-clinical marker of atherosclerosis and a strong predictor of stroke. Pericardial fat (PF), the fat depot around the heart, has been associated with several atherosclerosis risk factors. We sought to examine the association between carotid IMT and PF, and to examine whether such an association is independent from common atherosclerosis risk factors including measures of overall adiposity.

Methods—Unadjusted and multivariable adjusted linear regression analysis was used to examine associations between common (CCA-IMT) and internal (ICA-IMT) carotid IMT with PF in a random sample of 996 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) who underwent carotid ultrasound and chest CT at baseline examination.

Results—A significant positive correlation was observed between PF and CCA-IMT ($r = 0.27$, $P < 0.0001$) and ICA-IMT ($r = 0.17$, $P < 0.0001$). In an unadjusted sex-specific linear regression analysis, there was a significant association between PF (1-SD difference) and CCA-IMT (mm) in both women (β coefficient (95% CI): 0.06 (0.04, 0.08), $P < 0.0001$) and men (0.03 (0.01, 0.05), $P < 0.0002$), an association that persisted after further adjusting for age and ethnicity (0.02 (+0.00, 0.04), $P = 0.0120$ for women, and 0.02 (+0.00, 0.03), $P = 0.0208$ for men). However, after additional adjustment for atherosclerosis risk factors and either BMI or waist circumference, these relations were no longer significant in either sex. In similar analyses, PF was significantly associated with ICA-IMT in both men (0.11 (0.06, 0.15), $P < 0.0001$) and women (0.08 (0.02, 0.13), $P = 0.041$). These relations were no longer significant in women in multivariable adjusted models, but persisted in men in all models except after adjusting for age, ethnicity and waist circumference.

Name and complete address for correspondence: Elsayed Z. Soliman MD, MSc, MS, Epidemiological Cardiology Research Center (EPICARE), Department of Epidemiology and Prevention, Wake Forest University School of Medicine, 2000 West First St., Piedmont Plaza 2, Suite 505, Winston Salem, NC 27104, Phone: (336) 716-8632 Fax: (336) 716-0834, E-mail esoliman@wfubmc.edu.

DISCLOSURES

None

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Conclusions—In the general population PF is associated with carotid IMT, an association that possibly not independent from markers of overall adiposity or common atherosclerosis risk factors.

BACKGROUND

Carotid intima-media thickness (IMT) is a well-established subclinical marker of atherosclerosis and a strong predictor of cerebrovascular events including stroke (1,2). Identification of associations with carotid IMT could help in risk stratification of patients at risk of cerebrovascular disease especially stroke. Pericardial fat (PF), the fat depot around the heart, has been associated with several atherosclerosis risk factors (3,4,5), thereby possibly playing a role in adiposity-related atherosclerosis and increased carotid IMT. PF also releases more inflammatory cytokines than subcutaneous fat (6), another marker linked to atherosclerosis (7). Recent community-based data are in support of the atherogenic effect of PF on coronary heart disease and its subclinical markers (3), but limited data on the PF effect of on cerebrovascular disease or its subclinical marker, IMT. The limited data from patient-based populations suggest a possible association between cardiac fat depot and carotid IMT (8). The purpose of this analysis is to examine the relationship between ultrasound measures of carotid IMT and computed tomography (CT) measures of PF volume in a community-based sample from the Multi-Ethnic Study of Atherosclerosis (MESA), and to assess whether these relations are independent from measures of overall adiposity and common atherosclerosis risk factors.

METHODS

Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a community-based cohort study of subclinical cardiovascular disease (CVD) and its progression. In 2000 through 2002, a total of 6814 whites, blacks, Hispanics and Chinese without existing clinical CVD, aged 45–84 years, were recruited from 6 states in the U.S. Participant characteristics have been described in detail elsewhere (9). This analysis was conducted on a randomly selected sub-cohort (MESA 1000), which was designed to be representative of the entire MESA cohort to carry out special studies including carotid ultrasound for measurement of IMT and chest CT for PF volume measurement. After exclusion of 4 participants with incomplete PF and/or IMT data, 996 participants were included.

Pericardial fat (PF) measurement

CT scans were performed either with an ECG-triggered (at 80% of the RR interval) electron-beam scanner (Chicago, Los Angeles, and New York field centers; Imatron C-150, Imatron) or with prospectively ECG-triggered scan acquisition at 50% of the RR interval with a multi-detector system that acquired 4 simultaneous 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode (Baltimore, Forsyth Country, and St. Paul field centers; Lightspeed, General Electric or Volume Zoom, Siemens) (10,11). Two experienced CT analysts measured PF volume on the previously obtained images of the heart. For PF volume, slices within 15 mm above and 30 mm below the superior extent of the left main coronary artery were included. This region of the heart was selected because it includes the PF located around the proximal coronary arteries (left main, left anterior descending, right coronary, and circumflex arteries). Volume analysis software (GE Healthcare, Waukesha, WI) was used to discern fat from other tissues with a threshold of –190 to –30 Hounsfield units. The volume was the sum of all voxels containing fat. The validity of PF measurement in this study was assessed in a random subset of 10 individuals from 80 participants from Diabetes Health Study (DHS) (10) who had PF measures using the conventional method of PF measurement which is considered as the “gold standard”. The PF volume was measured using the method described

above in those 10 individuals and then compared with the measure used in DHS. The two measures were highly correlated (Pearson correlation coefficient: 0.93; $P < 0.0001$). The reproducibility of the PF measure in this study has been also examined. A random sample of 10 MESA participants was selected and re-read by both CT analysts. The intraclass correlation coefficients for intrareader and inter-reader reliability were 0.999 and 0.997, respectively. Detailed description and validation of the PF measurement in this study have been published elsewhere (11,12,13)

Carotid intima-media thickness (IMT) measurement

The left and right carotid arteries (CAs) were examined at all centers using Logiq 700 ultrasound machine (General Electric Medical Systems). The imaging protocol involved obtaining a single longitudinal lateral view of each common carotid artery (CCA) and 3 longitudinal views in different imaging planes of each internal carotid artery (ICA). All studies were recorded on optical disk and super VHS videotape and sent weekly to a central ultrasound reading center located at the Department of Radiology, Tufts Medical Center, Tufts University. The high-resolution images of the CCAs and ICAs were analyzed to calculate near- and far-wall IMT, lumen diameter, and vessel width at each arterial site. All measurements of lumen and wall thickness were calculated with a specially designed computer program. For the purposes of this article, the terms IMT and wall thickness are used interchangeably. To quantify the degree of thickening of the carotid arteries walls, the many measures of IMT were summarized into two variables: one for the CCA and one for the ICA. The maximum wall thickness of the CCA was defined as the mean of the maximum wall thicknesses for near and far wall on both the left and right sides: $(mLNW+mLFW+mRNW+mRFW)/4$. The maximum wall-thickness variable of the ICA was defined in the same way with the results from the three scans averaged. The number of measurements available for averaging thus ranged from 1 to 4 for the CCA and 1 to 12 for the ICA. The MESA carotid sonography protocol has been previously tested in the Cardiovascular Health Study (14).

Risk factors and covariates assessment

Assessment of the demographic and clinical data including atherosclerosis risk factors was based on information collected at MESA baseline clinical exams. Body mass index (BMI) was calculated in kg/m^2 from measured height (m) and weight (kg). Waist circumference at the umbilicus was measured to the nearest 0.1 cm with a steel measuring tape (standard 4-oz tension). Resting seated blood pressure was measured 3 times using an automated oscillometric sphygmomanometer (DINAMAP PRO 100), and the average of the last 2 measurements was used for analysis. Hypertension (HTN) was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, self-reported history of hypertension, or current use of antihypertensive medications. Blood samples were obtained from participants after 8 hours of fasting and analyzed at a central laboratory for glucose and lipid profile. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dl, self-reported history of diabetes, or the use of diabetes medications. Impaired fasting glucose was defined as fasting glucose 110 to 125 mg/dl (15). The self-reported ethnicity was classified as whites (Caucasians) and non-whites (blacks, Hispanics and Chinese). Smoking status was defined as current, former or never.

Statistical analysis

CCA-IMT and ICA-IMT mean values were calculated across quartiles of PF levels, and a test of linear trend was performed. Linear regression analysis was used to assess the significance of unadjusted and covariate adjusted cross-sectional associations between PF (1-standard deviation (SD) difference) with carotid IMT. With the CCA-IMT and ICA-IMT, separately, as dependent variables, five sex-specific linear regression models were tested with the independent variables in the models as follows: Model 1: PF (unadjusted); Model 2: PF + age

+ ethnicity; Model 3: PF + age + ethnicity + hypertension + diabetes + total cholesterol + smoking status; Model 4: PF + age + ethnicity + body mass index; Model 5: PF + age + ethnicity + waist circumference. Similar models were created to test associations between BMI and waist circumference, separately, with carotid IMT. Other analyses included examining pair-wise interactions between PF, BMI and waist circumference, separately, with either ethnicity or sex to determine the need for a stratified regression analysis, examining models assumptions, and comparing the correlation and regression coefficients between groups when needed (16–18). A 2-tailed probability value <0.05 was considered significant. The Statistical Analysis System, SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina) was used to perform all computations.

RESULTS

Study population characteristics

Table 1 describes demographic and clinical characteristics of the study population. Our analysis included 996 MESA participants. The mean age was 59 years, 57% were women and 54% non-whites (21% blacks, 23% Hispanic, and 10% Chinese). Mean PF volume was 79.5 cm³ (SD 42.7), mean CCA-IMT was 0.86 mm (SD 0.18) and mean ICA-IMT was 1.02 mm (SD 0.53).

Common carotid artery IMT (CCA-IMT)

A statistically significant positive correlation was observed between PF and CCA-IMT. The Spearman correlation coefficient (r) was 0.27 ($P<0.0001$) in the entire study sample, 0.24 ($P<0.0001$) in women and 0.22 ($P<0.0001$) in men.

When PF volume was categorized into its quartiles (cut points: 50 cm³, 70 cm³, 98 cm³), the mean values of CCA-IMT across the PF quartiles were significantly greater with greater PF levels ($P<0.01$ for trend) (Figure 1).

There was a statistically significant interaction between sex and PF ($P=0.0281$), and between sex and BMI ($P=0.0353$); findings warranted stratifying our linear regression models by sex. No other statistically significant interactions detected.

Table 2 shows the sex-specific association between PF volume and CCA-IMT in a linear regression analysis. For comparison, the results of similar models for BMI and waist circumference are also shown in tables 3 and 4 respectively. Statistically significant associations between PF and CCA-IMT were observed in the unadjusted and in the age and ethnicity adjusted models (models 1 and 2). In the unadjusted model (model 1), these associations were significantly stronger in women than in men ($P<0.0001$ for β comparison), a difference that diminished after adjusting for age and ethnicity ($P=0.1815$ for β comparison). After additional adjustment for common risk factors for atherosclerosis (HTN, diabetes, total cholesterol, and smoking status), BMI or waist circumference, these relations were no longer significant in either sex. In contrast, the associations between BMI and waist circumference with CCA-IMT persisted in all models including those models adjusting for PF (Tables 3 and 4).

Internal carotid artery IMT (ICA-IMT)

In contrast to CCA-IMT, a weaker, yet statistically significant, positive correlation was observed between PF and ICA-IMT ($r=0.17$, $P<0.0001$) ($P=0.0006$ for r comparison). These differences between CCA-IMT and ICA-IMT persisted after stratifying the study sample by sex. In women, the correlation between PF and ICA-IMT ($r=0.11$, $P=0.0097$) was weaker than that between PF and CCA-IMT ($r=0.24$, $P<0.0001$) ($P<0.0001$ for r comparison).

Similarly, in men, the correlation between PF and ICA-IMT ($r=0.13$, $P=0.0080$) was weaker than that between PF and CCA-IMT ($r=0.22$, $P<0.0001$) ($P<0.0001$ for r comparison).

Similar to CCA-IMT, the mean ICA-IMT was significantly greater at greater PF levels ($P<0.0001$ for trend) (Figure 1).

Table 2 shows the sex-specific association between PF volume and ICA-IMT in a linear regression analysis. In unadjusted model (model 1), PF was significantly associated with ICA-IMT, with no significant difference in strength of the association between men and women ($P=0.1289$ for β comparison). However, the associations between PF and ICA-IMT were no longer significant in women in multivariable adjusted models, but persisted in men in all models except model 5 (age, ethnicity and waist circumference adjusted). As shown in tables 3 and 4, the associations between ICA-IMT with BMI and waist circumference were not as significant as those associations with CCA-IMT in most of the regression models.

DISCUSSION

There are two major findings of this study. First, in a community-based sample of multiethnic participants free of CVD, there was a weak to moderate unadjusted correlation between PF volume and carotid IMT ($r=0.27$ for CCA-IMT and 0.17 for ICA-IMT, $P<0.0001$ for both). These correlation coefficients are much less than the correlation coefficient ($r=0.92$, $P<0.01$) that has been reported between carotid IMT and cardiac fat depot in a patient-based sample (8). Such discordant results could be possibly explained by differences in populations studied and also by other methodological issues that warrant highlighting. We used CT measures of PF volume instead of echocardiography measures of PF thickness, which is one of the strengths of our study. Echocardiography is not the optimal technique for quantification of PF; CT is more sensitive and specific (18). Further, differences in the measurement of what could be defined as pericardial fat could be another factor for differences in the results.

The second major finding of this study is that the association between PF and carotid IMT was not independent from markers of overall adiposity or common risk factors for atherosclerosis. In our linear regression models, the association between PF and carotid IMT did not persist after adjusting for BMI, waist circumference or common risk factors for atherosclerosis. Noteworthy, BMI and waist circumference showed statistically significant associations with carotid IMT (especially CCA-IMT) either when combined or not combined with PF in similar regression models. Hence, it is unlikely that undetected collinearity between PF with BMI or waist circumference might have affected the statistical significance of all independent variables including PF, BMI and waist circumference. Nevertheless, we have noticed that the associations between PF, BMI and waist circumference with ICA-IMT were statistically weaker than those associations with CCA-IMT. This could be explained by the known unavoidable increased variability in ICA-IMT ultrasound measures and subsequently dilution of its relationships with the independent variables in our models. Measurement variability for ICA-IMT has been shown to be approximately three times greater than that for CCA-IMT (13). Anatomical and technical considerations play a major role in these variations. The ICA usually lies deeper in the neck and, at its origin, the walls are not parallel, and it does not lie parallel to the surface of the neck. On the other hand, CCA has straight walls, is superficial, and usually lies parallel to the surface of the skin. The CCA is easier to study, and its IMT measures are more reproducible than that of ICA (20). For these reasons several studies (6, 21, 22) used only CCA-IMT as a subclinical marker of atherosclerosis risk. Despite its increased measurement variability, ICA-IMT provides unique biological information as it is more linked to focal atherosclerotic disease such as plaque (20, 23). It may therefore be that the associations between PF and ICA-IMT are stronger in men compared to women (as noticed in Table 3),

because men inherently have more plaques than women of the same mean age. Examining the relations between PF and both CCA-IMT and ICA-IMT is another strength of this study.

We believe that our reported association between PF and atherosclerosis should be interpreted within the context of the mechanisms by which PF could be related to atherosclerosis. A *systemic* effect is the only plausible mechanism by which PF could have an effect on carotid IMT. Lack of independent association between PF and carotid IMT, in our study, means that PF might not have an independent *systemic* effect on atherosclerosis. On the other hand, additional local (and independent) atherogenic effects of PF on coronary atherosclerosis may exist, given the proximity between PF and coronary arteries. In another analysis from MESA, there was an association between PF and calcified coronary plaque (11).

Limitations

One of the common concerns regarding measures of adiposity (especially PF and BMI) is that these measures might have been biased by body morphometry. For example, individuals with large body surface area would have bigger hearts with more pericardial surface and subsequently more PF than individuals with less body surface area. In the same sense, tall individuals would have higher BMI, not necessary reflecting fat content. Hence, to exclude the possibility that differences in body morphometry did not bias the measures of PF and BMI in our study, which would subsequently bias our results and conclusions, we reran all the PF and BMI models after adjusting for body surface area and height respectively. The results of these additional analyses did not in any way change the conclusions we made regarding the significant but not independent association between PF and carotid IMT (results not shown).

Conclusion

In this multiethnic community-based study, PF is associated with carotid IMT, an association that is not independent from markers of overall adiposity or common risk factors for atherosclerosis. Therefore, PF measures seemed to have little additional value as a risk factor for atherosclerosis, as measured by IMT, beyond BMI and waist circumference.

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Figure 1. Mean Values of Carotid IMT across Pericardial Fat Quartiles*

*P value for trend; Q1 through Q4 refers to pericardial fat quartiles (cut points: 50 cm³, 70 cm³, 98 cm³); CCA, common carotid artery; ICA, internal carotid artery; IMT, intima-media thickness measured in mm

Table 1

Baseline Characteristics of the Study Population (N= 996)

Variable	Value(Mean $\pm$ SD or %)
Age (years)	59.4 $\pm$ 9.8
Women (%)	57.1
Ethnicity (%)	
White (Caucasian)	46.0
Chinese	9.9
Blacks	20.8
Hispanic	23.3
Hypertension (%)	40.9
Systolic blood pressure (mmHg)	123.9 $\pm$ 21.1
Diastolic blood pressure (mmHg)	71.3 $\pm$ 10.2
Diabetes status (%)	
Diabetes	11.5
Impaired fasting glucose	9.7
Fasting blood glucose (mg/dl)	94.4 $\pm$ 28.7
Body mass index (kg/m ²)	28.4 $\pm$ 5.6
Waist circumference (cm)	97.8 $\pm$ 14.7
Pericardial fat volume (cm ³)	79.5 $\pm$ 42.7
Common carotid intima-media thickness (CCA-IMT) (mm)	0.86 $\pm$ 0.18
Internal carotid intima-media thickness (ICA-IMT) (mm)	1.02 $\pm$ 0.53
Total cholesterol (mg/dl)	195.1 $\pm$ 35.4
High-density lipoprotein cholesterol (mg/dl)	51.1 $\pm$ 14.5
Low-density lipoprotein cholesterol (mg/dl)	117.3 $\pm$ 30.8
Triglycerides (mg/dl)	134.5 $\pm$ 93.5
Smoking status (%)	
Ever smoked	49.7
Current smokers	15.5

Table 2

Sex-Specific Unadjusted and Multivariable-adjusted Regressions (β Coefficient (95% Confidence Interval)) for 1-SD Difference in Pericardial Fat on Carotid Intima-media Thickness

	Model 1: unadjusted	Model 2: Age + ethnicity	Model 3: Age + ethnicity + hypertension, diabetes, total cholesterol and smoking status	Model 4: age + ethnicity++ body mass index	Model 5: age + ethnicity+ waist circumference
Women					
Common Carotid Intima-media Thickness (mm)	0.06 (0.04, 0.08) <i>P</i> < 0.0001	0.02 (+0.00, 0.04) <i>P</i> = 0.0120	0.01 (-0.01, 0.03) <i>P</i> = 0.2009	+0.00 (-0.02, 0.02) <i>P</i> = 0.7879	-0.00 (-0.02, 0.02) <i>P</i> = 0.7928
Internal Carotid Intima-media Thickness (mm)	0.08 (0.02, 0.13) <i>P</i> = 0.0041	-0.00 (-0.05, 0.05) <i>P</i> = 0.9838	-0.04 (-0.09, 0.01) <i>P</i> = 0.1467	-0.04 (-0.10, 0.02) <i>P</i> = 0.2400	-0.04 (-0.10, 0.02) <i>P</i> = 0.2288
Men					
Common Carotid Intima-media Thickness (CCA-IMT) (mm)	0.03 (0.01, 0.05) <i>P</i> = 0.0002	0.02 (+0.00, 0.03) <i>P</i> = 0.0208	0.01 (-0.00, 0.02) <i>P</i> = 0.2071	-0.01 (-0.03, 0.01) <i>P</i> = 0.2184	-0.01 (-0.03, 0.01) <i>P</i> = 0.1740
Internal Carotid Intima-media Thickness (mm)	0.11 (0.06, 0.15) <i>P</i> < 0.0001	0.07 (0.03, 0.12) <i>P</i> = 0.0012	0.05 (0.01, 0.10) <i>P</i> = 0.0177	0.06 (-0.00, 0.11) <i>P</i> = 0.0510	0.07 (0.01, 0.13) <i>P</i> = 0.0169

* Values are approximated to the nearest two decimal places. For values approximated to 0.00, a negative sign (-) indicates an original value < 0, a positive sign (+) indicates an original value > 0 and no sign indicates an original value = 0

Table 3

Sex-Specific Unadjusted and Multivariable-adjusted Regressions (β Coefficient (95% Confidence Interval)) for 1-SD Difference in Body Mass Index on Carotid Intima-media Thickness

	Model 1: unadjusted	Model 2: Age + ethnicity	Model 3: Age + ethnicity + hypertension diabetes, total, cholesterol and smoking status	Model 4: age + ethnicity+ pericardial fat
Women				
Common Carotid Intima-media Thickness (mm)	0.02 (+0.00, 0.03) <i>P</i> =0.0151	0.02 (0.01, 0.03) <i>P</i> <0.0001	0.02 (+0.00, 0.03) <i>P</i> =0.0069	0.02 (0.01, 0.03) <i>P</i> =0.0014
Internal Carotid Intima-media Thickness (mm)	0.01 (−0.03, 0.05) <i>P</i> =0.5853	0.03 (−0.00, 0.06) <i>P</i> =0.0901	+0.00 (−0.03, 0.04) <i>P</i> =0.7846	0.04 (+0.00, 0.08) <i>P</i> =0.0397
Men				
Common Carotid Intima-media Thickness (CCA-IMT) (mm)	0.04 (0.02, 0.07) <i>P</i> =0.0002	0.05 (0.03, 0.07) <i>P</i> <0.0001	0.04 (0.02, 0.06) <i>P</i> <0.0001	0.06 (0.04, 0.08) <i>P</i> <0.0001
Internal Carotid Intima-media Thickness (mm)	0.07 (0.01, 0.14) <i>P</i> =0.0306	0.09 (0.03, 0.15) <i>P</i> =0.0057	0.07 (+0.00, 0.13) <i>P</i> =0.0470	0.04 (−0.04, 0.12) <i>P</i> =0.3096

* Values are approximated to the nearest two decimal places. For values approximated to 0.00, a negative sign (−) indicates an original value < 0, a positive sign (+) indicates an original value > 0 and no sign indicates an original value = 0

Table 4

Sex-Specific Unadjusted and Multivariable-adjusted Regressions (β Coefficient (95% Confidence Interval)) for 1-SD Difference in Waist Circumference on Carotid Intima-media Thickness

	Model 1: unadjusted	Model 2: Age + ethnicity	Model 3: Age + ethnicity + hypertension, diabetes, total cholesterol and smoking status	Model 4: age + ethnicity+ pericardial fat
Women				
Common Carotid Intima-media Thickness (mm)	0.03 (0.02, 0.05) <i>P</i> <0.0001	0.03 (0.02, 0.04) <i>P</i> <0.0001	0.02 (0.01, 0.03) <i>P</i> =0.0008	0.03 (0.01, 0.04) <i>P</i> <0.0001
Internal Carotid Intima-media Thickness (mm)	0.04 (0.01, 0.08) <i>P</i> =0.0210	0.03 (−0.01, 0.06) <i>P</i> =0.1062	−0.00 (−0.04, 0.03) <i>P</i> =0.9355	0.04 (+0.00, 0.09) <i>P</i> =0.0446
Men				
Common Carotid Intima-media Thickness (CCA-IMT) (mm)	0.05 (0.03, 0.07) <i>P</i> <0.0001	0.05 (0.03, 0.07) <i>P</i> <0.0001	0.04 (0.02, 0.06) <i>P</i> <0.0001	0.06 (0.04, 0.08) <i>P</i> <0.0001
Internal Carotid Intima-media Thickness (mm)	0.09 (0.03, 0.16) <i>P</i> =0.0045	0.07 (0.01, 0.13) <i>P</i> =0.0174	0.05 (−0.01, 0.11) <i>P</i> =0.1329	0.01 (−0.06, 0.09) <i>P</i> =0.7277

* Values are approximated to the nearest two decimal places. For values approximated to 0.00, a negative sign (−) indicates an original value < 0, a positive sign (+) indicates an original value > 0 and no sign indicates an original value = 0