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Carotid Plaque Characterization, Stenosis, and Intima-Media Thickness According to Age and Gender in a Large Registry Cohort

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Abstract

Carotid intima-media thickness (CIMT) is a well-established predictor of cardiovascular disease events. Not well described, however, is the prevalence of plaque and stenosis severity and how this varies according to extent of CIMT, age, and gender. We evaluated the extent of carotid plaque and stenosis severity according to CIMT, age, and gender in a large CIMT screening registry. We studied 9,347 women and 12,676 men (n = 22,023) who received carotid ultrasound scans. The presence and severity of both carotid plaque and stenosis was compared according to extent of CIMT (≥1 mm vs <1 mm), age, and gender using the chi-square test of proportions. Among those aged <45 to ≥80 years, the prevalence of CIMT ≥1 mm ranged from 0.13% to 29.3% in women and 0.6% to 40.1% in men, stenosis ≥50% from 0.1% to 14.9% in women and 0.1% to 13.2% in men, and mixed and/or soft plaque from 7.1% to 66.5% in women, and 9.2% to 65.8% in men (all p <0.001 across age groups). Even when CIMT levels were <1 mm, >30% of patients demonstrated mixed or soft plaque potentially prone to rupture. Of those with CIMT ≥1 mm, more than 70% had such mixed or soft plaque and more than 40% demonstrated stenoses of 30% or greater. In conclusion, we describe in a large CIMT registry study a substantial age-related increase in both men and women of increased CIMT, plaque presence, and severity, and stenosis. Even in those with normal CIMT, mixed or soft plaque was common, further demonstrating the value in assessing for plaque when doing carotid ultrasound.

Carotid ultrasound measurements of intima-medial thickness (CIMT) are noninvasive, safe, and inexpensive and provide information on subclinical atherosclerosis.[1,2] CIMT measures predict subsequent cardiovascular disease (CVD) events,[3] especially stroke[4] and improve prediction of events beyond global risk assessment.[5] Although a recent meta-analysis of more than a dozen prospective studies showed a limited clinical utility of CIMT to improve risk reclassification for CVD and stroke,[6] the Atherosclerosis Risk in Communities study[7] showed that more than a quarter of subjects had their CVD risk reclassified beyond

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traditional risk factor assessment when a combination of CIMT and plaque was added. Data are limited, however, regarding the age- and gender-related prevalence of carotid plaque and its severity and the association of the presence and extent of plaque with CIMT. Such information is potentially invaluable to provide risk stratification beyond measurements of CIMT alone. We evaluated the age- and gender-related differences in plaque and stenosis presence and severity in subjects undergoing CIMT screening in a large registry-based cohort.

Methods

A consecutive series of 9,347 women and 12,676 men (n = 22,023) who received carotid ultrasound scans (HeartSmart IMT, Irvine, California) during 2007 to 2015 were analyzed for carotid IMT, plaque presence and severity, and stenosis severity. Participants were patients of primary care and specialty physicians at practices around the United States. Most of the patients were asymptomatic and tested based on physician recommendation. Our study used deidentified data that are exempt from institutional review board review.

Patients were scanned in the physician’s office by either an ultrasound technician or by a medical assistant trained by HeartSmart. Ultrasound scans of the left and right carotid arteries were performed with a 7.5 to 10 MHz probe using a duplex B-mode scanner with a resolution of 0.1 to 0.2 mm. A wide range of scanners, including those manufactured by Siemens, SonoScape, Toshiba, and Hewlett-Packard were used. Scans were recorded as continuous video audio video interleave files and uploaded to a server through secure file transfer protocol connection or were recorded on 1/2-inch super video home system tape. The scan depth was set at approximately 4 cm (below the skin). The common carotid artery (CCA), bifurcation, internal carotid artery (ICA), and the external carotid artery (ECA) up to 1 cm beyond the bifurcation were imaged in the transverse view. The probe was then rotated to obtain the longitudinal view at the location of the carotid bulb and bifurcation. Subsequently, the probe was moved up the patient’s neck to obtain the longitudinal view of the ICA and ECA and then back down the neck to image the entire CCA. Longitudinal views of the CCA carotid bulb and ICA were obtained to image the distal wall of the CCA and any lesions detected in the transverse views.

The scans were recorded as continuous video and sent to a centralized laboratory (HeartSmart, Inc.) for analysis. The carotid scans were reviewed frame-by-frame, with the analyst selecting the area for measurement of CIMT in the distal wall of the CCA approximately 1 cm below the beginning of the bulb. Carotid plaques were analyzed and reported by location, severity, and composition for up to 2 lesions per side. To ensure consistency with analysis, the scans were analyzed at a centralized laboratory by credentialed vascular ultrasound technicians who receive additional training from HeartSmart. The scans were analyzed offiine as opposed to during the scanning process by the sonographer to ensure a more comprehensive, accurate, and reproducible result. Location was marked as one of the following: bulb, ICA, ECA, or CCA. Severity was reported as a range of estimated stenosis: none; nominal where there was early buildup due to thickening near the bulb within the intima; less than 30% (but visible intrusion beyond the intima), 30% to 50%; and greater than 50%. Stenosis was estimated by the vascular technician by comparing the lumen containing a lesion to adjacent open lumen to give the percentage of stenosis to open lumen from viewing pathology in both the transverse and sagittal plane to see lesions that might be on the side walls of the artery that may not appear at all from viewing the sagittal plane alone. The relative space occupied by a lesion was deducted from the total open lumen to deduce the stenosis percentage. Plaque composition was reported based on observed echogenicity: (1) none: early buildup “calcified,” where there was a thick calcified cap over the lesion, (2) soft: where there was little or no calcification of the plaque, and (3) mixed: where there was a combination of calcified and soft plaque. Soft plaque had lower level echoes appearing more echolucent. Calcified plaque had a more echo-dense appearance from sound waves that are more intensely reflected. Generally, most plaques were mixed with both echolucent and echo-dense components.

Cross-sectional views of the carotid artery were obtained to image intrusive lesions. Longitudinal views of the CCA, carotid bulb, and ICA were obtained to image the far wall of the CCA and any lesions detected with the cross-sectional view. Automated computerized measurements of the IMT over the CCA far wall region of interest and involving edge detection were taken resulting in minimum, maximum, and average IMT values presented to 2 decimal places from the multiple measurements made as comparable to other major studies.[8–10] The results of the analysis for each patient were stored in an SQL database and included: (1) average IMT measurement for right and left sides, (2) lesion location and type for up to 2 lesions for left and right sides, and (3) range of stenosis for each lesion.

SAS Enterprise Guide 6.1 was used for analysis. Age groups were defined beginning at <45 years and ending with ≥80 years in 5-year age groups in between with mean left and right CIMT values calculated (with standard deviation and range) and the proportion of subjects with >1 mm CIMT in either the left or right carotid artery determined by age group and gender; this cutpoint has been used in past studies as an indicator of significant CIMT[11–13] associated with increased CVD risk. The chi-square test of proportions was performed comparing the prevalence of increased CIMT (defined as ≥1 mm in either the left or right carotid artery), plaque composition (none, early buildup, soft, mixed, or calcified), and stenosis severity (none, nominal, <30%, 30% to <50%, 50% to 70%, and >70% with the greatest percentage stenosis between the left and right taken as the measure) across gender and age groups. Plaque composition and stenosis severity was also compared according to CIMT ≥1 mm versus <1 mm using similar analyses and analysis of variance was used to compare the mean CIMT (averaged between left and right) across plaque composition and stenosis severity categories.

Results

Data were analyzed for 9,347 women and 12,676 men (n = 22,023). Overall, there was an increase across age groups (from <40 years by 5-year age groups to ≥80 years) in the prevalence of CIMT ≥1 from 0.1% to 29.3% in women and from 0.6% to 40.1% in men (p <0.001 for trend; Figure 1). The mean CIMT levels across these same age groups ranged from 0.67 mm to 0.95 mm in men and from 0.63 mm to 0.91 mm in women for left CIMT and from 0.66 mm to 0.95 mm in men and 0.62 mm to 0.92 mm in women for right CIMT (Table 1).

The extent of stenosis increased by age group with the prevalence of stenosis greater than 50% increasing from 0.06% to 14.9% in women from the youngest to the oldest age group ($p < 0.001$ for trend; Figure 2). In men, the prevalence of stenosis greater than 50% increased from 0.07% to 13.2% ($p < 0.001$ for trend; Figure 2).

When analyzing plaque composition by age category, the prevalence of mixed and/or soft plaque ranged from less than 10% in those aged <45 years to more than 60% in those aged ≥80 years in both men and women (Figure 3; $p < 0.001$ comparing plaque composition distribution across age groups).

When the prevalence of plaque by categories was analyzed by IMT category, men with a CIMT <1 mm had a prevalence of mixed and/or soft plaque of 30.2%, compared with 76.5% in those with a CIMT ≥1 mm; for women, these prevalences ranged from 25.0% to 79.8% ($p < 0.001$). Of interest, the prevalence of calcified plaque was not substantially different in those with CIMT <1 mm versus ≥1 mm (5.5% vs 6.2% in men and 5.2% vs 7.3% in women) (Figure 4). Mean CIMT (averaged right and left) also varied directly according to worsening plaque category ranging from 0.70 to 0.84 in men with no plaque to mixed calcified and soft plaque and 0.68 mm to 0.85 mm in women with no plaque to soft plaque ($p < 0.001$ across plaque categories, unadjusted and after age adjustment; Table 2).

When examining the extent of stenosis within IMT categories, the prevalence of stenosis greater than 50% increased from 0.9% in males with CIMT <1 mm to 6.9% in men with CIMT ≥1 mm and from 1.1% in women with CIMT <1 mm to 11.9% in women with CIMT ≥1 mm ($p < 0.001$ for stenosis severity distribution between those with CIMT ≥1 mm vs <1 mm for both genders; Figure 5). Mean CIMT (averaged right and left) also varied directly according to increasing plaque stenosis ranging from 0.70 mm to 0.94 mm in men and 0.68 mm to 0.92 mm in women in those with no plaque to those with ≥50% stenosis ($p < 0.001$ across stenosis categories unadjusted and after age adjustment; Table 2).

Discussion

We show in the largest known carotid ultrasound registry cohort to date a substantial prevalence of carotid artery plaque and increased stenosis that is present even when CIMT levels are not elevated, indicating the limited information that measurement of CIMT alone provides. Both carotid plaque and stenosis show to increase directly with age and are greater in men than in women. Even when CIMT levels are not elevated, more than 30% of subjects have soft or mixed plaque, with a substantial age-related prevalence that exceeds 50% in older men and women. We also show a prevalence of carotid stenosis of 30% or greater in over 50% of both men and women by age 80 years. The discordance of abnormal CIMT levels and presence of soft or mixed plaque may explain the relative underperformance of CIMT as a CVD event predictor. Echolucent, fatty plaques are less stable and more prone to rupture,[14] and given our study shows almost one-third with a normal CIMT may have such plaque, this suggests reliance on CIMT alone may miss subjects with potential residual risk from the presence of plaque. Of those with CIMT ≥1 mm, more than 70% had such soft or mixed plaque and over 40% had carotid stenosis of 30% or greater. Data are lacking, however, regarding whether treatment of such patients with medical or other interventions would ultimately improve clinical outcomes.

Normative data on CIMTs have previously been reported from a large black and white sample of more than 13,000 middle-aged (ages 45 to 64 years) adults in the Atherosclerosis Risk in Communities Study, where median wall thicknesses ranged from between 0.5 and 1 mm at all ages studied, with projected increases in CIMT of 0.01 mm/y in both men and women based on the cross-sectional data.[8] Our report shows the increase in mean CIMT levels across an even wider age range extending to >80 years along with corresponding increases in mixed/fatty plaque prevalence and extent of stenosis.

The value of CIMT alone in prediction of CVD events is well established from multiple cohort studies,[2] including recently in the Multiethnic Study of Atherosclerosis.[5] However, CIMT and plaque together can better classify patient CVD risk categories and provide added risk prediction over traditional global risk assessment. In a recent report among middle-aged persons from Atherosclerosis Risk in Communities Study, adding CIMT and plaque information was found to significantly improve coronary heart disease event risk prediction and clinical net reclassification over traditional risk factors (21.7); even plaque added to CIMT and risk factors provided a modest improvement (10.6) in clinical net reclassification.[4] Although traditional coronary factors explain only 15% to 17% of IMT, they account for over half of the carotid plaque total area.[15] A recent meta-analysis of 11 population studies showed that carotid plaque compared to CIMT had a much higher diagnostic accuracy for the prediction of future myocardial infarction; however, this improvement in diagnostic accuracy was less striking when diagnostic cohort studies were examined.[16] Others have also noted the value of femoral ultrasound beyond that of carotid ultrasound, with 56% of women and 31% of men with plaque aged 50 to 64 years having exclusively femoral plaque.[17] In the Framingham Offspring Study cohort comprising 2,965 subjects with CIMT measures, the presence of plaque, defined as an internal CIMT of more than 1.5 mm, provided an increase in the net reclassification index of 7.4% and C-statistic of 0.014 for the prediction of future cardiovascular events.[18] In a Chinese study of 1,734 subjects, a total burden score consisting of CIMT and the number of segments with plaque was shown to improve C-statistic and net reclassification over either component alone.[19] Furthermore, in a large cohort of 1,288 eastern Finnish men, although increased CIMT conferred a nonsignificant 2.2-fold increased risk of acute myocardial infarction, those with small carotid plaques had a significant 4.2-fold greater risk and those with large stenotic plaques had a 6.7-fold increased risk compared with those without structural changes in the carotid wall.[20] Most recently, in the High Risk Plaque BioImage study among 6,101 asymptomatic subjects of average age 68.8 years, carotid plaque prevalence was very high (78%) and was more closely associated with atherosclerosis than other measures of subclinical disease[2]; carotid plaque burden was shown to predict primary major adverse cardiovascular events (2.4-fold greater risk among those in the third tertile vs no atherosclerosis) and with improved model fit and reclassification (net reclassification improvement 0.23 over risk factors alone).[21]

B-mode ultrasound CIMT measurements have been recommended by several US and European guidelines for the purpose of risk stratification beyond global risk assessment, primarily in patients at intermediate risk.[22,23] The recent 2014 American College of Cardiology/American Heart Association cardiovascular risk assessment guidelines,[24] however, no longer recommend CIMT measurements alone (e.g., without assessment of plaque) because of their failure improve reclassification of risk beyond traditional risk factors.[6] Because carotid plaque is a stronger predictor of coronary events than CIMT, it has been recommended that to increase sensitivity in identifying subclinical vascular disease, ultrasound assessment of the carotid (and femoral) arteries should include plaque assessment.[15] Consequently, it might be important for future guidelines writing groups to consider the role that plaque presence and severity and stenosis severity can play in additional risk stratification beyond CIMT. Moreover, other noninvasive imaging techniques for atherosclerosis, namely coronary calcium scanning, have been shown to demonstrate superior predictive value for CVD events compared with CIMT or other measures[10,25,26] and are believed to be the most useful of the currently available tools for CVD risk assessment beyond global risk scoring.[24]

Our study had a number of limitations. We did not have access to information on clinical history, including the presence of CVD, as well as different risk factors which influence the extent and severity of the carotid measures we examined, nor did we have information about the race and/ or ethnicity of our population. Therefore, because our study population did not exclude subjects with clinical CVD or other comorbidities that may relate to increased CIMT with increased stenosis and/or plaque, our prevalence of these characteristics may be overestimated compared with an exclusively disease-free population. Our study population selected largely by referring physicians may not be broadly representative of the general population. We also did not have follow-up information for events so could not examine prospectively the prognostic impact of our CIMT, plaque, and stenosis measures.

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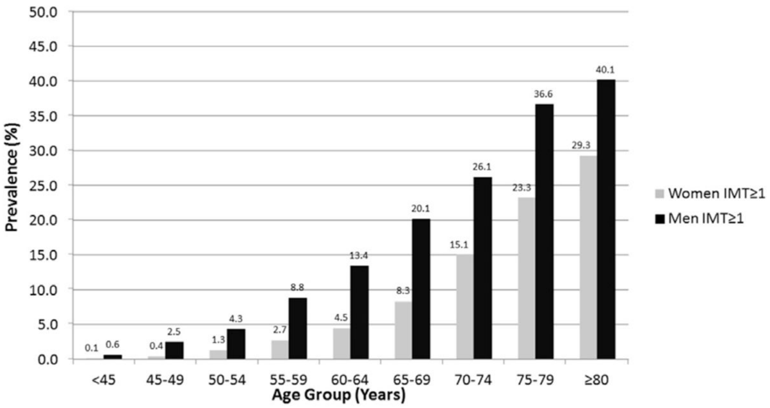

Figure 1.

Prevalence of CIMT ≥1 by age group and gender (n = 22,023). p<0.001 across age groups for both genders.

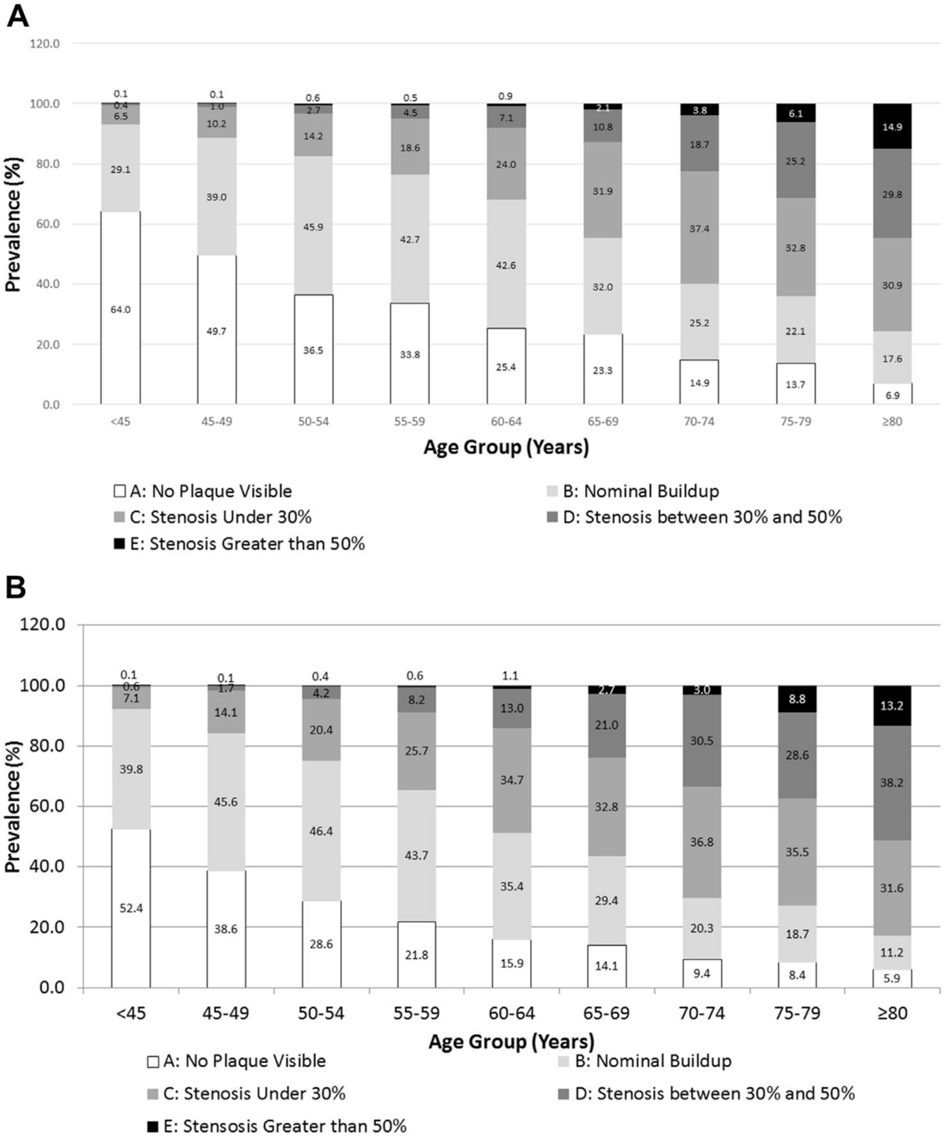

Figure 2.

(A) Prevalence of stenosis by category across age group in women (n = 9,347). p <0.001 for severity of stenosis category across age groups. *(B)* Prevalence of stenosis by category across age group in men (n = 12,676). p <0.001 for severity of stenosis category across age groups.

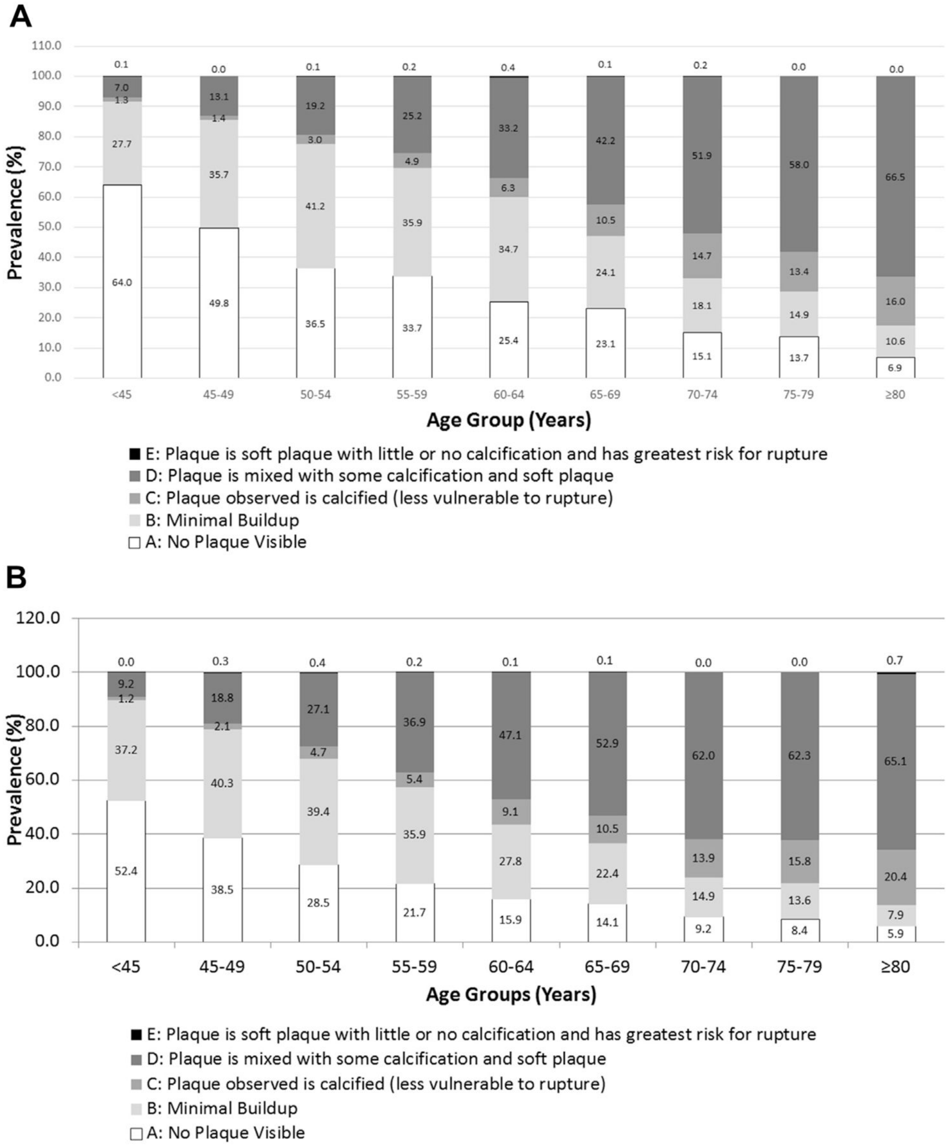

Figure 3.

(A) Prevalence of plaque type within each age group in women (n = 9,347). p <0.001 for difference in plaque type across age groups. *(B)* Prevalence of plaque type within each age group in men (n = 12,676). p <0.001 for difference in plaque type across age groups.

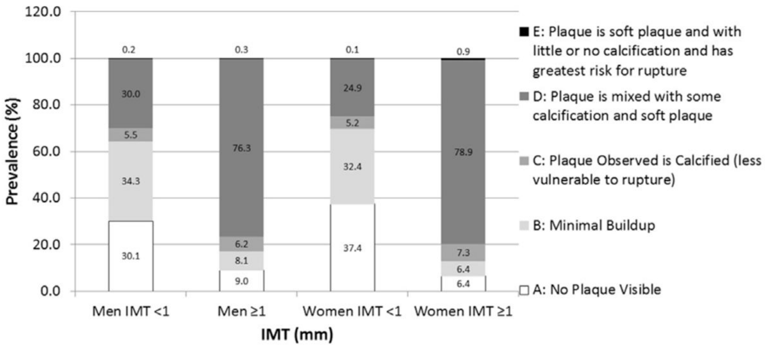

Figure 4.

Prevalence of plaque within IMT category and gender. $p < 0.001$ for difference in plaque type between IMT category for men and women.

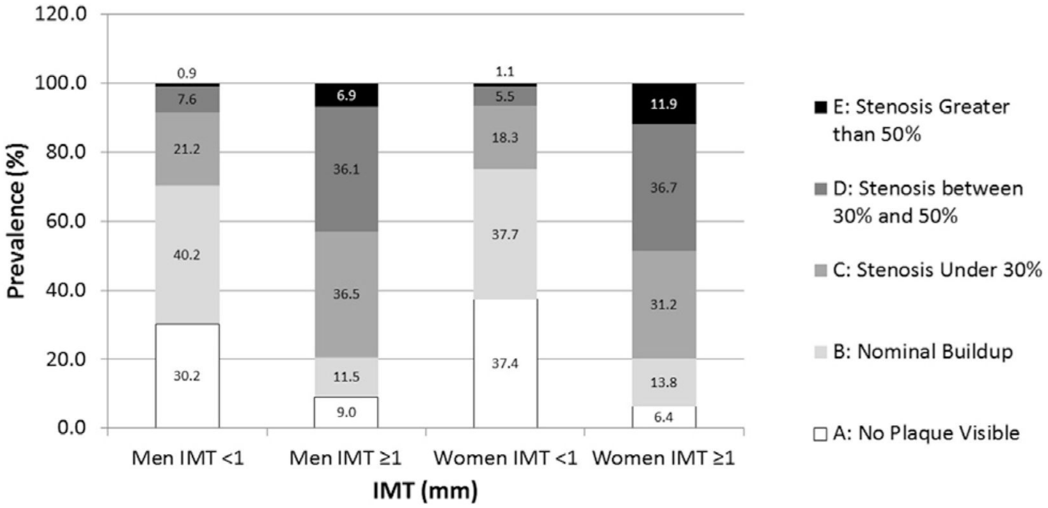

Figure 5.

Prevalence of stenosis by IMT category and gender. p <0.001 comparing plaque severity between IMT category for men and women.

Table 1

Comparison of mean (SD) of carotid intimal medial thickness within each age group and gender

Age group	Men: IMT left	Men: IMT right	Women: IMT left	Women: IMT right
<45	0.67 (0.10) [0.06–1.18]	0.66 (0.10) [0.07–1.19]	0.63 (0.09) [0.06–1.03]	0.62 (0.09) [0.07–1.05]
45–49	0.73 (0.12) [0.01–1.77]	0.71 (0.11) [0.06–1.18]	0.68 (0.09) [0.01–1.18]	0.68 (0.09) [0.01–1.44]
50–54	0.76 (0.12) [0.01–1.37]	0.74 (0.12) [0.08–1.45]	0.72 (0.10) [0.07–1.41]	0.71 (0.01) [0.01–1.16]
55–59	0.79 (0.14) [0.07–2.09]	0.77 (0.13) [0.06–1.45]	0.75 (0.10) [0.06–1.36]	0.74 (0.10) [0.45–1.34]
60–64	0.82 (0.14) [0.08–1.72]	0.81 (0.13) [0.12–1.49]	0.77 (0.11) [0.07–1.45]	0.77 (0.10) [0.08–1.46]
65–69	0.86 (0.14) [0.07–1.55]	0.85 (0.13) [0.41–1.60]	0.82 (0.11) [0.51–1.32]	0.82 (0.11) [0.44–1.37]
70–74	0.90 (0.15) [0.53–1.79]	0.89 (0.14) [0.08–1.49]	0.86 (0.13) [0.54–1.86]	0.86 (0.11) [0.56–1.44]
75–79	0.93 (0.17) [0.09–1.34]	0.92 (0.15) [0.12–1.65]	0.88 (0.14) [0.54–1.52]	0.89 (0.12) [0.59–1.35]
≥80	0.95 (0.14) [0.58–1.36]	0.95 (0.12) [0.67–1.31]	0.91 (0.15) [0.56–1.63]	0.92 (0.15) [0.06–1.48]

Standard deviation reported in parentheses and range in brackets.

Table 2

Mean (SD) and range of CIMT* according to stenosis and plaque category

	Men	Women
Stenosis Category		
No Plaque	0.70 (0.11) [0.30–1.26]	0.68 (0.10) [0.07–1.46]
Nominal Buildup	0.75 (0.10) [0.06–1.37]	0.73 (0.10) [0.31–1.31]
<30% Stenosis	0.82 (0.12) [0.35–1.60]	0.79 (0.11) [0.38–1.24]
30–50% Stenosis	0.89 (0.14) [0.39–1.60]	0.86 (0.12) [0.60–1.38]
>50% Stenosis	0.94 (0.16) [0.53–1.54]	0.92 (0.14) [0.60–1.28]
p-across categories	<0.001	<0.001
Plaque Category		
No Plaque	0.70 (0.11) [0.30–1.26]	0.68 (0.001) [0.07–1.46]
Minimal Buildup	0.74 (0.11) [0.30–1.26]	0.73 (0.09) [0.31–1.31]
Calcified Plaque	0.81 (0.12) [0.51–1.22]	0.79 (0.11) [0.48–1.25]
Mixed Calcified and Soft Plaque	0.84 (0.13) [0.35–1.60]	0.81 (0.12) [0.38–1.38]
Soft Plaque	0.78 (0.14) [0.55–1.18]	0.85 (0.13) [0.69–1.06]
p-across categories	<0.001	<0.001

[*] CIMT measures represented are the mean of right and left CIMT. Standard deviation reported in parentheses and range in brackets.