Polyvascular subclinical atherosclerosis: correlation between ankle brachial index and carotid atherosclerosis in a population-based sample

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ABSTRACT

To assess the correlation between the biomarkers of lower limb atherosclerosis (e.g., ankle-brachial index [ABI]) and of carotid atherosclerosis (e.g., common carotid intima media thickness (IMT) and presence of atherosclerotic plaque) in the general population, a population-based cohort of individuals from Girona (Northwest Spain) was recruited in 2010. ABI and carotid ultrasound were performed in all participants. Generalized additive multivariable models were used to adjust a regression model of common carotid IMT on ABI. Logistic regression multivariable models were adjusted to assess the probability of carotid plaque in individuals with peripheral artery disease. We included 3,307 individuals (54.2% women), mean age 60 years (standard deviation 11). Two patterns of association were observed between subclinical biomarkers of atherosclerosis at the lower limb and carotid artery. ABI and common carotid IMT showed a linear trend in men [beta coefficient (95% confidence interval) =-0.068 (-0.123; -0.012); p=.016]. Women with peripheral artery disease presented with high risk of atherosclerotic plaque at the carotid artery [Odds ratio (95% confidence interval) =2.61, (1.46; 4.69); p=.001]. Men showed a significant linear association between ABI levels and common carotid IMT values. Women with peripheral artery disease presented with high risk of atherosclerotic plaque at the carotid artery.

Keywords

Ankle-brachial index; intima media thickness; epidemiology; subclinical cardiovascular disease; atherosclerosis

Introduction

Cardiovascular diseases are the main cause of death in western countries.[1] The common basis of this group of diseases is atherosclerosis, a chronic and degenerative process that mainly occurs in large and medium-sized arteries morphologically characterized by asymmetric focal thickenings of the innermost layer of the artery, the intima.[2] The presence of atherosclerosis in different vascular beds defines polyvascular subclinical disease, pointing out the systemic nature of the atherosclerotic process.[3,4,5]

The long induction period of atherosclerosis makes it suitable for the study of subclinical disease for preventive purposes. On the one hand, low ankle-brachial index (ABI) values, as a subclinical indicator of lower extremity peripheral artery disease, provide a potent predictor of future cardiovascular events and death.[6,7] On the other hand, carotid ultrasound can be used to detect subclinical disease because it measures intima-media thickness (IMT) and the presence of atherosclerotic plaques.[8,9,10] Most studies have addressed the coexistence of atherosclerosis at the lower limb and at the carotid artery in selected samples (e.g., patients with diabetes, history of stroke, or advanced age).[11,12,13,14] However, these correlations have not been assessed in general population or specifically in individuals with no history of intermittent claudication. In addition, most of the studies did not use automated methods based on machine learning procedures that minimize the reproducibility problem linked to IMT and carotid plaque interpretation.[15,16]

To assess the correlation between the biomarkers of lower limb atherosclerosis (ABI) and of carotid atherosclerosis (e.g., common carotid IMT and presence of atherosclerotic plaque) in the general population and in a subsample with no history of intermittent claudication.

Methods

Cross-sectional study conducted in the context of the REGICOR study (REgistre Gironi del COR, or Girona Heart Registry). The details have been described elsewhere.[17] Briefly, participants were randomly selected from the city of Girona (approximately 70,000 inhabitants) and three surrounding rural towns in 2005 and reexamined in 2010, when ABI and carotid ultrasound were performed. The participants included were free of terminal disease, not institutionalized, and residents of the reference area for at least six months/year (reflecting the stable seasonal presence of a large number of retirees). Participants were contacted by a letter informing them of the aims of the study and the tests to be performed. If willing to participate, they were asked to fast for at least 10 hours before their appointment at the health examination site. The participation rate in the reexamination was 78.1%.[18] All participants were duly informed and provided their written consent to participate in the study and the results of the examination were sent to each of them. The study protocol was approved by the local ethics committee (CEIm-PSMAR 2008/3046/I).

Measurements

Examinations were performed by a team of trained nurses and interviewers using the same methods. A precision scale of easy calibration was used for weight and height measurement with participants in underwear and barefoot. Body mass index was determined as weight divided by squared height (kg/m^2). Blood pressure was measured with a periodically calibrated sphygmomanometer (OMRON 711). A cuff adapted to the upper arm perimeter (young, adult, obese) was selected for each participant. Measurements were performed in a seated position after a 5-minute rest. Two

measurements were taken and the lower value was recorded for the study. Standardized questionnaires were used to collect sociodemographic and lifestyle variables, along with previous history and treatments for diabetes, hypertension, and hypercholesterolemia. Current smoking was defined as actively smoking within the preceding year. Claudication was assessed using the Edinburgh questionnaire.[19] Blood was withdrawn after 10-14 h of fasting. Total and high-density lipoprotein (HDL) cholesterol concentrations were determined by direct methodology (Roche Diagnostics, Basel, Switzerland). Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald equation whenever triglycerides were <3.4mmol/l (300 mg/dl).

Ankle-brachial index measure

Ankle-brachial index was measured in accordance with current guidelines.[6] After 5-min rest and with the participant in supine position, systolic blood pressure was measured in the brachial artery in the antecubital fossa in the control arm with a continuous Doppler device, then in the distal calf, using the Doppler probe to determine systolic blood pressure in the supine position at the right and left posterior and anterior tibial arteries. Right and left ABI were calculated as the ratio of the higher of two systolic pressures in the lower limbs (posterior and anterior tibial arteries) to the control brachial systolic pressures. The lowest of the values obtained was used for analysis. We discarded the individuals with ABI >1.4 because of the high probability of medial arterial calcification.[6]

Carotid ultrasound

Two trained sonographers performed the carotid ultrasound examinations. An Acuson XP128 ultrasound machine equipped with an L75-10 MHz transducer and extended frequency software was used (Acuson-Siemens, Mountainview, California, United States). B-mode ultrasound images of the common carotid artery segment were obtained in DICOM format with a resolution of 0.043 mm/p. Image files were recorded and sent to the Academic Vascular Image Centre in Amsterdam (AVICA). Measurements of IMT were made in a 1-cm segment in the distal common carotid artery (1 cm proximal to the dilation of the carotid bulb) of both right and left arteries. Measurements were made every 1 mm in the 1-cm segment, from which the mean values were calculated. To interpret the full set of images, a fully automatic deep-learning method able to properly localize the intima media region and then estimate the IMT was used (Supplementary Table 1). This deep-learning procedure is based on convolutional neural networks and was validated using the subset of IMT estimates performed in AVICA as the gold standard.[15] Left and right common carotid IMT were obtained for each participant and the mean was considered in the analysis. For those individuals with just one estimate (e.g. left or right), this single value was considered. Finally, the presence of carotid plaque was also assessed with a deep-learning model and according to the definition in the Mannheim consensus: focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value, or a thickness >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface.[8]

Statistical analysis

According to the sample size, a correlation coefficient of 0.05 between ABI and common carotid IMT could be found as statistically significant accepting an alpha risk of 0.05 and a beta risk of 0.2.

All analysis was stratified by sex. Continuous variables were summarized as mean (standard deviation), or median [interquartile range] when their distribution departed from normal, and categorical variables as proportions. The correlation between the terciles of ABI was ascertained using the mean values of carotid IMT, the prevalence of carotid plaque and other cardiovascular risk factors, ANOVA, Wilcoxon, and Chi-square, as appropriate. To compare the prevalence of cardiovascular risk factors and the mean values of ABI by the presence of atherosclerotic plaque, the Chi-Square, Student-t, and Mann-Whitney U tests were used as appropriate.

Unadjusted generalized additive models were fitted to find associations of ABI and other cardiovascular risk factors (independent variables) with IMT (dependent variable). This more flexible modelling approach allows for non-linearity in the relationship and contributes to a more accurate exploration of continuous variables, providing a pattern which reflects the shape and trend of the association. Breakpoint regression analysis was used to test whether an apparent change in the correlation trend between ABI and IMT was statistically significant.[20] Multivariable models were fitted by potential confounders that showed significant associations with the terciles of ABI and common carotid IMT. Finally, to assess the probability of carotid plaque in individuals with peripheral artery disease (symptomatic or asymptomatic), multivariable logistic regression models were adjusted for age. A subanalysis was performed,

excluding participants with history of intermittent claudication reported by the participant or assessed with the Edinburg questionnaire.

The effect modification of the relationship of ABI with common carotid IMT by age[21] was tested with the -2 loglikelihood test of nested models with and without interaction terms. In a secondary analysis, the sample was stratified by age (<60 and ≥60 years).

Statistical analysis was done with the R Statistical Package (R Foundation for Statistical Computing, Vienna, Austria; Version 4.0.5).

Results

We included 3,307 individuals (1,516 men and 1,791 women), mean age 60 years (standard deviation 11). Table 1 includes the sociodemographic and clinical characteristics of the sample by sex.

Common carotid IMT significantly decreased by ABI terciles, both in men [ABI tercile (T) 1: 0.70 mm (standard deviation 0.14); T2: 0.69 (0.16); T3: 0.67 (0.13); p <.001] and in women [T1: 0.67 (0.13); T2: 0.66 (0.16); T3: 0.64 (0.14); p =.005]. No significant differences were found in the prevalence of atherosclerotic plaque by terciles of ABI (Table 2).

In the regression of common carotid IMT on ABI, we found similarly significant associations in men [Beta-coefficient (95% confidence interval) = -0.173 (-0.232; -0.114); p <.001] and in women [-0.134 (-0.200; -0.068); p <.001]. Individuals with no claudication also presented with significant correlations (p <.001) between IMT and ABI [-0.182 (-0.243; -0.122) and -0.124 (-0.192; -0.056) in men and women, respectively] (Figure 1).

We adjusted generalized additive multivariable models for the whole sample and for where the slope changed (i.e., breakpoint). The results were only significant in men overall and in those with no claudication [-0.068 (-0.123; -0.012); p=.016 and -0.073 (-0.130; -0.017); p=.011, respectively]. No differences were found in women (Table 3).

The adjusted risk of atherosclerotic plaque at the carotid artery in individuals with peripheral artery disease significantly increased in all women and in those with no claudication [Odds ratio (95% confidence interval) =2.61, (1.46; 4.69); p=.001 and 2.49 (0.99; 6.28); p=0.053, respectively]. The risk was also significant in men with no claudication [2.08 (1.09; 3.96); p=0.026] (Figure 2).

The analysis stratified by age found similar results in the correlation between ABI and IMT, with significant associations only in men (Supplementary Tables 8-13 and Supplementary Figure 1). In addition, the probability of carotid plaque in individuals with peripheral artery disease was only significant in older men and women (>60 years) [2.03, (1.13; 3.63); p=.017 and 2.84 (1.47; 5.49); p=.002, respectively] (Supplementary Figure 2).

Discussion

Polyvascular subclinical disease, defined as the coexistence of atherosclerosis in different vascular beds within the same individual, should be considered a systemic process. We measured the coexistence of subclinical atherosclerosis at the lower limb, as measured with ABI, and at the common carotid artery, as measured with IMT or with the presence of atherosclerotic plaque. In men, a linear negative dose-response association between the degree of atherosclerosis at the lower limb and at the common carotid arteries was observed. In women, peripheral artery disease (symptomatic or

asymptomatic) significantly increased the risk of atherosclerotic plaque in the carotid arteries

Recognition of the atherosclerosis process as a systemic disease, as reported by numerous authors, is necessary to improve the prevention outcomes.[3] First, core risk factors such as smoking, diabetes, hypertension, hypercholesterolemia, obesity, and family history appear to be shared among all vascular diseases, regardless of the territory affected.[22,23] Second, subclinical peripheral artery disease in patients with coronary artery disease is associated with a poor prognosis during the first year after an acute coronary syndrome event.[24] Third, common carotid IMT or the presence of atherosclerotic plaques at the carotid arteries improve the prediction of incident cardiovascular disease.[16,25,26,27] In general, the presence of subclinical atherosclerosis at different locations has been associated with higher risk of cardiovascular events in individuals with familial hypercholesterolemia[28] or in percutaneous coronary intervention patients.[29]

Our analysis, consistent with previous studies, showed increased burden of subclinical disease in men, compared to women.[30,31] On the one hand, men presented with a continuous dose-response association between ABI and IMT, particularly up to ABI values around 1.2, where a nonsignificant change in the trend was observed. A U-shaped pattern was previously described by Wang et al. in a cross-sectional analysis not stratified by sex in a Chinese population of inner Mongolia.[32] In addition, The Copenhagen City Heart Study showed that the magnitude of association between these biomarkers was higher in individuals with diabetes, compared to those without the disease.[11] The slope described in the latter group was similar to that observed in men in our results. In contrast, Zhang et al. found that the association between IMT and ABI in

patients with diabetes did not remain after adjusting for cardiovascular risk factors, but the IMT association with toe-brachial index persisted.[12] Finally, no association was found between ABI and IMT in the ARTICO Study, performed in individuals with history of a noncardioembolic stroke in the preceding 3 months.[13] Less specific is the assessment of subclinical burden with magnetic resonance imaging (MRI) performed in the KORA-MRI cohort. In this study, the carotid plaque in different arteries, together with other markers of subclinical disease, were measured in individuals without cardiovascular disease. Thus, the comprehensive analysis of all markers showed that early signs of metabolic and cardio-cerebrovascular complications were more present in individuals with prediabetes, compared to controls.[33]

On the other hand, women did not present with a dose-response association, but a critical increase in the probability of carotid plaque was observed once peripheral artery disease (symptomatic or asymptomatic) was present. This finding, also highlighted by Colledanchise et al.,[34] may have particular value for cardiovascular risk assessment in women. Indeed, the Atherosclerosis Risk in Communities study showed that accounting for carotid plaque presence in addition to IMT leads to greater improvement of risk prediction in women than in men.[35] Thus, a combined assessment of subclinical atherosclerosis at the lower limb and carotid arteries may improve disease detection over an assessment of either artery alone in both men and women, but particularly in women, in whom traditional risk assessments are less effective.[36]

Our study has several limitations. The degree of atherosclerosis in the lower limb and the carotid artery was measured using different techniques. Although the final measurement can be comparable, future cohort studies could assess the extent of atherosclerosis using the same technique in both vascular beds (e.g., ultrasound at

femoral and carotid arteries). Selection bias may affect any cross-sectional study, but is likely to be modest in magnitude in this study because it was population-based and participant selection was not based on the presence or absence of subclinical atherosclerosis. In addition, this design cannot establish temporality.

In conclusion, our study showed two patterns of association between subclinical biomarkers of atherosclerosis at the lower limb and at the carotid artery: Men showed a significant linear association between ABI levels and common carotid IMT values, while women with symptomatic or asymptomatic peripheral artery disease presented with high risk of atherosclerotic plaque at the carotid artery. Our study points out the systemic nature of the atherosclerotic process. Individuals with biomarkers of atherosclerosis in a given territory are more likely to present with subclinical disease in another. The increased risk of ischemic events associated with this condition, and the differences found between men and women have important implications for cardiovascular risk management.

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Conflict of interest

None

Author's contributions

Maria del Mar Vila: Statistical analysis, manuscript writing, manuscript review

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References

1. World Health Statistics. Monograph on the Internet. Geneva: World Health Organization; 2011 [cited 2011 Oct 13]. Available at: https://apps.who.int/infobase/
2. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005;352:1685-1695.

3. Yakubov S. Polyvascular atherosclerotic disease: recognizing the risks and managing the syndrome. Curr Med Res Opin. 2009;25:2631-2641.
4. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018;39:763-816.
5. Danese MD, Pemberton-Ross P, Catterick D and Villa G. Estimation of the increased risk associated with recurrent events or polyvascular atherosclerotic cardiovascular disease in the United Kingdom. Eur J Prev Cardiol. 2020:2047487319899212. doi: 10.1177/2047487319899212.
6. Aboyans V, Criqui MH, Abraham P, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012;126:2890-2909.
7. Sartipy F, Sigvant B, Lundin F and Wahlberg E. Ten Year Mortality in Different Peripheral Arterial Disease Stages: A Population Based Observational Study on Outcome. Eur J Vasc Endovasc Surg. 2018;55:529-536.
8. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th,

15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis. 2012;34:290-296.

9. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. 2008;21:93-111.
10. Zhang Y, Fang X, Hua Y, et al. Carotid Artery Plaques, Carotid Intima-Media Thickness, and Risk of Cardiovascular Events and All-Cause Death in Older Adults: A 5-Year Prospective, Community-Based Study. Angiology. 2018;69:120-129.
11. Winckler K, Wiinberg N, Jensen AK, et al. Carotid intima media thickness and ankle brachial index are inversely associated in subjects with and without diabetes. Scand J Clin Lab Invest. 2018;78:464-469.
12. Zhang Y, Peng K, Liu J, et al. Carotid intima-media thickness and plagues are associated with indicators of peripheral artery diseases in patients with diabetes. Diabetes Res Clin Pract. 2018;144:245-251
13. García García J, Roquer J, Serena J, et al. Carotid Intima-Media Thickness is Not Associated with Markers of Atherosclerosis in Stroke Patients. J Stroke Cerebrovasc Dis. 2016;25:1070-1075.

14. Pan FF, Xu CC, Hu TJ, Fu GX and Zhong Y. Carotid plague formation is associated with ankle-brachial index in elderly people. Aging Clin Exp Res. 2020;32:2217-2223.
15. Vila MDM, Remeseiro B, Grau M, et al. Semantic segmentation with DenseNets for carotid artery ultrasound plaque segmentation and CIMT estimation. Artif Intell Med. 2020;103:101784.
16. Polak JF and O'Leary DH. Carotid Intima-Media Thickness as Surrogate for and Predictor of CVD. Glob Heart. 2016;11:295-312.e3.
17. Grau M, Subirana I, Elosua R, et al. Trends in cardiovascular risk factor prevalence (1995-2000-2005) in northeastern Spain. Eur J Cardiovasc Prev Rehabil. 2007;14:653-659.
18. Grau M, Subirana I, Agis D, et al. Carotid intima-media thickness in the Spanish population: reference ranges and association with cardiovascular risk factors. Rev Esp Cardiol (Engl Ed). 2012;65:1086-1093.
19. Leng GC and Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. J Clin Epidemiol. 1992;45:1101-1109.
20. Muggeo VRM. Testing with a nuisance parameter present only under the alternative: a score-based approach with application to segmented modelling. J Stat Comput Simul. 2016;86:3059-3067.
21. Ramos R, Quesada M, Solanas P, et al. Prevalence of symptomatic and asymptomatic peripheral arterial disease and the value of the ankle-brachial index to stratify cardiovascular risk. Eur J Vasc Endovasc Surg. 2009;38:305-311.

22. Velescu A, Clara A, Peñafiel J, et al. Peripheral Arterial Disease Incidence and Associated Risk Factors in a Mediterranean Population-based Cohort. The REGICOR Study. Eur J Vasc Endovasc Surg. 2016;51:696-705.
23. Grau M, Subirana I, Elosua R, et al. Why should population attributable fractions be periodically recalculated? An example from cardiovascular risk estimation in southern Europe. Prev Med. 2010;51:78-84.
24. Morillas P, Quiles J, Cordero A, et al. Impact of clinical and subclinical peripheral arterial disease in mid-term prognosis of patients with acute coronary syndrome. Am J Cardiol. 2009;104:1494-1498.
25. Polak JF, Szklo M and O'Leary DH. Carotid Intima-Media Thickness Score, Positive Coronary Artery Calcium Score, and Incident Coronary Heart Disease: The Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc. 2017;6:e004612.
26. Geisel MH, Bauer M, Hennig F, et al. Comparison of coronary artery calcification, carotid intima-media thickness and ankle-brachial index for predicting 10-year incident cardiovascular events in the general population. Eur Heart J. 2017;38:1815-1822.
27. Grubic N, Colledanchise KN, Liblik K, et al. The Role of Carotid and Femoral Plaque Burden in the Diagnosis of Coronary Artery Disease. Curr Cardiol Rep. 2020;22:121.
28. Mattina A, Giammanco A, Giral P, et al. Polyvascular subclinical atherosclerosis in familial hypercholesterolemia: The role of cholesterol burden and gender. Nutr Metab Cardiovasc Dis. 2019;29:1068-1076.

29. van der Meer MG, Cramer MJ, van der Graaf Y, Appelman Y, Doevendans PA and Nathoe HM; SMART Study Group. The impact of polyvascular disease on long-term outcome in percutaneous coronary intervention patients. Eur J Clin Invest. 2014;44:231-239.

30. Bermúdez-López M, Martínez-Alonso M, Castro-Boqué E, et al. Subclinical atheromatosis localization and burden in a low-to-moderate cardiovascular risk population: the ILERVAS study. Rev Esp Cardiol (Engl Ed). 2021;74:1042-1053.

31. López-Melgar B, Fernández-Friera L, Oliva B, et al. Subclinical Atherosclerosis Burden by 3D Ultrasound in Mid-Life: The PESA Study. J Am Coll Cardiol. 2017;70:301-313.

32. Wang Y, Li J, Guo X, et al. A U-shaped relationship between ankle-brachial index and carotid intima-media thickness in a Chinese population of Inner Mongolia. Int Angiol. 2011;30:451-457.

33. Bamberg F, Hetterich H, Rospleszcz S, et al. Subclinical Disease Burden as Assessed by Whole-Body MRI in Subjects With Prediabetes, Subjects With Diabetes, and Normal Control Subjects From the General Population: The KORA-MRI Study. Diabetes. 2017;66:158-169.

34. Colledanchise KN, Mantella LE, Bullen M, et al. Combined Femoral and Carotid Plaque Burden Identifies Obstructive Coronary Artery Disease in Women. J Am Soc Echocardiogr. 2020;33:90-100.

35. Nambi V, Chambless L, Folsom AR, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk:

the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol. 2010;55:1600-1607.

36. Marrugat J, Vila J, Baena-Díez JM, et al. Relative validity of the 10-year cardiovascular risk estimate in a population cohort of the REGICOR study. Rev Esp Cardiol. 2011;64:385-394.

FIGURE LEGENDS

Figure 1. Correlations between ankle-brachial index and common carotid intima media thickness by sex in all participants and in those with no claudication

Figure 2. Probability of carotid plaque in all individuals and in those with no claudication. Models adjusted for age

Table 1. Characteristics of the sample at baseline and follow-up, by sex

	Men N=1516	Women N=1791
Age, mean (SD)	61 (12)	60 (11)
University studies, n (%)	399 (26.5)	398 (22.4)
Ankle-brachial index, mean (SD)	1.11 (0.12)	1.09 (0.10)
Peripheral arteriopathy, n (%)	114 (7.5)	116 (6.5)
Asymptomatic peripheral arteriopathy, n (%)	63 (4.2)	38 (2.1)
Claudication, n (%)	51 (3.4)	78 (4.4)
Smoker, n (%)	712 (47.3)	301 (16.9)
Body mass index, mean (SD)	27.7 (3.7)	26.7 (4.9)
Systolic blood pressure (mmHg), mean (SD)	134 (18)	126 (20)
Diastolic blood pressure (mmHg), mean (SD)	79 (10)	75 (10)
Hypertension, n (%)	718 (48.1)	681 (38.7)
Total cholesterol (mg/dl), mean (SD)	196 (36)	206 (35)
HDL cholesterol (mg/dl), mean (SD)	47 (10)	56 (11)
LDL cholesterol (mg/dl), mean (SD)	127 (31)	132 (30)
Lipid-lowering treatment, n (%)	338 (22.8)	338 (19.2)
Triglycerides, median [IQR]	92 [68; 126]	79 [59; 111]
Glycemia (mg/dl), median [IQR]	95 [88; 105]	88 [83; 96]
Diabetes, n (%)	300 (20.3)	192 (11.0)
Common carotid intima media thickness, mean (SD)	0.69 (0.14)	0.66 (0.14)
Atherosclerotic plaque, n (%)	129 (8.5)	97 (5.4)

HDL: High-density lipoprotein. IQR: Interquartile range. LDL: Low-density lipoprotein. SD: Standard deviation

Table 2. Characteristics of participants by terciles of ankle-brachial index

	Men				Women			
	1st tercile [0.52, 1.08) N=515	2nd tercile [1.08, 1.17) N=532	3rd tercile [1.17, 1.40] N=469	*P*	1st tercile [0.50, 1.06) N=614	2nd tercile [1.06, 1.14) N=633	3rd tercile [1.14, 1.40] N=544	*P*
Age, mean (SD)	63 (12)	60 (11)	59 (11)	<.001	62 (12)	59 (11)	59 (11)	<.001
University studies, n (%)	105 (20.6)	160 (30.3)	134 (28.8)	.001	108 (17.8)	149 (23.6)	141 (26.2)	.002
Smoker, n (%)	268 (52.2)	248 (46.8)	196 (42.3)	.008	88 (14.4)	120 (19.0)	93 (17.2)	.095
Body mass index, mean (SD)	27.4 (3.5)	27.6 (3.7)	28.0 (4.0)	.026	26.9 (4.9)	26.5 (5.1)	26.8 (4.8)	.315
Systolic blood pressure (mmHg), mean (SD)	138 (20)	133 (17)	130 (17)	<.001	132 (22)	124 (19)	121 (17)	<.001
Diastolic blood pressure (mmHg), mean (SD)	79 (11)	79 (10)	78 (9)	.281	76 (10)	74 (10)	73 (9)	<.001
Hypertension, n (%)	284 (55.9)	248 (47.4)	186 (40.3)	<.001	304 (50.6)	214 (34.5)	163 (30.2)	<.001
Total cholesterol (mg/dl), mean (SD)	196 (39)	197 (34)	193 (35)	.284	207 (36)	207 (34)	205 (35)	.640
HDL cholesterol (mg/dl), mean (SD)	47 (11)	48 (11)	47 (10)	.431	55 (11)	57 (12)	57 (11)	.040
LDL cholesterol (mg/dl), mean (SD)	127 (33)	127 (29)	127 (31)	.973	132 (31)	132 (30)	131 (30)	.708
Triglycerides, median [IQR]	93 [70; 132]	95 [68; 130]	86 [66; 116]	.002	85 [61; 118]	78 [58; 107]	76 [58; 103]	.002
Glycemia (mg/dl), median [IQR]	96 [89; 108]	94 [88; 103]	95 [88; 104]	.080	89 [83; 98]	88 [83; 96]	88 [83; 95]	.514
Diabetes, n (%)	124 (24.7)	97 (18.8)	79 (17.3)	.009	89 (14.9)	63 (10.3)	40 (7.5)	<.001
Common carotid intima media thickness, mean (SD)	0.70 (0.14)	0.69 (0.16)	0.67 (0.13)	<.001	0.67 (0.13)	0.66 (0.16)	0.64 (0.14)	.005
Atherosclerotic plaque, n (%)	52 (10.1)	44 (8.3)	33 (7.1)	.222	41 (6.7)	31 (4.9)	25 (4.6)	.229

HDL: High-density lipoprotein. LDL: Low-density lipoprotein. IQR: Interquartile range. PAD. Peripheral artery disease. SD: Standard deviation

Table 3. Common carotid intima media thickness by ankle-brachial index in the whole sample and stratified by breakpoints in all participants and in those with no claudication

Men				Women			
		Model[a]				Model[b]	
ABI range	N	Beta Coefficient (95% CI)[a]	*p*	ABI range	N	Beta Coefficient (95% CI)[a]	*p*
All	1516	-0.068 (-0.123; -0.012)	.016	All	1791	-0.011 (-0.070; 0.048)	.723
[0.5; 1.2)	1181	-0.071 (-0.147; 0.005)	.066	[0.5; 1.2]	1586	-0.029 (-0.105; 0.047)	.456
[1.2; 1.4]	335	0.121 (-0.149; 0.391)	.382	(1.2; 1.4]	1829	0.007 (-0.340; 0.492)	.721
Men with no claudication				Women with no claudication			
All	1402	-0.073 (-0.130; -0.017)	.011	All	1713	-0.006 (-0.067; 0.055)	.848
[0.5; 1.0]	169	-0.027 (-0.195; 0.141)	.751	[0.4; 1.2)	1419	-0.010 (-0.079; 0.060)	.786
(1.0; 1.4]	1273	-0.048 (-0.133; 0.036)	.261	[1.2; 1.4]	292	0.031 (-0.089; 0.008)	.617

ABI, Ankle-brachial index. CI, confidence interval.
[a]Model adjusted for age and body mass index
[b]Model adjusted for age

Figure 1.

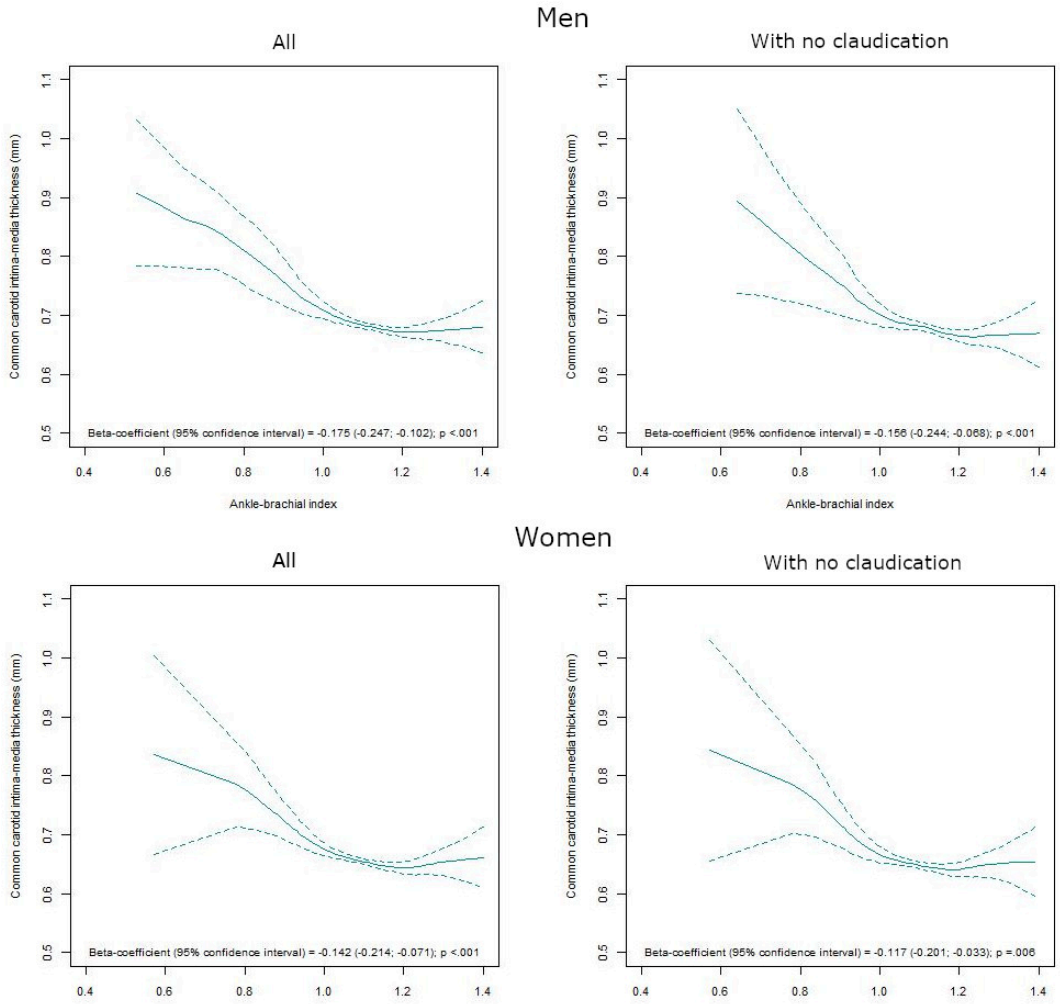
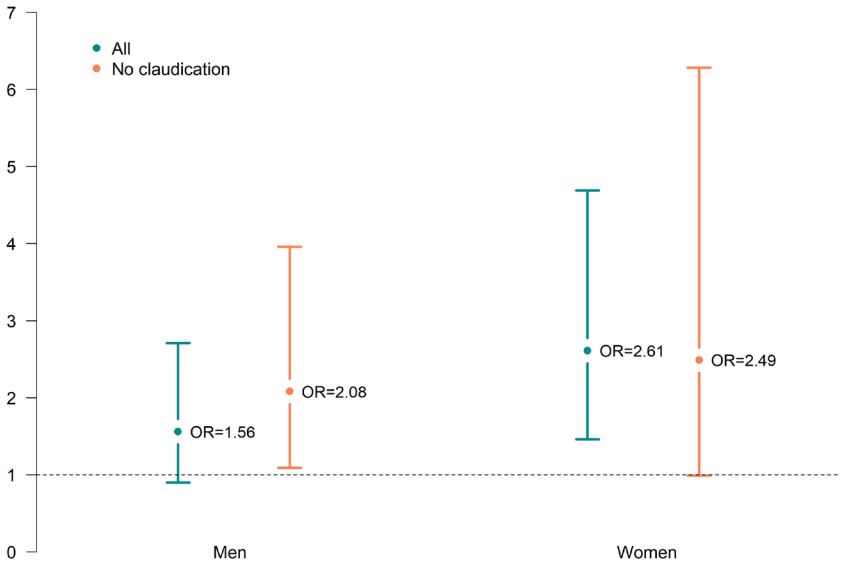

Men
All
With no claudication
Common carotid intima-media thickness (mm)
Ankle-brachial index
Beta-coefficient (95% confidence interval) = -0.175 (-0.247; -0.102); p <.001
Beta-coefficient (95% confidence interval) = -0.156 (-0.244; -0.068); p <.001
Women
All
With no claudication
Beta-coefficient (95% confidence interval) = -0.142 (-0.214; -0.071); p <.001
Beta-coefficient (95% confidence interval) = -0.117 (-0.201; -0.033); p =.006

Figure 2.


7
6
5
4
3
2
1
0
All
No claudication
OR=1.56
OR=2.08
OR=2.61
OR=2.49
Men
Women