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Prevalence of Silent Atherosclerosis across Adult Life

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Abstract

Background

Atherosclerosis may begin in early adulthood and remain clinically silent for decades before cardiovascular disease becomes manifest. Although silent atherosclerosis is associated with cardiovascular events and death independently of traditional cardiovascular disease risk factors, its age- and sex-specific prevalence, vascular territory distribution, and plaque volume across adult life remains incompletely defined.

Methods

We conducted a prospective cohort study in Denmark and Spain. Adults 18 to 70 years of age without known atherosclerotic cardiovascular disease were enrolled in five prespecified age strata, with equal numbers of women and men. Silent atherosclerosis was assessed at baseline by three-dimensional vascular ultrasound of the carotid and femoral arteries and by coronary computed tomography angiography.

Results

A total of 16,808 adults were enrolled in the study. The mean (±SD) age of participants was 45±12.5 years and 51.4% were women. Silent atherosclerosis was present in 57.1% of participants (95% confidence interval, 56.3 to 58.0). In the youngest age strata (18 to 29 years), atherosclerosis was present in 8.7% of men and 6.7% of women, and the prevalence increased with age, with a later, steeper midlife rise in women. At younger ages, atherosclerosis was most often peripheral and confined to a single vascular territory; with increasing age, plaque volume increased exponentially and the prevalence of multiterritory involvement became more frequent. Isolated coronary artery atherosclerosis was uncommon in every age stratum (≤9.3% in men and ≤5.0% in women).

Conclusions

This atlas of silent atherosclerosis showed that it was detectable from early adulthood, with age- and sex-associated increases in the cross-sectional prevalence, across arterial territories, and marked increases in plaque volumes.

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INTRODUCTION

Cardiovascular disease remains the leading cause of morbidity and mortality worldwide.[1] Atherosclerosis is the principal pathological process underlying coronary heart disease, ischemic stroke, peripheral artery disease, sudden cardiac death and other cardiovascular manifestations. Accordingly, preventing the development and progression of atherosclerosis is central to efforts to reduce the global burden of atherosclerotic cardiovascular disease.[2,3] However, contemporary primary prevention is guided largely by estimated event risk and risk-factor thresholds, rather than by the presence, vascular distribution, or volume of established atherosclerosis. This distinction is important because atherosclerosis may be present for decades before clinical cardiovascular disease becomes manifest.

Imaging studies in asymptomatic adults have consistently shown that silent atherosclerosis is common, although the reported prevalence varies according to age, population characteristics, vascular territory, and imaging modality. In studies of middle-aged and older adults, coronary artery calcium scoring, coronary computed tomography angiography, and carotid or femoral ultrasound imaging have detected silent atherosclerosis in approximately 40% to 80% of participants. Consistently, greater plaque burden has been associated with higher risks of subsequent atherosclerotic cardiovascular events and death.[4-8] Longitudinal imaging studies have also shown that plaque burden may progress over time, with known modifiable risk factors particularly relevant to plaque burden progression at younger ages. [5,9]

Despite this evidence, the epidemiology of silent atherosclerosis across adult life remains incompletely defined. Most large imaging cohorts have enrolled participants from middle age onward, whereas studies in adults younger than 40 years have often been small, selected, or based on surrogate markers rather than direct quantification of plaque.[10-13] As a result, there is no clear age- and sex-specific atlas to demonstrate when atherosclerosis is already present, where it is distributed, and differences in the accumulation of atherosclerosis in a cross-sectional cohort from early adulthood through later adult life.

The REACT Initiative was designed to address this gap. We systematically assessed silent atherosclerosis in adults 18 to 70 years of age without known clinical atherosclerotic cardiovascular disease, using standardized multimodal imaging of the carotid, femoral, and coronary arteries together with comprehensive clinical and biological phenotyping. Here, we report the baseline age- and sex-specific prevalence, vascular distribution, and plaque volume across adult life, and examine the extent to which conventional cardiovascular risk assessment identifies participants with established but clinically silent atherosclerosis.

METHODS

Study design and oversight

REACT is a multicenter Danish and Spanish prospective cohort study, as described previously.[14,15] The study was designed by the academic investigators and conducted in accordance with the protocol, which is available with the full text of this article online at NEJM.org. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by ethics committees in Denmark (H-24047468) and in Spain (CEI PI 76_2024). All participants provided written informed consent and were informed about their own results. The funder had no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; the preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication. All authors had access to the data and vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol. Expanded information on trial oversight and responsibilities can be found in the Supplementary Appendix available online at NEJM.org.

Study participants and assessments

Adults 18 to 70 years of age were eligible if they had no history of established clinical atherosclerotic cardiovascular disease such as myocardial infarction, ischemic stroke, coronary revascularization, or peripheral artery disease. Symptoms such as angina or claudication in the absence of established clinical atherosclerotic cardiovascular disease were not formally excluded. Enrollment was designed a priori to include approximately 2000 participants in each of the 18 to 29-year and 60 to 70-year age strata and approximately 4000 participants in each of the 30 to 39-year, 40 to 49-year and 50 to 59-year age strata, with balance according to country and sex within each stratum (Tables S1 and S2 in the Supplementary Appendix).

Participants underwent multimodal imaging for silent atherosclerosis in the carotid, femoral, and coronary arteries. Carotid and femoral atherosclerosis was assessed by three-dimensional vascular ultrasound. Coronary atherosclerosis was assessed by coronary computed tomography angiography, and coronary calcification by non-contrast computed tomography. Cardiovascular risk was estimated according to the Systematic Coronary Risk Evaluation 2 (SCORE2) framework, which predicts the 10-year risk of fatal and non-fatal cardiovascular disease in European individuals 40 to 69 years of age (a higher score indicates a higher risk). In Denmark, participants were identified by stratified random sampling from the Civil Registration System; in Spain, participants were recruited by open advertisement to the general public. Details of recruitment, sampling, eligibility criteria, imaging definitions, clinical

assessments, laboratory methods, and statistical handling of imaging variables are provided in the protocol and the Supplementary Appendix.

Outcomes

The primary outcome was the presence of silent atherosclerosis, defined as plaque in at least one examined vascular territory. Secondary outcomes included the presence of plaque in each vascular territory, plaque volume in each territory, global peripheral plaque volume, coronary plaque volume, and coronary artery calcium score. Global peripheral plaque volume was defined as the sum of plaque volumes in the bilateral carotid and femoral arteries. Coronary plaque volume was defined as the sum of plaque volumes in the coronary arteries. Coronary artery calcium score was expressed in Agatston units.

Statistical analysis

Prevalence of silent atherosclerosis was calculated as the percentage of participants with plaque in at least one examined vascular territory. Estimates are presented with 95% confidence intervals (CI). Cross-sectional age trajectories of silent atherosclerosis were estimated with cubic splines with three degrees of freedom fitted for age; observed prevalence within each age stratum was superimposed on the fitted curves at the mean age of the age stratum. To evaluate the association between any two variables, multivariable regression models were used. Continuous, normally distributed variables were analyzed using linear regression, whereas highly skewed continuous variables were log-transformed and evaluated via log-linear regression models. Logistic regression was applied to binary outcomes. Categorical variables were assessed using multinomial logistic regression, and ordinal outcomes were modeled via ordinal logistic regression. All models were adjusted by country, sex and age excluding collinear variables, e.g., age, sex, or country were not adjusted for themselves. Adjusted odds ratios are reported. For comparative purposes, continuous clinical biomarkers and biochemical metrics were standardized (mean of 0, standard deviation of 1) to express associations per 1-standard-deviation increase. To assess the effect of age on atherosclerosis prevalence, continuous age was divided by 10 and entered into the multivariable logistic regression model. Consequently, the resulting regression coefficient represents the change in the log-odds of silent atherosclerosis per 10-year increment of age, and its exponentiated value is interpreted as the adjusted odds ratio per decade of life. There was no adjustment for multiplicity, the unadjusted CI should be interpreted as descriptive and the intervals may not be used in place of hypothesis testing. Analyses were performed with R statistical software, version 4.4.0 (R Project for Statistical Computing). Further details are listed in the Supplementary Material.

RESULTS

Participants

From November 2024 through June 2026, a total of 16,808 participants were enrolled, of whom 50.3% were recruited in Spain and 49.7% in Denmark; the mean age of participants was 45±12.5 years and 51.4% were women. Imaging for analysis was available for the carotid arteries in 16,317 participants, the femoral arteries in 15,844, and the coronary arteries in 14,140. Complete three-territory imaging was available in 13,186 participants, who constituted the primary analysis population for prevalence (Figs. S1 and S2). Baseline characteristics and estimated (SCORE2) risk are shown in Table 1, and Tables S3 to S5. Overall, the study population seemed to be representative to the background populations (Table S2).

Prevalence of silent atherosclerosis

Silent atherosclerosis in at least one vascular territory was present in 57.1% (95% CI, 56.3 to 58.0) of participants with complete imaging and was more prevalent in men (63.4%; 95% CI, 62.2 to 64.6) than in women (50.9%; 95% CI, 49.7 to 52.1) with an adjusted odds ratio of 0.44 (95% CI, 0.40 to 0.48) for women versus men (Tables S6 and S7). Silent atherosclerosis was detectable in the youngest age stratum, affecting 8.7% (95% CI, 6.7 to 11.1) of men and 6.7% (95% CI, 5.1 to 8.7) of women 18 to 29 years of age, and was present in 34.6% (95% CI, 32.2 to 37.0) of men and 21.3% (95% CI, 19.2 to 23.5) of women 30 to 39 years of age (Table S6 and S7). The prevalence of silent atherosclerosis increased with the age strata in both sexes (adjusted odds ratio per 10-year increase, 4.52 [95% CI, 4.21 to 4.87] for men; 3.85 [95% CI, 3.61 to 4.12] for women). The age-related pattern differed between men and women: in men, the prevalence of silent atherosclerosis increased from the third decade age strata and began to plateau by midlife; in women, the steepest increase occurred in the age strata after 40 years of age, narrowing the sex difference with increasing age (Fig. 1A-B, Table S6). Among participants 60 to 70 years of age, only 1.9% (95% CI, 1.1 to 3.0) of men and 8.1% (95% CI, 6.4 to 10.0) of women had no plaque detected in any examined territory (Fig. 2). By vascular territory, carotid, femoral, and coronary atherosclerosis prevalence increased broadly in parallel in men, whereas in women carotid atherosclerosis predominated and femoral and coronary involvement were less frequent until later adult life age strata (Fig. 1B-D). The prevalence of silent atherosclerosis was similar in Spain and Denmark, except among women 50 to 59 years of age, for whom the prevalence was lower in Spain (Fig. S3).

Distribution of silent atherosclerosis across vascular territories

Peripheral atherosclerosis

Among younger participants, silent atherosclerosis was usually identified in the peripheral vasculature, confined to a single vascular territory, and most often detected in the carotid arteries. Within the increasing age strata, combined carotid and femoral artery involvement became more common, particularly among men (Table S6).

Coronary atherosclerosis

Isolated coronary artery atherosclerosis was uncommon in every age stratum, reaching at most 9.3% (95% CI, 7.9 to 10.8) in men and 5.0% (95% CI, 4.0 to 6.1) in women (Table S6 and Fig. 2). Coronary atherosclerosis severity and calcification increased with age in both sexes (Fig. 3A-B, and Fig. S4). Coronary plaque was frequently present without detectable calcium, particularly at younger ages: among participants 30 to 39 years of age with coronary plaque, 41.8% (95% CI, 32.5 to 51.6) of men and 48.4% (95% CI, 30.2 to 66.9) of women had a coronary artery calcium score of 0; this proportion declined with age but was still observed in the 60 to 70-year stratum (Figs. S5 to S8).

Comparison across Vascular Territories

Atherosclerosis in different vascular territories was strongly interrelated. Among participants with coronary plaque, 82.0% (95% CI, 80.7 to 83.2) also had peripheral arterial plaque, as compared with 41.5% (95% CI, 40.5 to 42.5) among those without coronary artery plaque (Fig. 1B and Fig. S9). The probability of coronary artery atherosclerosis increased with greater peripheral plaque volume, with odds ratios of 1.32, 1.85, and 3.70 across increasing plaque-volume quartiles, respectively, as compared with no peripheral plaque. Atherosclerosis was increasingly multiterritorial with increasing age. Among participants 30 to 39 years of age, two or three territories were involved in 6.0% (95% CI, 4.9 to 7.3) of men and 2.6% (95% CI, 1.8 to 3.6) of women, whereas among those 60 to 70 years of age, all three territories were involved in 56.3% (95% CI, 53.0 to 59.6) of men and 30.7% (95% CI, 27.8 to 33.7) of women (Table S6; Fig. 2).

Plaque Volume

Among participants with plaque, the median plaque volume was 23.9 mm^3 (interquartile range, 10.2 to 58.4) in the carotid arteries, 44.8 mm^3 (interquartile range, 16.0 to 120.3) in the femoral arteries, and 39.7 mm^3 (interquartile range, 13.4 to 116.6) across the combined peripheral territories; the median coronary plaque volume was 74.7 mm^3 (interquartile range, 32.0 to 181.4). Plaque volume increased with age, with cross-sectional age-related patterns consistent with an exponential increase (Fig. 3C and 3D). Carotid and coronary artery plaque volume increased more steeply with age in men than in women, whereas femoral artery plaque growth was similar between the sexes (Fig. S10).

Silent Atherosclerosis and Cardiovascular Risk Classification

Participants with silent atherosclerosis had older age, more cardiovascular risk factors, and higher SCORE2 risk than those without plaque; these differences were greatest among participants with combined peripheral and coronary artery atherosclerosis (Table S8). SCORE2 classified only 17 participants (0.5%) with single-territory silent atherosclerosis and 97 participants (3.8%) with combined peripheral and coronary artery silent atherosclerosis as being in the high 10-year risk category. A high SCORE2 risk was highly specific (99.8%) but had low sensitivity (1.9%) for silent atherosclerosis, whereas a moderate-to-high SCORE2 risk had a specificity of 87.9% and a sensitivity of 34.1%. The discordance was most pronounced in younger participants and varied according to individual risk factors (Fig. 4); findings were similar when excluding participants on lipid-lowering or antihypertensive therapy (Fig. S11). There were a total of 115 adverse events and 10 serious adverse events associated with the study procedures (Table S9).

DISCUSSION

In this large, systematic cross-sectional imaging study of adults 18 to 70 years of age without known atherosclerotic cardiovascular disease, silent atherosclerosis was already detectable in approximately 1 in 13 adults 18 to 29 years of age and increased sigmoidally to 9 in 10 by 60 to 70 of age. Prevalence increased earlier in men, whereas women showed a later and particularly steep midlife increase. In addition, increasing age was associated with more frequent multiterritory atherosclerosis and an exponential increase in plaque volume. These data support the concept of silent atherosclerosis as a systemic, progressive disease process with men showing an approximately 5-to-10-year earlier atherosclerotic phenotype than women.

Imaging studies have consistently shown that atherosclerosis is common in apparently healthy adults. In BioImage (A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population) that enrolled asymptomatic participants 55 to 80 years of age, it was present in 58% of participants, and greater carotid artery plaque and coronary artery calcium levels independently predicted cardiovascular events and death.[4,5] In MESA (Multi-Ethnic Study of Atherosclerosis) that included participants 45 to 84 years of age, about half had coronary calcium, which predicted coronary events independent of traditional risk factors.[6] In PESA (Progression of Early Subclinical Atherosclerosis) that included participants 40 to 54 years of age, the carotid, iliac, femoral arteries, , the aorta, and the coronary arteries found that silent atherosclerosis was present in 63% of participants.[16] Plaque burden progressed over time, with modifiable risk factors most influential at younger ages.[9] In SCAPIS (Swedish

CardioPulmonary bioImage Study) that included individuals 50 to 64 years of age, silent coronary artery atherosclerosis was present in 42.1% of participants, and obstructive in 5.2%.[7] Coronary CT angiography in the Copenhagen General Population Study that included participants 40 years of age or older showed silent coronary atherosclerosis in 46%, being obstructive in 10%.[8] In both the SCAPIS and the Copenhagen General Population Study, the highest myocardial-infarction risk was demonstrated in individuals with obstructive or extensive coronary artery disease.[17]

The present study extends these earlier observations across the full adult life course, with equal representation of women and men using standardized imaging of the carotid, femoral, and coronary arteries. Because silent atherosclerosis predicts ischemic events and death independent of traditional risk factors,[4,5,8,12,18] its detection in young adults may identify a population at increased long-term risk, at a stage where the benefit of risk-factor control seems greatest.[19,20]

We observed that plaque volume increased more steeply with age in men despite sex differences in cardiovascular risk factors being more pronounced at younger than older ages. This apparent paradox may reflect the cumulative rather than cross-sectional effects of cardiovascular risk exposure. Sex-related biological mechanisms may also play a role. The observed marked increase in coronary artery calcification after the age of 50 may have been influenced by the higher use of statins in older participants, particularly in men.

The results reported here have implications for detection strategies. Our findings suggest that imaging of the carotid arteries provided the highest diagnostic yield. Still, 18% of individuals with atherosclerosis in femoral arteries but not carotids would be misclassified if only the carotid arteries were examined. In younger adults, coronary artery plaque was frequently present despite the absence of calcification, indicating that calcium scoring alone does not exclude early coronary atherosclerosis.

Current primary-prevention guidelines rely predominantly on absolute-risk estimation tools, including the PREVENT (Predicting the Risk of Cardiovascular Disease Events) equations in the United States and SCORE2 in Europe, to guide the intensity of risk-factor modification.[21-24] However, these scores are strongly influenced by age and tend to assign low risk to young adults, even in the presence of relevant risk-factor exposure. Moreover, these tools are not calibrated for adults younger than 30 and 40 years of age in the US and Europe, respectively. Consistent with this, a high or moderate-to-high risk SCORE2 classification identified only a small minority of participants who actually had silent atherosclerosis. Thus, risk-factor-based scores and direct imaging capture different information, especially at younger ages. These

results support that primary prevention strategies informed by imaging may improve risk assessment and start early in life.

The age-related increase in prevalence differed between the sexes, with women showing a steeper rise between 40 and 60 years of age, broadly overlapping with the menopausal transition. Menopause, especially early, has been associated with higher cardiovascular risk.[25-27]

Our study has limitations. The analyses are cross-sectional, and the age-related patterns should not be interpreted directly as within-person progression. Enrollment was stratified by age, sex, and country; therefore, the overall prevalence should be interpreted as a cross-sectional estimate rather than as a population-weighted estimate. Complete three-territory imaging was available in 13,186 of 16,808 enrolled participants, and incomplete imaging may have introduced selection bias. The cohort comprised individuals without known clinical atherosclerotic cardiovascular disease, and atherosclerosis outside the carotid, femoral, and coronary territories was not assessed. Healthy-participant bias may have led to underestimation of the true prevalence and extent of silent atherosclerosis. Exclusion criteria included history of atherosclerotic cardiovascular disease events but not symptoms such as chest pain or leg-pain during walking.

In conclusion, this cross-sectional study provides a large-scale atlas of silent atherosclerosis across adult life in men and women. Silent atherosclerosis showed age- and sex-related increases in cross-sectional prevalence and extent of systemic involvement. Most individuals with silent coronary atherosclerosis had peripheral atherosclerosis. Conventional 10-year risk classification identified only a minority of participants with established silent atherosclerosis.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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FIGURE LEGENDS

Figure 1: Prevalence of peripheral and coronary silent atherosclerosis across life

(a) Cross-sectional age pattern of silent atherosclerosis prevalence in men and women. (b) Atherosclerosis distribution in the three arterial vascular territories (coronary, femoral, carotid) stratified by age and sex. (c) Atherosclerosis prevalence for male participants in any territory (same as a) and for each vascular site. (d) Same as (c) for female participants. Age strata: 18-29, 30-39, 40-49, 50-59, and 60-70 years. For each age stratum, the prevalence and exact Clopper-Pearson 95% CI are shown. The lines represent logistic regression models with age modelled using natural cubic spline (df=3) and the shaded bands are pointwise 95% CI intervals. The confidence intervals should be interpreted as descriptive and not used for hypothesis testing.

Figure 2: Age-Related Distribution of Silent Atherosclerosis across Vascular Territories According to Sex

Bars show the percentage of participants within each age stratum with plaque in the indicated combination of arterial vascular territories: no plaque, carotid only, femoral only, coronary only, carotid and femoral, carotid and coronary, femoral and coronary, or all three territories. Percentages were calculated among all participants of the same sex and age stratum. Error bars indicate 95% confidence intervals. The confidence intervals should be interpreted as descriptive and not used for hypothesis testing.

Figure 3: Age-related differences in plaque burden across vascular territories

(a) Coronary atherosclerosis classified as obstructive (≥50% in at least one of the 17 coronary segments) or nonobstructive (<50% stenosis in all segments) and as extensive (stenosis in more than 5 of the 17 coronary segments) or non-extensive (stenosis in fewer than 5 segments). (b) Cross-sectional calcium score (Agatston unit) in participants with calcium>0 for male (R^2=11.4%) and female (R^2=6.4%). (c, d) Cross-sectional plaque volume fit in participants with plaque. Each line is the exponential fit of age predicting plaque volume in participants with plaque present for the respective territory: (c) males with plaque in carotid (R^2=17.6%), femoral (R^2=17.5%), and coronary (R^2=10.7%). (d) females with plaque in carotid (R^2=14.4%), femoral (R^2=15.0%), and coronary (R^2=7.0%).

Figure 4: Association between CV risk factors and silent atherosclerosis

(a) Age-specific discrimination (AUC) of SCORE2 for predicting silent atherosclerosis. For each age, the AUC is calculated for participants within ±5 years (e.g. at age 50 the AUC is calculated for participants 45 to 55 years of age). The line represents the AUC, and the shaded

area indicates pointwise 95% confidence intervals (DeLong). The prediction at ages <40 is shown in dashed line and a lighter gray to highlight that SCORE2 is not calibrated for participants <40 years of age. (b) Age-specific associations of SCORE2 components with silent atherosclerosis. Curves show adjusted odds ratios for each component as a function of age, estimated from logistic models using a natural cubic spline for age and the component-age interaction. Shaded area is the pointwise 95% confidence intervals. Points are odds ratios within each age strata and error bars show the 95% confidence interval. All the models were adjusted for country and the other SCORE2 components. The confidence intervals should be interpreted as descriptive and not used for hypothesis testing.

Table 1: Baseline characteristics and prevalence of CV risk factors in the REACT cohort

	Overall Population				Men						Women					
Characteristic	**All N = 16808**	**Men N = 8165**	**Women N = 8643**	**Est. (95% CI)**	**18–29 n = 982**	**30–39 n = 1917**	**40–49 n = 2105**	**50–59 n = 2124**	**60–70 n = 1037**	**Est. (95% CI)**	**18–29 n = 1233**	**30–39 n = 1957**	**40–49 n = 2040**	**50–59 n = 2247**	**60–70 n = 1166**	**Est. (95% CI)**
Age — yr	45.0± 12.5	45.1± 12.3	44.9± 12.7	-0.19 (-0.57, 0.19)	24.5± 3.2	35.3± 2.8	44.9± 2.9	54.2± 2.9	64.1± 3.0		24.5± 3.2	35.3± 2.9	45.1± 2.9	54.2± 2.8	64.1± 3.0	
Age [IQR] — yr	46.0 [36.0, 55.0]	46.0 [36.0, 54.0]	46.0 [35.0, 55.0]	0.00 (-0.00, 1.00)	25.0 [22.0, 27.0]	36.0 [33.0, 38.0]	45.0 [42.0, 47.0]	54.0 [52.0, 57.0]	64.0 [61.0, 67.0]		25.0 [22.0, 27.0]	36.0 [33.0, 38.0]	45.0 [43.0, 48.0]	54.0 [52.0, 57.0]	64.0 [61.0, 66.0]	
Country — no. (%)				0.99 (0.93, 1.05)												
Spain	8,462 (50.3%)	4,097 (50.2%)	4,365 (50.5%)		496 (50.5%)	923 (48.1%)	1,063 (50.5%)	1,060 (49.9%)	555 (53.5%)		732 (59.4%)	960 (49.1%)	944 (46.3%)	1,096 (48.8%)	633 (54.3%)	
Denmark	8,346 (49.7%)	4,068 (49.8%)	4,278 (49.5%)		486 (49.5%)	994 (51.9%)	1,042 (49.5%)	1,064 (50.1%)	482 (46.5%)		501 (40.6%)	997 (50.9%)	1,096 (53.7%)	1,151 (51.2%)	533 (45.7%)	
Body-mass index	26.2± 4.8	26.9± 4.2	25.4± 5.1	-1.45 (-1.59, -1.31)	24.9± 4.1	26.7± 4.3	27.2± 4.2	27.6± 4.0	27.4± 3.9	0.59 (0.52, 0.67)	23.5± (4.6)	25.3± (5.5)	25.6± (5.0)	26.2± (5.1)	26.1± (4.7)	0.62 (0.54, 0.71)
Systolic BP —mmHg	128.2± 16.5	133.9± 15.1	122.8± 16.0	-11.04 (-11.47, -10.61)	129.8± 12.1	130.4± 12.8	131.9± 14.4	137.0± 15.8	141.9± 16.9	3.24 (2.98, 3.49)	115.6± (10.3)	116.9± (12.1)	120.3± (14.5)	127.4± (16.3)	135.6 ± (18.0)	5.06 (4.82, 5.30)
Diastolic BP — mmHg	79.3± 11.4	81.6± 11.5	77.2± 10.9	-4.28 (-4.57, -3.98)	75.3± 10.2	78.9± 11.1	81.6± 11.4	85.1± 11.2	85.1± 10.5	2.76 (2.59, 2.94)	72.8± (9.2)	74.9± (10.1)	76.9± (11.0)	79.9± (10.9)	81.3± (10.5)	2.20 (2.04, 2.36)
LDL cholesterol — mmol/L	3.2± 0.9	3.3± 0.9	3.1± 0.8	-0.14 (-0.17, -0.12)	2.8± 0.8	3.3± 0.8	3.4± 0.8	3.4± 0.9	3.2± 0.9	0.09 (0.07, 0.10)	2.8± (0.7)	2.9± (0.7)	3.1± (0.8)	3.4± (0.8)	3.4± (0.9)	0.19 (0.18, 0.20)
HDL cholesterol —	1.5±	1.3±	1.6±	0.29	1.3±	1.3±	1.3±	1.4±	1.4±	0.03	1.6±	1.6±	1.6±	1.7±	1.8±	0.06

mmol/L	0.4	0.3	0.4	(0.28, 0.30)	0.3	0.3	0.3	0.3	0.3	(0.02, 0.03)	(0.3)	(0.4)	(0.4)	(0.4)	(0.4)	(0.05, 0.06)
Triglycerides [IQR] — mmol/L	0.9 [0.7, 1.4]	1.1 [0.7, 1.6]	0.8 [0.6, 1.2]	-0.13 (-0.14, -0.12)	0.9 [0.6, 1.4]	1.0 [0.7, 1.6]	1.1± [0.8, 1.7]	1.1 [0.8, 1.7]	1.1 [0.8, 1.6]	0.03 (0.02, 0.03)	0.7 [0.5, 1.0]	0.8 [0.6, 1.1]	0.8 [0.6, 1.1]	0.9 [0.7, 1.4]	1.0 [0.8, 1.5]	0.04 (0.04, 0.05)
Lipoprotein(a) [IQR] —nmol/L	23.1 [10.0, 77.9]	22.0 [9.1, 75.0]	24.4 [10.4, 79.5]	0.08 (0.05, 0.12)	18.6 [7.5, 63.0]	21.0 [9.0, 77.0]	22.3 [9.9, 74.1]	23.2 [10.5, 74.0]	26.0 [9.8, 94.0]	0.06 (0.04, 0.08)	20.6 [8.7, 68.0]	21.6 [9.0, 67.5]	23.3 [10.4, 73.3]	28.4 [12.0, 95.0]	30.5 [12.7, 103.2]	0.10 (0.08, 0.12)
C-reactive protein [IQR] — (mg/L)	1.0 [0.4, 2.0]	1.0 [0.6, 2.0]	1.0 [0.4, 2.0]	0.03 (0.01, 0.05)	1.0 [0.0, 1.2]	1.0 [0.4, 2.0]	1.0 [0.6, 2.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	0.05 (0.03, 0.06)	1.0 [0.0, 2.0]	1.0 [0.4, 2.0]	1.0 [0.4, 2.0]	1.0 [0.6, 2.0]	1.0 [1.0, 2.0]	0.03 (0.02, 0.05)
Lipid-lowering therapy — no./total no. (%)	1,708/16611 (10.3%)	959/7980 (12.0%)	749/8631 (8.7%)	0.66 (0.60, 0.74)	8/967 (0.8%)	54/1884 (2.9%)	167/1970 (8.5%)	384/2122 (18.1%)	346/1037 (33.4%)	2.53 (2.36, 2.73)	5/1233 (0.4%)	32/1957 (1.6%)	63/2032 (3.1%)	302/2244 (13.5%)	347/1165 (29.8%)	3.32 (3.04, 3.65)
Antihypertensive therapy — no./total no. (%)	1,893/16611 (11.4%)	997/7980 (12.5%)	896/8631 (10.4%)	0.79 (0.71, 0.87)	9/967 (0.9%)	44/1884 (2.3%)	145/1970 (7.4%)	436/2122 (20.5%)	363/1037 (35.0%)	2.74 (2.55, 2.96)	25/1233 (2.0%)	50/1957 (2.6%)	126/2032 (6.2%)	333/2244 (14.8%)	362/1165 (31.1%)	2.59 (2.40, 2.79)
Antidiabetic therapy — no./total no. (%)	1,169/16611 (7.0%)	452/7980 (5.7%)	717/8631 (8.3%)	1.52 (1.34, 1.71)	13/967 (1.3%)	62/1884 (3.3%)	97/1970 (4.9%)	165/2122 (7.8%)	115/1037 (11.1%)	1.60 (1.47, 1.74)	37/1233 (3.0%)	156/1957 (8.0%)	185/2032 (9.1%)	235/2244 (10.5%)	104/1165 (8.9%)	1.24 (1.16, 1.32)
Hormones after menopause — no./total no. (%)	-	-	476/8631 (5.5%)	-	-	-	-	-	-	-	3/1233 (0.2%)	9/1957 (0.5%)	76/2032 (3.7%)	256/2244 (11.4%)	132/1165 (11.3%)	2.49 (2.25, 2.75)
History of hypertension — no./total no. (%)	5,402/16684 (32.4%)	3,322/8055 (41.2%)	2,080/8629 (24.1%)	0.39 (0.36, 0.42)	215/969 (22.2%)	535/1891 (28.3%)	726/2034 (35.7%)	1,143/2124 (53.8%)	703/1037 (67.8%)	1.77 (1.70, 1.84)	88/1232 (7.1%)	218/1955 (11.2%)	375/2032 (18.5%)	755/2245 (33.6%)	644/1165 (55.3%)	2.25 (2.14, 2.37)
History of diabetes	1,242/16	502/7896	740/85	1.41	13/960	67/1871	111/1944	181/2088	130/1033	1.63	39/1217	158/1936	189/2001	243/2203	111/1158	1.25

mellitus — no./total no. (%)	411 (7.6%)	(6.4%)	15 (8.7%)	(1.25, 1.58)	(1.4%)	(3.6%)	(5.7%)	(8.7%)	(12.6%)	(1.51, 1.77)	(3.2%)	(8.2%)	(9.4%)	(11.0%)	(9.6%)	(1.17, 1.33)
Dyslipidemia — no./total no. (%)	5,408/16410 (33.0%)	3,159/7904 (40.0%)	2,249/8506 (26.4%)	0.52 (0.48, 0.55)	211/956 (22.1%)	606/1874 (32.3%)	787/1947 (40.4%)	993/2095 (47.4%)	562/1032 (54.5%)	1.42 (1.37, 1.48)	111/1212 (9.2%)	282/1935 (14.6%)	390/2002 (19.5%)	830/2200 (37.7%)	636/1157 (55.0%)	1.97 (1.89, 2.07)
Total cholesterol ≥240 mg/dL — no./total no. (%)	2,051/16416 (12.5%)	959/7907 (12.1%)	1,092/8509 (12.8%)	1.08 (0.98, 1.19)	34/958 (3.5%)	193/1875 (10.3%)	275/1953 (14.1%)	314/2090 (15.0%)	143/1031 (13.9%)	1.29 (1.22, 1.36)	44/1212 (3.6%)	122/1935 (6.3%)	195/2010 (9.7%)	457/2196 (20.8%)	274/1156 (23.7%)	1.76 (1.67, 1.87)
LDL-C ≥160 mg/dL — no./total no. (%)	2,183/16407 (13.3%)	1,198/7903 (15.2%)	985/8504 (11.6%)	0.73 (0.67, 0.80)	48/958 (5.0%)	276/1875 (14.7%)	345/1954 (17.7%)	378/2086 (18.1%)	151/1030 (14.7%)	1.20 (1.14, 1.26)	48/1212 (4.0%)	118/1934 (6.1%)	201/2007 (10.0%)	399/2196 (18.2%)	219/1155 (19.0%)	1.61 (1.52, 1.70)
HDL-C <40 mg/dL — no./total no. (%)	1,533/16413 (9.3%)	1,217/7906 (15.4%)	316/8507 (3.7%)	0.20 (0.18, 0.23)	159/958 (16.6%)	320/1875 (17.1%)	335/1953 (17.2%)	297/2089 (14.2%)	106/1031 (10.3%)	0.89 (0.85, 0.94)	47/1212 (3.9%)	111/1935 (5.7%)	86/2009 (4.3%)	49/2195 (2.2%)	23/1156 (2.0%)	0.78 (0.71, 0.85)
Obesity — no./total no. (%)	2,989/16798 (17.8%)	1,595/8162 (19.5%)	1,394/8636 (16.1%)	0.79 (0.73, 0.86)	103/982 (10.5%)	339/1916 (17.7%)	441/2103 (21.0%)	505/2124 (23.8%)	207/1037 (20.0%)	1.18 (1.13, 1.24)	101/1231 (8.2%)	324/1957 (16.6%)	334/2037 (16.4%)	428/2246 (19.0%)	207/1165 (17.8%)	1.19 (1.13, 1.24)
Family history of CVD — no./total no. (%)	4,073/16567 (24.6%)	1,868/8058 (23.2%)	2,205/8509 (25.9%)	1.16 (1.08, 1.25)	152/947 (16.1%)	411/1885 (21.8%)	515/2083 (24.7%)	518/2113 (24.5%)	272/1030 (26.4%)	1.13 (1.08, 1.18)	201/1183 (17.0%)	473/1928 (24.5%)	500/2018 (24.8%)	661/2227 (29.7%)	370/1153 (32.1%)	1.19 (1.15, 1.24)
Smoking status — no./total no. (%)																
Current	1,861/16533 (11.3%)	938/8046 (11.7%)	923/8487 (10.9%)	0.92 (0.84, 1.02)	127/945 (13.4%)	267/1884 (14.2%)	243/2080 (11.7%)	211/2107 (10.0%)	90/1030 (8.7%)	0.86 (0.81, 0.91)	150/1181 (12.7%)	221/1918 (11.5%)	209/2011 (10.4%)	240/2226 (10.8%)	103/1151 (8.9%)	0.91 (0.87, 0.96)
Former	5,730/16533 (34.7%)	2,724/8046 (33.9%)	3,006/8487 (35.4%	1.08 (1.01, 1.15)	182/945 (19.3%)	530/1884 (28.1%)	677/2080 (32.5%)	814/2107 (38.6%)	521/1030 (50.6%)	1.39 (1.34, 1.45)	233/1181 (19.7%)	511/1918 (26.6%)	737/2011 (36.6%)	940/2226 (42.2%)	585/1151 (50.8%)	1.44 (1.38, 1.49)

			)													
Never	8,942/16533 (54.1%)	4,384/8046 (54.5%)	4,558/8487 (53.7%)	0.96 (0.91, 1.03)	636/945 (67.3%)	1,087/1884 (57.7%)	1,160/2080 (55.8%)	1,082/2107 (51.4%)	419/1030 (40.7%)	0.79 (0.77, 0.82)	798/1181 (67.6%)	1,186/1918 (61.8%)	1,065/2011 (53.0%)	1,046/2226 (47.0%)	463/1151 (40.2%)	0.75 (0.72, 0.77)

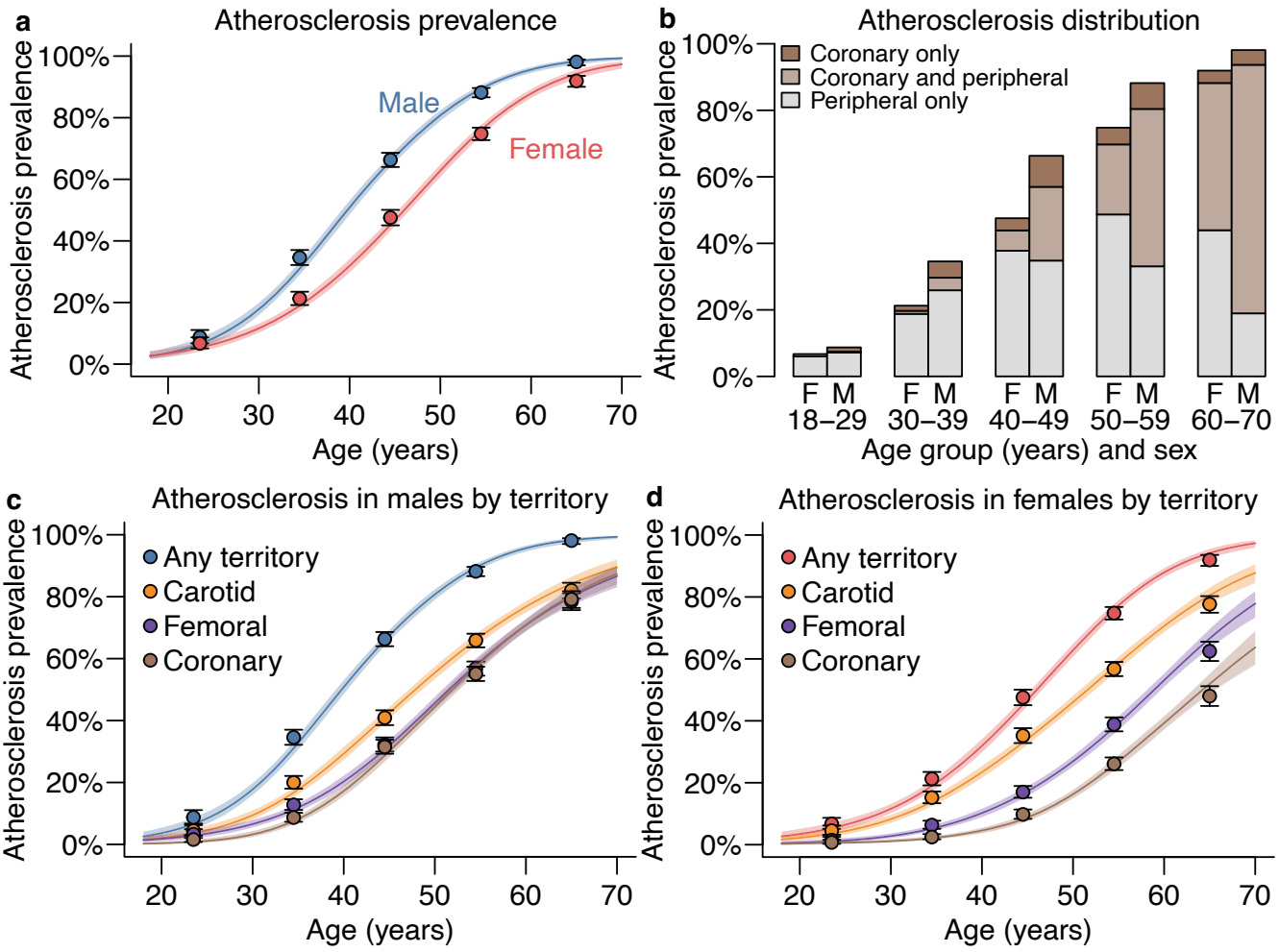
Notes: Descriptive data are presented as mean (standard deviation), median [interquartile range] for skewed variables, or n (column percentage) for categorical variables. Effect Estimates: To evaluate sex differences and age trends, data are presented as effect estimates with 95% confidence intervals (CIs). Continuous variables with normal distributions represent the Mean Difference calculated via linear regression. Skewed continuous variables (e.g., triglycerides, Lp(a), CRP, plaque volumes, and calcium scores) were log-transformed (log1p) prior to linear regression, representing log-scale mean differences. Categorical variables represent the Odds Ratio calculated via logistic regression (with multi-level/ordinal variables evaluated level-by-level). Comparisons: The Overall Population estimates compare Females vs. Males (reference). The Men and Women trend estimates represent the change per 10-year increase in age. Models are adjusted for age and country where applicable. Statistical Disclaimer: Given the absence of a prespecified method to adjust for multiplicity of inferences, all endpoints are reported as point estimates with 95% CIs without multiplicity adjustment and may not be used in place of formal hypothesis testing.

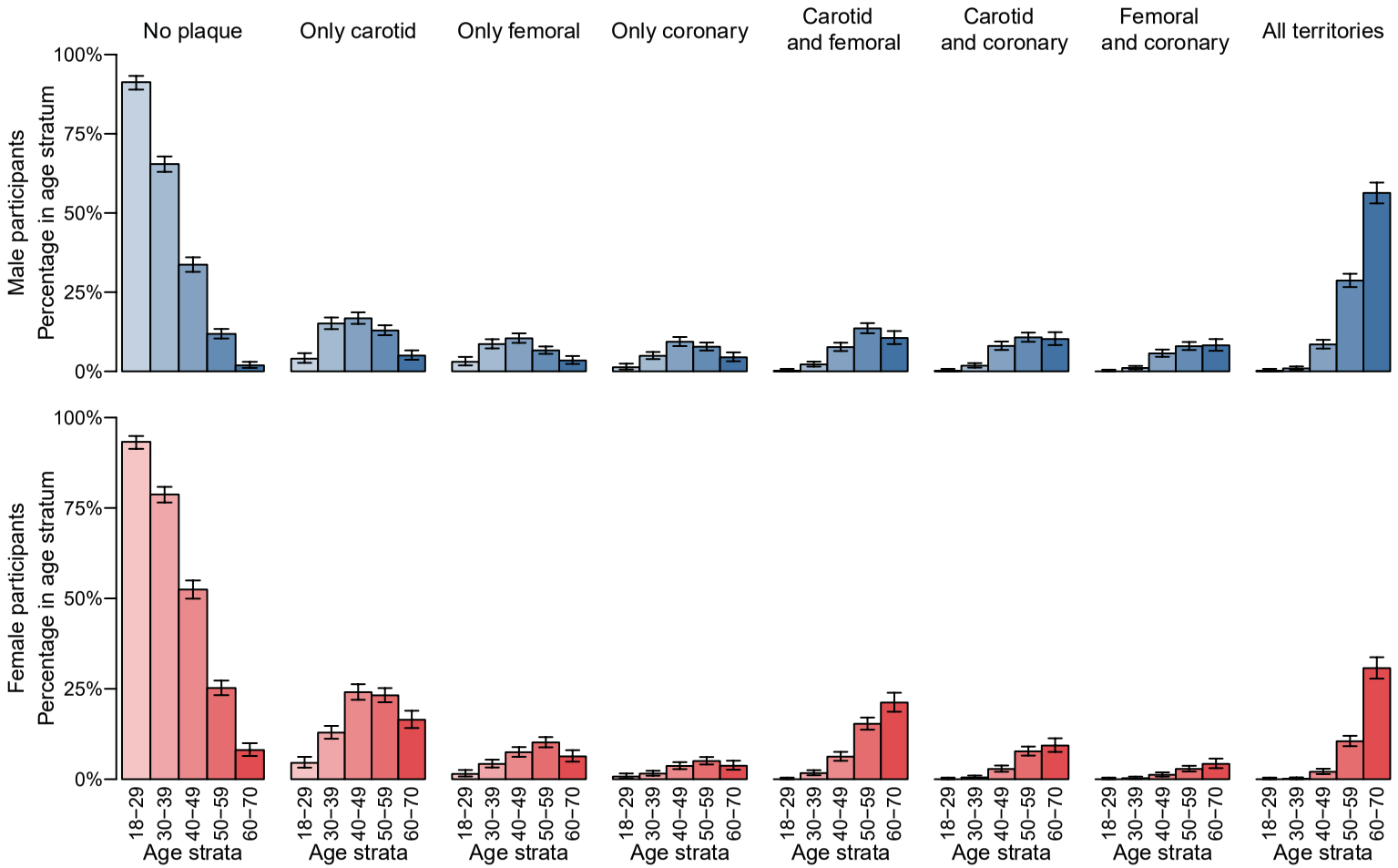
Participants were classified as positive for a risk factor if they met ≥ 1 of the following criteria: Hypertension: mean systolic blood pressure ≥ 140 mmHg, mean diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medication. Dyslipidemia: total cholesterol >6.21 mmol/L (240 mg/dL), LDL cholesterol ≥ 4.14 mmol/L (160 mg/dL), HDL cholesterol <1.03 mmol/L (40 mg/dL), or use of lipid-lowering medication. Diabetes: HbA1c ≥ 48 mmol/mol or use of antidiabetic medication. Obesity: Body Mass Index (BMI) ≥ 30 kg/m ². Family history of cardiovascular disease: History of heart or brain disease in a first-degree relative (father, mother, sibling, or child) at age <50 years for males or <60 years for females. Smoking status: classified as 'Never' (no history of smoking), 'Former' (history of smoking but currently stopped), or 'Current' (active smoker).

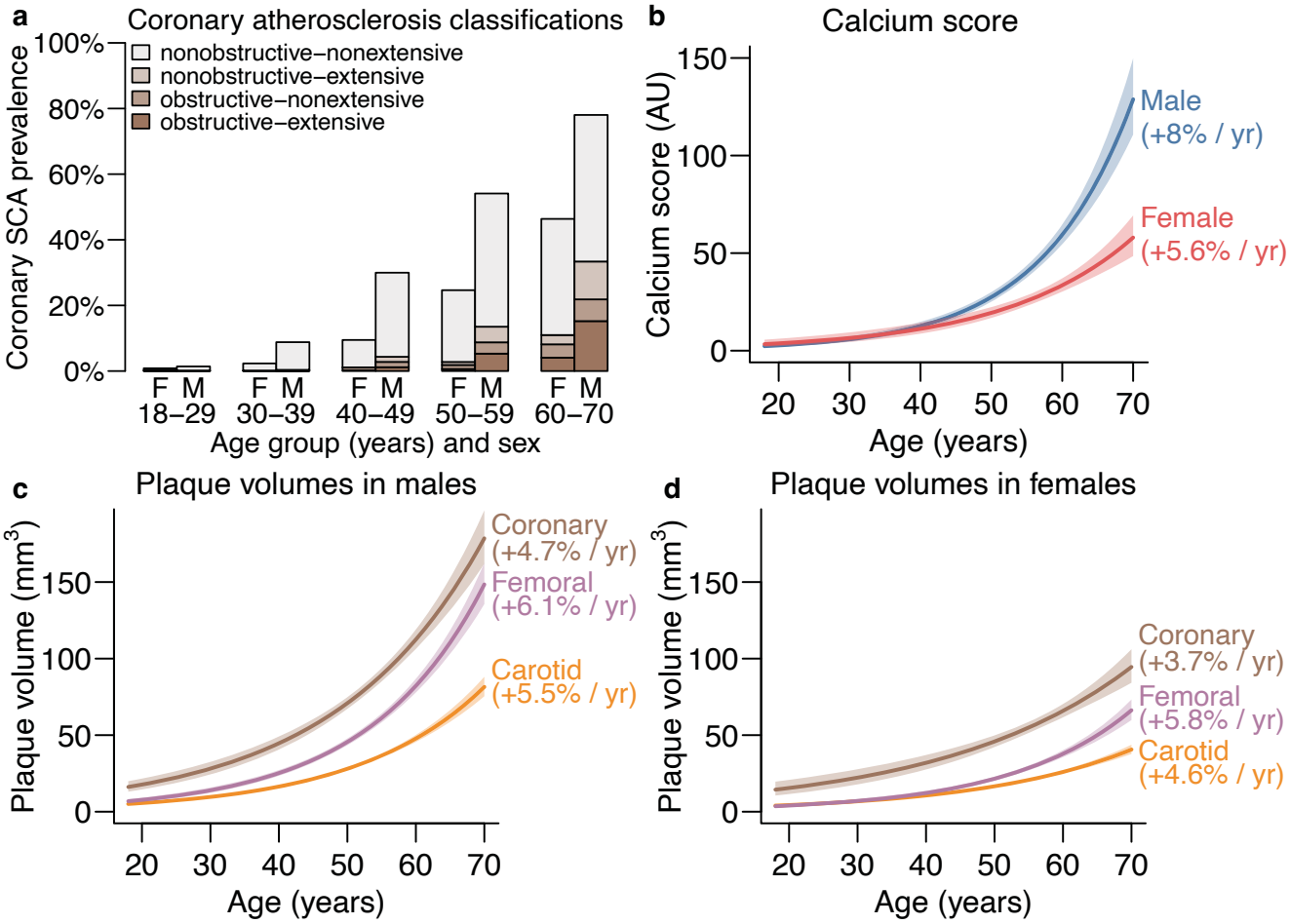
Using an LDL-cholesterol threshold of ≥190 mg/dL, the prevalence of dyslipidemia was 2.8% overall (3.3% in men and 2.4% in women), with age-specific prevalence of 0.7%, 3.4%, 4.1%, 4.1%, and 2.4% in men and 0.6%, 0.9%, 2.0%, 3.6%, and 5.3% in women across the 18–29, 30–

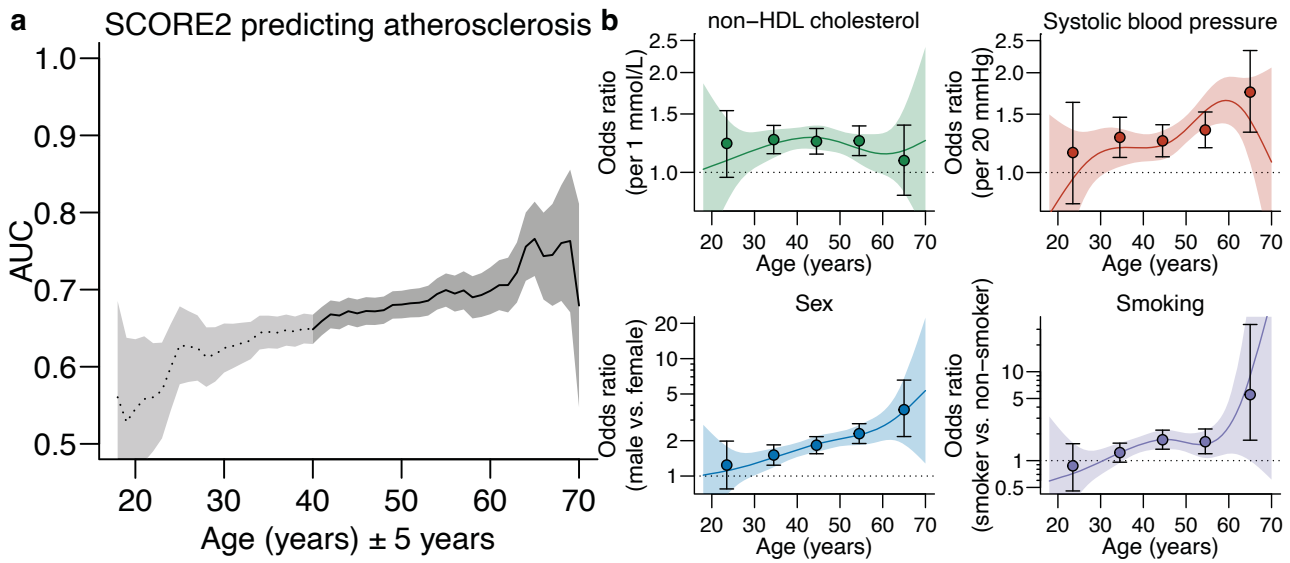
39, 40–49, 50–59, and 60–70 year old age groups, respectively.

For continuous variables, missing data were as follows: body mass index, 10 persons (3 men, 7 women); systolic BP, 7 (1 man, 6 women); diastolic BP, 7 (1 man, 6 women); LDL cholesterol, 401 (262 men, 139 women); HDL cholesterol, 395 (259 men, 136 women); triglycerides, 393 (257 men, 136 women); lipoprotein(a), 671 (391 men, 280 women); and C-reactive protein, 4,473 (2,185 men, 2,288 women).


a
Atherosclerosis prevalence
Atherosclerosis prevalence
100%
80%
60%
40%
20%
0%
Male
Female
20
30
40
50
60
70
Age (years)
b
Atherosclerosis distribution
Coronary only
Coronary and peripheral
Peripheral only
F M
18–29
30–39
40–49
50–59
60–70
Age group (years) and sex
c
Atherosclerosis in males by territory
Any territory
Carotid
Femoral
Coronary
d
Atherosclerosis in females by territory


No plaque
Only carotid
Only femoral
Only coronary
Carotid and femoral
Carotid and coronary
Femoral and coronary
All territories
Male participants
Percentage in age stratum
Female participants
Percentage in age stratum
100%
75%
50%
25%
0%
18–29
30–39
40–49
50–59
60–70
Age strata


a
Coronary atherosclerosis classifications
nonobstructive–nonextensive
nonobstructive–extensive
obstructive–nonextensive
obstructive–extensive
Coronary SCA prevalence
100%
80%
60%
40%
20%
0%
F M
18–29
30–39
40–49
50–59
60–70
Age group (years) and sex
b
Calcium score
Calcium score (AU)
150
100
50
0
Male
(+8% / yr)
Female
(+5.6% / yr)
20
30
40
50
60
70
Age (years)
c
Plaque volumes in males
Plaque volume (mm3)
150
100
50
0
Coronary
(+4.7% / yr)
Femoral
(+6.1% / yr)
Carotid
(+5.5% / yr)
20
30
40
50
60
70
Age (years)
d
Plaque volumes in females
Plaque volume (mm3)
150
100
50
0
Coronary
(+3.7% / yr)
Femoral
(+5.8% / yr)
Carotid
(+4.6% / yr)
20
30
40
50
60
70
Age (years)


a
SCORE2 predicting atherosclerosis
AUC
1.0
0.9
0.8
0.7
0.6
0.5
20
30
40
50
60
70
Age (years) ± 5 years
b
non−HDL cholesterol
Odds ratio
(per 1 mmol/L)
2.5
2.0
1.5
1.0
Age (years)
Systolic blood pressure
Odds ratio
(per 20 mmHg)
Sex
Odds ratio
(male vs. female)
20
10
5
2
1
Smoking
Odds ratio
(smoker vs. non−smoker)
0.5