Prevalence, Vascular Distribution, and Multiterritorial Extent of Subclinical Atherosclerosis in a Middle-Aged Cohort

The PESA (Progression of Early Subclinical Atherosclerosis) Study

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Background—Data are limited on the presence, distribution, and extent of subclinical atherosclerosis in middle-aged populations.

Methods and Results—The PESA (Progression of Early Subclinical Atherosclerosis) study prospectively enrolled 4184 asymptomatic participants 40 to 54 years of age (mean age, 45.8 years; 63% male) to evaluate the systemic extent of atherosclerosis in the carotid, abdominal aortic, and iliofemoral territories by 2-/3-dimensional ultrasound and coronary artery calcification by computed tomography. The extent of subclinical atherosclerosis, defined as presence of plaque or coronary artery calcification ≥1, was classified as focal (1 site affected), intermediate (2–3 sites), or generalized (4–6 sites) after exploration of each vascular site (right/left carotids, aorta, right/left iliofemorals, and coronary arteries). Subclinical atherosclerosis was present in 63% of participants (71% of men, 48% of women). Intermediate and generalized atherosclerosis was identified in 41%. Plaques were most common in the iliofemorals (44%), followed by the carotids (31%) and aorta (25%), whereas coronary artery calcification was present in 18%. Among participants with low Framingham Heart Study (FHS) 10-year risk, subclinical disease was detected in 58%, with intermediate or generalized disease in 36%. When longer-term risk was assessed (30-year FHS), 83% of participants at high risk had atherosclerosis, with 66% classified as intermediate or generalized.

Conclusions—Subclinical atherosclerosis was highly prevalent in this middle-aged cohort, with nearly half of the participants classified as having intermediate or generalized disease. Most participants at high FHS risk had subclinical disease; however, extensive atherosclerosis was also present in a substantial number of low-risk individuals, suggesting added value of imaging for diagnosis and prevention.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01410318.

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Key Words: atherosclerosis ■ epidemiology ■ multidetector computed tomography ■ population ■ risk assessment ■ ultrasonography

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The natural history of atherosclerosis involves a protracted subclinical phase, with disease often detected only at an advanced stage or after a cardiovascular event. This is of particular importance because cardiovascular events are often fatal and many deaths attributable to coronary artery disease are sudden. There is thus a clear need to identify disease at an early stage, and as a result, primary prevention forms the cornerstone of management. Currently, risk stratification scores have well-recognized limitations, notably in lower-risk groups such as women and younger people. Detection of atherosclerosis in its subclinical stage may help identify strategies to arrest disease development. Indeed, the significance of subclinical carotid atherosclerosis and coronary artery calcification (CAC) in relation to clinical outcomes has been established in the Multi-Ethnic Study of Atherosclerosis (MESA) study6,6 and in the recently published US High Risk Plaque Study.7

Clinical Perspective on p 2113

The introduction of noninvasive imaging techniques has unlocked the potential to evaluate atherosclerosis in asymptomatic populations. Specific imaging modalities include vascular ultrasound, computed tomography, and magnetic resonance imaging. Many imaging studies evaluated individual vascular territories, but given the systemic nature of atherosclerosis, a multiterritorial analysis has the potential to provide a more comprehensive overview of the distribution and burden of atherosclerosis.

The PESA (Progression of Early Subclinical Atherosclerosis) study evaluates atherosclerosis in the carotid, aortic, coronary, and iliofemoral territories using accessible noninvasive imaging techniques in asymptomatic middle-aged individuals. By evaluating multiple vascular beds in relatively young adults, we aim to improve our understanding of the origin and progression of atherosclerosis. Here, we present the prevalence, vascular distribution, and extent of subclinical atherosclerosis in the PESA cohort and their relation to cardiovascular risk algorithms.

Methods

Study Sample

The rationale and design of the PESA study have been described. Briefly, PESA-CNIC-Santander is a prospective cohort study of asymptomatic employees of the Santander Bank in Madrid who are 40 to 54 years of age and were consecutively recruited between June 2010 and February 2014. Participants with prior cardiovascular disease and any condition reducing life expectancy or affecting study adherence were not included. Participants were examined at baseline by ankle-brachial index (ABI), vascular ultrasound, and noncontrast computed tomography and will be followed up at 3 and 6 years. In addition, each visit includes clinical interviews, physical examination, fasting blood draw, urine sample, and a 12-lead ECG. The study protocol has been approved by the Instituto de Salud Carlos III Ethics Committee, and all eligible participants have provided written informed consent.

Traditional cardiovascular risk factors were determined from blood samples and interviews as follows: (1) diabetes mellitus: fasting plasma glucose ≥126 mg/dL, or treatment with insulin or oral hypoglycemic medication12; (2) arterial hypertension: systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication1; (3) dyslipidemia: total cholesterol ≥240 mg/dL, low-density lipoprotein cholesterol ≥160 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, or use of lipid-lowering drugs12; (4) smoking: current smoking status or a lifetime consumption of >100 cigarettes11; and (5) family history of cardiovascular disease: first-degree relative diagnosed with atherosclerosis before 55 years of age in men and 65 years of age in women.14 Obesity, defined as body mass index ≥30 kg/m², was also assessed.14 Cardiovascular risk was evaluated by the 10-year risk of coronary heart disease and the 30-year risk of cardiovascular disease from the Framingham Heart Study (FHS).7,7,8 as well as by the European Society of Cardiology’s SCORE (Systematic Coronary Risk Evaluation), which calculates 10-year risk of fatal cardiovascular disease, using the low cardiovascular risk charts applicable to Spain. FHS scores were classified as low (<10%), moderate (10–20%), or high (20%) risk and the SCORE risks as low (<1%) and moderate to high (≥1%). In light of recent US guidelines for statin therapy,16 we also calculated 10-year risk using the atherosclerotic cardiovascular disease (ASCVD) algorithm, an atherosclerotic risk calculator based on Pooled Cohort Equations,9 and cutoff values were defined as <5%, 5% to <7.5%, and ≥7.5% risk.

Vascular Ultrasound Imaging

The 2-/3-dimensional vascular ultrasound protocol has been described. The presence of atherosclerotic plaques was assessed by cross-sectional sweep of carotids, infrarenal abdominal aorta, and iliofemoral arteries. Plaque was defined as a focal protrusion into the arterial lumen of thickness >0.5 mm or >50% of the surrounding intima-media thickness or a diffuse thickness >1.5 mm measured between the media-adventitia and intima-lumen interfaces. Many semiautomated detection of carotid and femoral intima-media thickness was also assessed (details are given in the online-only Data Supplement). Ultrasound studies were analyzed with QLAB (Philips Healthcare, Bothell, WA) at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) Core Imaging Laboratory. Imaging quality was evaluated as optimal, suboptimal, or noninterpretable, and inclusion of studies was determined by consensus. Good reproducibility was found for the presence of plaque in all territories (κ = 0.75 for carotids, 0.89 for aorta, 0.88 for iliofemorals). The ABI was calculated as the ratio of systolic blood pressure in the posterior tibial artery to systolic blood pressure in the brachial artery using Doppler ultrasound and a standard sphygmomanometer. ABI values <0.9 were considered abnormal.

CAC by Computed Tomography

CAC was detected with a 16-slice computed tomography scanner (Philips Brilliance, Philips Healthcare, Andover, MA) using noncontrast prospective electrocardiography-gated acquisition. Estimated absorbed radiation was 0.6 to 1.2 mSv. CAC score (CACS) was calculated by the Agatston method and graded as 1 to 99, 100 to 399, and ≥400. Three trained technicians blinded to other imaging results and supervised by experienced physicians quantified CACS.

Definition of Subclinical Atherosclerosis

Subclinical atherosclerosis was defined as the presence of atherosclerotic plaques in the carotid, aortic, or iliofemoral territories or CACS ≥1. The multiterritorial extent of subclinical atherosclerosis was defined according to the number of vascular sites affected (right carotid, left carotid, abdominal aorta, right iliofemoral, left iliofemoral, and coronary arteries). Participants were classified as disease free (0 vascular sites affected) or having focal (1 site), intermediate (2–3 sites), or generalized (4–6 sites) atherosclerosis.

Statistical Analysis

Baseline characteristics were calculated using mean and standard deviation for continuous variables and count and proportions for categorical variables. Differences between continuous variables and categorical variables were tested with unpaired t tests and χ² tests.
Table 1. Demographic Characteristics and Cardiovascular Risk Factors

| Risk Factor                             | Total (n=4066) | Men (n=2573) | Women (n=1493) | P Value |
|-----------------------------------------|----------------|--------------|----------------|---------|
| **Baseline characteristics**            |                |              |                |         |
| Age, y                                  | 45.8±4.3      | 46.3±4.4     | 45±3.9         | <0.001  |
| BMI, kg/m²                               | 26.2±3.8      | 27.4±3.4     | 24.1±3.6       | <0.001  |
| Obesity (BMI ≥30 kg/m²), n (%)           | 598 (15)      | 493 (19)     | 105 (7)        | <0.001  |
| SBP, mm Hg                              | 116±12.5      | 121±11.1     | 109±11         | <0.001  |
| DBP, mm Hg                              | 72.5±9.4      | 74.7±9.1     | 68.7±8.7       | <0.001  |
| Total cholesterol, mg/dL                | 201±33.3      | 203±34.2     | 196±31.2       | <0.001  |
| LDL-C, mg/dL                            | 132±29.8      | 136±30.3     | 125±27.5       | <0.001  |
| HDL-C, mg/dL                            | 49±12.2       | 44.8±10.2    | 56.3±11.9      | <0.001  |
| Triglycerides, mg/dL                    | 95±57.2       | 109±64       | 70.6±29.9      | <0.001  |
| Fasting glucose, mg/dL                  | 90.6±13.8     | 93.4±15      | 85.7±9.7       |         |
| Hemoglobin A1c, %                       | 5.44±0.5      | 5.49±0.5     | 5.36±0.4       | <0.001  |
| Lipid-lowering therapy, n (%)           | 287 (7)       | 242 (9)      | 45 (3)         |         |
| Antihypertensive therapy, n (%)         | 309 (8)       | 266 (10)     | 43 (3)         |         |
| Antidiabetic therapy, n (%)             | 64 (2)        | 56 (2)       | 8 (0.5)        |         |
| **Traditional CV risk factors, n (%)**  |                |              |                |         |
| Dyslipidemia                             | 1691 (42)     | 1374 (53)    | 317 (21)       | <0.001  |
| Total cholesterol ≥240 mg/dL            | 475 (12)      | 345 (13)     | 130 (9)        | <0.001  |
| LDL-C ≥160 mg/dL                        | 688 (17)      | 522 (20)     | 166 (11)       | <0.001  |
| HDL-C <40 mg/dL                         | 983 (24)      | 880 (34)     | 103 (7)        | <0.001  |
| Current smoking                         | 835 (21)      | 486 (19)     | 349 (23)       | <0.001  |
| Family history of CV disease            | 646 (16)      | 398 (16)     | 248 (17)       | 0.337   |
| Hypertension                            | 481 (12)      | 409 (16)     | 72 (5)         | <0.001  |
| Diabetes mellitus                       | 81 (2)        | 72 (3)       | 9 (0.6)        | <0.001  |
| No. of CV risk factors, n (%)           |                |              |                |         |
| 0                                       | 1535 (38)     | 777 (30)     | 758 (51)       | <0.001  |
| 1                                       | 1572 (39)     | 1053 (41)    | 519 (35)       | <0.001  |
| 2                                       | 746 (18)      | 569 (22)     | 177 (12)       | <0.001  |
| >2                                      | 213 (5)       | 174 (7)      | 39 (3)         | <0.001  |

Data are expressed as mean±SD when appropriate. P values are derived from independent t tests for continuous variables and χ² for categorical variables. BMI indicates body mass index; CV, cardiovascular; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

respectively. Nonnormally distributed variables (triglycerides, fasting glucose, hemoglobin A1c, CACS, and cardiovascular risk scales) were log transformed before analysis to normalize the distribution. Age- and sex-adjusted associations between vascular disease in each territory were examined by use of logistic regression models. The reproducibility of ultrasound measurements was studied by replicating the analysis of a random sample of 60 studies 3 months after the initial assessment, and the Cohen κ was used for the agreement analysis. Statistical analyses were conducted with Stata 12 (StataCorp, College Station, TX).

Results

The PESA cohort comprised 4184 participants (78% of the eligible population). At the time of publication, 34 individuals (0.8%) had discontinued the study, and 84 (2%) either were excluded for missing data or were pending evaluation, resulting in 4066 participants available for analysis. After exclusion of noninterpretable images (64 participants, 1.5%), the sample available for imaging analysis was 4002 (98% of the cohort). Only 1 case of abnormal ABI was detected in the first 2536 participants; therefore, the protocol was amended to discontinue measurement of ABI in subsequent examinations. Baseline demographic characteristics and cardiovascular risk factors are summarized in Table 1. The average age of the participants was 45.8 years; 63% were male, and 99.9% were white. The most prevalent traditional risk factor was dyslipidemia (42%), followed by smoking (21%), family history (16%), hypertension (12%), and diabetes mellitus (2%). Additionally, obesity was found in 15% of PESA participants. The presence of traditional risk factors and obesity was higher in men, with the exception of smoking (23% women and 19% men) and family history (17% women and 16% men). Most participants (62%) had at least 1 traditional risk factor, 18% had 2 risk factors, and 5% had ≥3 risk factors. Aside from family history, the prevalence of traditional risk factors except for smoking and diabetes mellitus in women increased with age (Table I in the online-only Data Supplement). Risk-factor distribution was not significantly different in the participants not included in the imaging analysis (1.5%), thus excluding systematic bias.

Prevalence, Vascular Distribution, and Extent of Subclinical Atherosclerosis

The prevalence of subclinical atherosclerosis (presence of plaque or CACS ≥1) was 63%. Plaques were detected by ultrasound in 60% of participants (31% in the carotids, 25% in the aorta, and 44% in the iliofemoral arteries), and 18% had CAC (CACS: 1–99 in 14%, 100–399 in 3%, and ≥400 in 0.7%). In men, subclinical atherosclerosis was more prevalent (71% versus 48% in women) across all vascular territories, with differences most pronounced in the iliofemoral and coronary arteries (Figure 1). Of the 23 participants with CACS ≥400, only 1 participant was female (Table I in the online-only Data Supplement). Atherosclerosis prevalence increased with age for both sexes and across all vascular territories, and only the presence of aortic disease was found to be independent of sex (Figure 2). Associations between subclinical atherosclerosis in different territories and each individual risk factor are shown in Table II in the online-only Data Supplement (details are provided in the online-only Data Supplement).

The presence of iliofemoral disease was more strongly correlated with aortic disease and CAC than with carotid disease (Table 2). Furthermore, having disease in the iliofemorals corresponds to a 70% probability of finding disease in any other territory explored. Conversely, the absence of plaque in the
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disease in 21% versus 35% versus 42%, CACS ≥1 in 12% versus 33% versus 45%, and iliofemoral disease in 37% versus 64% versus 79% (P<0.001 for all comparisons). Figure 5 shows the relation between the extent of atherosclerosis and the groups who meet the American Heart Association/American College of Cardiology criteria for statin treatment (≥7.5% ASCVD risk, diabetes mellitus, or low-density lipoprotein ≥190 mg/dL), those considered for statin (5%–<7.5% ASCVD risk), and those not considered for statin (<5% ASCVD risk). Interestingly, the prevalence of generalized disease increased with higher ASCVD risk score (8% versus 24% versus 37% in the <5%, 5%–<7.5%, and ≥7.5% risk groups, respectively).

**Discussion**

The main findings from the PESA cohort are as follows: Subclinical atherosclerosis is highly prevalent in this middle-aged asymptomatic sample; the iliofemoral territory is the most frequently affected vascular site in the early stages of atherosclerosis; and most individuals classified at high risk by traditional scales (FHS and European SCORE) had subclinical

**Table 2. Associations Between the Presence of Atherosclerosis in Individual Vascular Territories**

| Carotid Disease | Coronary Calcification | Aortic Disease | Iliofemoral Disease |
|-----------------|------------------------|----------------|---------------------|
| OR (95% CI)     | 2.06 (1.73–2.47)       | 2.80 (2.40–3.27) | 2.13 (1.84–2.46)    |
| P value         | <0.001                 | <0.001          | <0.001              |
| Coronary calcification | 2.06 (1.73–2.47) | ...            | 2.48 (2.06–2.99) | 3.16 (2.60–3.84) |
| P value         | <0.001                 | <0.001          | <0.001              |
| Aortic disease  | 2.80 (2.40–3.27)       | 2.48 (2.06–2.99) | ...                | 4.85 (4.09–5.75) |
| P value         | <0.001                 | <0.001          | <0.001              |
| Iliofemoral disease | 2.13 (1.84–2.46) | 3.16 (2.60–3.84) | 4.85 (4.09–5.75) |
| P value         | <0.001                 | <0.001          | <0.001              |

Data are expressed as odds ratio (OR) and 95% confidence interval (CI) adjusted by age and sex and calculated with logistic regression models. Coronary artery calcification (CAC) was defined as a CAC score ≥1.
Subclinical Atherosclerosis Is Prevalent in Middle-Aged Individuals

Few population studies have investigated the prevalence and extent of subclinical atherosclerosis across multiple vascular sites in a middle-aged sample, despite atherosclerosis being a systemic disease with a long latent subclinical phase. In the MESA and Coronary Artery Risk Development in Young Adults (CARDIA) studies, evaluation of atherosclerosis was limited to carotid intima-media thickness and CAC.3,4 The Atherosclerosis Risk in Communities (ARIC) study focused only on carotid and popliteal territories assessed by ultrasound.9 The Heinz Nixdorf Recall, High Risk Plaque, and Rotterdam studies recruited older individuals with prior cardiovascular disease or a high-risk profile.1,7,20 Using a multiterritorial approach, the PESA study detected a high prevalence of subclinical disease, with nearly half the participants classified as having intermediate or generalized disease despite being predominantly at low risk according to traditional scales. This finding is probably attributable to the examination of several territories, including vascular areas more susceptible to disease such as the iliofemoral arteries, which were not explored in earlier studies. Other studies that investigated multiple vascular sites included only men with at least I risk factor,21 examined participants at higher risk,22 or explored fewer territories.23

An innovation of PESA is the early detection of atherosclerosis in other vascular territories even in the absence of CAC. A CACS of 0 could be considered indicative of absence of disease, but among PESA participants with CACS=0, nearly 60% had plaques at other vascular sites. Therefore, in this low-risk sample, the absence of CAC does not necessarily indicate that a participant is disease free. We hypothesize that by studying other vascular territories in subjects with CACS=0, we could identify those who will develop CAC in the future and who would likely benefit from more intensive preventive management. Although follow-up will be needed to confirm this hypothesis, multiterritorial assessment with vascular ultrasound—a safe, cost-efficient, reproducible, and simple technique—might be especially important at early stages of atherosclerosis in younger people with a high probability of zero CAC.

The added clinical value of a multiterritorial vascular evaluation is supported by the Carotid-Femoral Ultrasound Morphology and Cardiovascular Events (CAFES-CAVE) study, which showed that scanning only carotids or only femorals predicts 15% and 13% fewer events than examining both territories in a 10-year follow-up.24 This finding supports the view that the wider sampling that comes from exploring several territories overcomes the problem of not detecting a lesion when only 1 territory is examined. The predictive value of multiterritorial imaging will be assessed in detail with the appearance of events during PESA follow-up. The prognostic relevance of subclinical atherosclerosis is also supported by the MESA study14 and the recently published US High Risk Plaque Study,7 in which strong associations have been shown between cardiovascular events and subclinical carotid and coronary disease. Similarly, the Northern Manhattan Study demonstrated that subclinical carotid plaque is a precursor of cardiovascular events.25 These studies highlight the potential value of evaluating subclinical

| Table 3. Comparison of Demographics, Physical Examination, Traditional Cardiovascular Risk Factors, and Risk Scores Between Participants With Atherosclerosis in a Single Territory (Focal Disease) and Those With Multiple Territories Affected (Intermediate or Generalized Disease) |
|---------------------------------------------------------------|
|                                                                 |
| **Demographics and physical examination**                      |
| Age, y                                                        |
| Male sex, n (%)                                               |
| BMI, kg/m²                                                    |
| SBP, mm Hg                                                   |
| DBP, mm Hg                                                   |
| Total cholesterol, mg/dL                                      |
| LDL-C, mg/dL                                                  |
| HDL-C, mg/dL                                                  |
| Triglycerides, mg/dL                                          |
| Fasting glucose, mg/dL                                        |
| Hemoglobin A₁, %                                              |
| Lipid-lowering treatment, n (%)                               |
| Antihypertensive treatment, n (%)                             |
| Antidiabetic treatment, n (%)                                 |
| Total cholesterol ≥240 mg/dL                                 |
| LDL-C ≥160 mg/dL                                              |
| HDL-C <40 mg/dL                                               |
| Current smoking                                               |
| Family history of CV disease                                  |
| Hypertension                                                  |
| Diabetes mellitus                                             |
| No. of risk factors                                           |
| CV risk scores, %                                             |
| 10-y FHS                                                      |
| 30-y FHS                                                      |
| European SCORE                                               |
| ASCVD score                                                   |
| **Data are expressed as mean±SD when appropriate. P-values are derived from independent t tests for continuous variables and χ² for categorical variables. ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CV, cardiovascular; DBP, diastolic blood pressure; FHS, Framingham Heart Study; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; and SCORE, Systematic Coronary Risk Evaluation.** |

atherosclerosis, but atherosclerosis is also present in nearly 60% of participants classified at low risk, with intermediate or generalized disease in one third. Ongoing PESA follow-up over at least 6 years will enable study of associations between subclinical disease evaluated at baseline and subsequent cardiovascular events.
atherosclerosis in multiple territories for cardiovascular event prediction.

The association of increased subclinical atherosclerosis prevalence with male sex and age is consistent with previous reports and may be related to the natural history of the disease. In fact, the risk of atherosclerosis in men is similar to that in women 5 to 10 years older in this cohort. This discovery may assist in determining the most appropriate time window for atherosclerosis screening and intensification of primary cardiovascular prevention. We interestingly found that individuals at ≥7.5% ASCVD risk had substantial atherosclerosis compared with lower-risk individuals, especially in terms of CAC, and had a 4-fold higher prevalence of generalized disease. This interesting finding is in line with the proposed intensification of statin treatment in the most recent guidelines on the treatment of blood cholesterol.

The Iliofemoral Territory Is the Most Frequently Affected Vascular Site

The clear predominance of disease in the iliofemoral arteries is possibly related to specific patterns of shear stress and disturbed flow caused by the vessel curvature. In PESA participants, the presence of iliofemoral disease increases the risk of concurrent CAC and is predictive of disease elsewhere. Moreover, the absence of iliofemoral disease is strongly associated with the absence of atherosclerosis at other vascular sites. Thus, imaging of peripheral arteries may be a useful population-wide screening tool for detecting atherosclerosis in its early stages. Follow-up will be extremely valuable to clarify the impact of early detection of iliofemoral disease on the primary prevention of peripheral arterial disease because advanced stages are associated with higher risk of myocardial infarction and stroke.

The iliofemoral territory has traditionally not been examined as extensively as the carotids and CAC. Because of the inclusion of this territory in PESA, comparisons with other more commonly examined vascular sites are available. Indeed, evaluation of the iliofemoral arteries appears to be more valuable than CAC for detecting subclinical atherosclerosis, given the high prevalence (82%) of an CACS of 0 in this low-risk middle-aged sample, suggesting that CAC represents a more advanced stage of disease. Notably, the prevalence of abnormal ABI is low in PESA, consistent with previous studies that found a low prevalence in middle-aged individuals. This finding supports the idea that ABI adds little valuable information to the assessment of subclinical atherosclerosis.
information to the screening of subclinical atherosclerosis in the early stages of the disease.

Subclinical Atherosclerosis and Traditional Cardiovascular Risk Scales

Current risk stratification strategies have successfully identified individuals at risk of cardiovascular events. Traditional risk scales include the widely used FHS and SCORE, an adaptation of FHS that avoids risk overestimation in European populations with less coronary heart disease.14,32 However, the impact of these scales in younger, low-risk populations is limited, with many individuals still experiencing cardiovascular events and little success in promoting lifestyle changes.3 In a cohort of 122,458 patients with coronary disease, 9% to 13% of those <55 years of age had no conventional risk factors,33 indicating a disparity between traditional risk factors and the presence of disease in younger populations. The limited value of cardiovascular risk assessment by FHS alone in young healthy adults was raised in a recent study by Armstrong et al34 that demonstrated improved discrimination when risk classification includes left ventricular mass as an additional independent predictor of cardiovascular disease.

Although the FHS and the European SCORE scales were designed to assess risk of cardiovascular events derived from atherosclerosis, not the presence of subclinical atherosclerosis, we aimed to complement these predictive models by comparing the presence across different risk categories. Most individuals classified at high risk have subclinical atherosclerosis, with a high proportion having intermediate or generalized disease. However, subclinical atherosclerosis is also present in nearly 60% of PESA participants at low risk, with one third having at least 2 sites affected. In this regard, a substudy of the MESA and CARDIA participants detected higher carotid intima-media thickness and higher CAC in individuals with low 10-year but high lifetime risk compared with individuals with low 10-year and low lifetime risk. Together, these results strongly suggest an association of atherosclerosis with characteristics not considered in standard risk scales, and that will be the basis of further investigation in PESA.

We also propose that individuals presenting multiterritorial atherosclerosis, despite being classified at low risk, will be more likely to develop clinical events. Future confirmation of this hypothesis in longitudinal follow-up could support the broader application of multiterritorial imaging, a reasonable expectation given the systemic nature of atherosclerosis. Multiterritorial vascular imaging therefore appears to have the potential to help identify new factors and thus complement traditional risk scales, helping to achieve the goal of individualized risk assessment.

Limitations

This study presents a cross-sectional analysis of the PESA cohort at baseline and therefore cannot yet evaluate clinical events, precluding the possibility of establishing causality; these current findings will be complemented by long-term monitoring of atherosclerosis progression. Follow-up data from PESA will help to clarify the clinical significance of early detection of nonobstructive disease, including iliofemoral atherosclerosis, and the predictive value of multiterritorial atherosclerosis in low-risk individuals. The present analysis of the PESA baseline cohort sets the basis for understanding the relationship between the extent and progression of subclinical disease and future cardiovascular events. The PESA sample consists of middle-aged, predominantly male white-collar workers, which may limit the generalizability of the results. Although the prevalence of disease might not be universally representative given the specific characteristics of our participants, the observed associations between cardiovascular risk profile and the presence and extent of atherosclerosis could be extrapolated to other cohorts. It is challenging to assess whether the distribution of risk factors in PESA is similar to that in an age- and sex-matched representative population because we included younger individuals than in most previous population-based studies. The present results, however, will complement ongoing studies on atherosclerosis by giving considerable insight into the early stages of atherosclerosis. Detection of plaques in the iliac arteries may be limited by the penetration of the vascular probe used and the presence of air (23% of iliac studies were suboptimal.
Comparing with 2% for carotids, 10% for aorta, and 6% for femorals). However, a further evaluation of variability in the iliac arteries showed good results (κ=0.84), and only 1% of iliac studies were noninterpretable. In the classification of the extent of subclinical atherosclerosis, aortic and coronary sites were considered single territories, with greater weight therefore given to carotid and iliofemoral territories; however, the multiterritorial extent of disease includes the concept of lat- erality and introduces a novel evaluation of atherosclerosis. Although CAC is a well-established evaluation of subclinical coronary disease, it is not suitable for noncalcified plaques. In the interest of clarity and ease of clinical application, atherosclerotic plaques and CAC were considered dichotomized variables (presence or absence) to evaluate the extent of subclinical atherosclerosis.

Conclusions
Subclinical atherosclerosis is highly prevalent in this mid- aged, asymptomatic cohort, with nearly half the partici- pants presenting with intermediate or generalized disease. Prevalence is higher in men and in the iliofemoral arteries, highlighting the value of screening this territory. Because a substantial proportion of low-risk participants had subclinical atherosclerosis, imaging of early atherosclerosis may be particularly valuable in this setting. Long-term follow-up will determine whether detection of early atherosclerosis has any impact on predicting and preventing cardiovascular events.

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Disclosures
None.

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**CLINICAL PERSPECTIVE**

Atherosclerosis is a slow-progressing disease characterized by a long latent stage; it is often detected only at an advanced stage or after a cardiovascular event. Detection of atherosclerosis in its subclinical stage may help to arrest disease development. Noninvasive bioimaging is one of the most promising approaches to improving early atherosclerosis detection and cardiovascular prevention. In the PESA (Progression of Early Subclinical Atherosclerosis) study, we performed an exhaustive vascular evaluation using ultrasound and computed tomography to detect subclinical atherosclerosis in >4000 individuals 40 to 54 years of age. Given the systemic nature of atherosclerosis, PESA includes a multiterritorial imaging assessment of the carotid arteries, abdominal aorta, and coronary and iliofemoral arteries to better characterize the vascular distribution and extent of the disease in the early asymptomatic phases. Interestingly, the most frequently affected vascular site at these early stages is the iliofemoral territory. This novel finding suggests the value of exploring this territory, which has received less attention than more commonly evaluated sites such as the carotids or the coronary arteries. We also explored the relationship between the systemic extent of atherosclerosis and cardiovascular risk scores. As expected, individuals classified at high risk have subclinical disease; however, atherosclerosis is also present in nearly 60% of low-risk participants, with one third having multiple vascular sites affected, suggesting added value of imaging for prevention. The PESA study provides a new and comprehensive overview of the distribution and extent of early multiterritorial atherosclerosis in a relatively young cohort and has the potential to complement traditional risk scales.

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Prevalence, Vascular Distribution, and Multiterritorial Extent of Subclinical Atherosclerosis in a Middle-Aged Cohort: The PESA (Progression of Early Subclinical Atherosclerosis) Study

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SUPPLEMENTAL MATERIAL

Supplemental Methods

IMT was also assessed by vascular ultrasound at the level of the posterior wall of the common carotid and femoral arteries in longitudinal views. Values >0.9 were considered abnormal, as established in previous studies\(^1\) and guidelines\(^2\). Reproducibility of IMT measurements was evaluated by replicating the analysis of a random sample of 60 studies 3 months after the initial assessment and determining intraclass correlation coefficients (ICC). Excellent values (ICC>0.95) were found for both carotid and femoral IMT measurements.

Supplemental Results

Associations between risk factors and subclinical atherosclerosis in different territories are shown in Table S2. Age and male gender were significantly associated with the presence of plaque in any territory, and particularly with CAC. All risk factors were associated with atherosclerosis across all territories, although results did not reach significance for the association of diabetes or hypertension with aortic disease and of family history with carotid disease. Diabetes was most strongly associated with carotid disease and CAC, whereas smoking had a stronger association with aortic and ilio-femoral disease and family history had a stronger association with CAC.

Regarding IMT measurements, the mean value was 0.59 mm in carotid arteries and 0.61 mm in femoral arteries. Abnormal IMT (>0.9 mm)\(^1\) was detected in 9% of participants, and was more frequent in femoral than in carotid arteries (8% vs. 1%). The prevalence of abnormal IMT was higher in men and increased with age (Table S1). The sensitivity, specificity, and positive and negative predictive values for IMT to detect subclinical
atherosclerosis were 14%, 99%, 99% and 41%, respectively. Consistent with previous studies\textsuperscript{3,5}, IMT measurements did not correlate with the presence of subclinical atherosclerosis (presence of plaque or CACS\textgreater{}1). Prevalence of abnormal IMT was low (9%), especially in the carotid arteries (0.8%), despite the overall high prevalence of subclinical disease (63%). The increasing rate of abnormal IMT with age suggests a confounding influence of factors not directly related to atherosclerosis. In addition, almost all participants with abnormal IMT also had disease (99%), indicating that IMT provides little information that cannot be derived by directly determining the presence of plaques. Further evidence of the limited utility of IMT for assessing subclinical atherosclerosis is provided by its low sensitivity in our sample (14%), the lack of standard cut-off values for normal age reference intervals\textsuperscript{6}, and its reported poor predictive value for CV disease compared with plaque-based markers\textsuperscript{4}. In this regard, the most recent American College of Cardiology/American Heart Association (ACC/AHA) Guide on the assessment of CV risk no longer recommends carotid IMT for routine clinical assessment of the risk of a first atherosclerotic CV event\textsuperscript{7}. 
Supplemental Tables

**Table S1.** Prevalence of cardiovascular risk factors, risk scale scoring, CACS and IMT values in PESA participants stratified by age and gender

|                      | MEN                               | WOMEN                            |
|----------------------|-----------------------------------|-----------------------------------|
|                      | 40-44 yo (n=1000)                 | 45-49 yo (n=822)                  | 50-54 yo (n=702)                  | 40-44 yo (n=747) | 45-49 yo (n=506) | 50-54 yo (n=225) |
| **Traditional CV risk factors** |                                  |                                  |                                  |                  |                    |                   |
| Dyslipidemia         | 483 (48)                          | 449 (55)                         | 406 (58)                         | 113 (15)         | 121 (24)          | 81 (36)           |
| Smoking              | 170 (17)                          | 159 (19)                         | 146 (21)                         | 163 (22)         | 131 (26)          | 50 (22)           |
| Family history       | 148 (15)                          | 136 (17)                         | 104 (15) NS                      | 123 (17)         | 91 (18)           | 32 (14) NS        |
| Hypertension         | 84 (8)                            | 124 (15)                         | 179 (26)                         | 13 (2)           | 34 (7)            | 25 (11)           |
| Diabetes             | 12 (1)                            | 18 (2)                           | 37 (5)                           | 3 (0.4)          | 2 (0.4)           | 2 (0.89) NS       |
| **Number of risk factors** |                                  |                                  |                                  |                  |                    |                   |
| 0                    | 365 (37)                          | 234 (29)                         | 173 (25)                         | 419 (56)         | 238 (47)          | 96 (43)           |
| 1                    | 415 (42)                          | 353 (43)                         | 267 (38) NS                      | 249 (33)         | 180 (36)          | 81 (36) NS        |
| 2                    | 181 (18)                          | 181 (22)                         | 193 (28)                         | 71 (10)          | 67 (13)           | 38 (17)           |
| >2                   | 39 (4)                            | 54 (7)                           | 69 (10)                          | 8 (1)            | 21 (4)            | 10 (4)            |
| **CV risk scales (%)** |                                  |                                  |                                  |                  |                    |                   |
| 10y SCORE            | 0.39 ± 0.23                       | 0.77 ± 0.37                      | 1.43 ± 0.73                      | 0.06 ± 0.05      | 0.17 ± 0.09       | 0.42 ± 0.25       |
| 10y FHS              | 5.84 ± 3.07                       | 7.78 ± 3.80                      | 10.3 ± 5.16                      | 1.81 ± 0.96      | 3.3 ± 1.98        | 4.9 ± 2.73        |
| 30y FHS              | 17.3 ± 8.37                       | 23.4 ± 10.1                      | 30.4 ± 12.0                      | 6.68 ± 3.49      | 10.5 ± 6.0        | 14.4 ± 8.15       |
| 10y ASCVD            | 2.7 ± 2.27                        | 4.3 ± 2.81                       | 6.9 ± 3.97                       | 0.9 ± 0.84       | 1.4 ± 1.24        | 2.0 ± 1.57        |
| **CACS**             |                                  |                                  |                                  |                  |                    |                   |
| CACS*                | 6.73 ± 30.9                       | 18.6 ± 101.0                     | 45.4 ± 152.0                     | 0.36 ± 2.66      | 1.52 ± 10.9       | 4.37 ± 30.9 NS    |
| (Agatston units)     |                                  |                                  |                                  |                  |                    |                   |
| CACS 0               | 854 (85)                          | 629 (77)                         | 401 (57)                         | 727 (97)         | 480 (95)          | 203 (90)          |
| CACS 1-99            | 126 (13)                          | 159 (19)                         | 227 (32)                         | 20 (3)           | 24 (5)            | 20 (9)            |
| CACS 100-399         | 19 (2)                            | 26 (3)                           | 57 (8)                           | 0 (0)            | 2 (0.4)           | 1 (0.4)           |
| CACS ≥400            | 1 (0.1)                           | 8 (1)                            | 17 (2)                           | 0 (0)            | 0 (0)             | 1 (0.4)           |
| **IMT (mm)**         |                                  |                                  |                                  |                  |                    |                   |
| Carotid IMT*         | 0.59 ± 0.09                       | 0.61 ± 0.10                      | 0.64 ± 0.11                      | 0.53 ± 0.06      | 0.56 ± 0.07       | 0.60 ± 0.08       |
| Femoral IMT*         | 0.60 ± 0.21                       | 0.66 ± 0.26                      | 0.73 ± 0.32                      | 0.50 ± 0.11      | 0.55 ± 0.16       | 0.57 ± 0.16       |
| Carotid IMT > 0.9    | 7 (0.7)                           | 4 (0.5)                          | 18 (3)                           | 0 (0)            | 0 (0)             | 2 (0.9)           |
| Femoral IMT > 0.9 | 67 (7) | 99 (12) | 128 (18) | 8 (1)  | 19 (4) | 15 (7) |

Data are expressed as mean ± standard deviation or n (%). *Non-normally distributed variables were log-transformed before analysis to normalize the distribution. Linear trend tests for categorical variables were performed by using orthogonal polynomial contrasts in logistic regression analyses. For continuous variables, an extension of the non-parametric Wilcoxon rank-sum test was used to assess trends across ordered groups. ASCVD: Atherosclerotic cardiovascular disease. CACS: Coronary artery calcium score. CV: Cardiovascular. FHS: Framingham Heart Study. IMT: Intima-media thickness. NS: Non-significant (p-trend >0.05). Supplemental Tables are calculated from a complete imaging dataset of PESA participants (n=4002).
**Table S2.** Associations between the presence of atherosclerosis in individual vascular territories and age, gender and traditional CV risk factors

| Age and gender | Carotid disease | Coronary calcification | Aortic disease | Ilio-femoral disease |
|----------------|-----------------|------------------------|---------------|---------------------|
| 40-44 years    | 1 (ref)         | 1 (ref)                | 1 (ref)       | 1 (ref)             |
| 45-49 years    | OR (95%CI)      | <0.001                 | <0.001        | <0.001              |
| 50-54 years    | OR (95%CI)      | <0.001                 | <0.001        | <0.001              |
| Female         | 1 (ref)         | 1 (ref)                | 1 (ref)       | 1 (ref)             |
| Male           | OR (95%CI)      | <0.001                 | <0.001        | 0.004               |

**Traditional CV risk factors**

| Risk factor   | OR (95%CI) | p-value |
|---------------|------------|---------|
| Dyslipidemia  | 1.43(1.23-1.65) | <0.001 |
| Smoking       | 1.75(1.48-2.06) | <0.001 |
| Family history| 1.16(0.97-1.40) | 0.111 |
| Hypertension  | 1.36(1.11-1.68) | 0.003 |
| Diabetes      | 1.89(1.17-3.04) | 0.009 |

Data are expressed as odds ratio (OR) and 95% confidence interval (CI). Age- and gender-adjusted associations were examined using logistic regression models (no adjustments were performed for the age and gender categories). Coronary calcification was defined as CACS ≥ 1.
**Table S3.** Associations between the extent of atherosclerosis and age, male gender, obesity and cardiovascular risk factors

|                      | No disease (n=1502) | Focal disease (n=849) | Intermediate disease (n=1113) | Generalized disease (n=538) | P-trend |
|----------------------|---------------------|-----------------------|-------------------------------|-----------------------------|---------|
| Age                  | 44.2 ± 3.77         | 45.4 ± 4.1            | 46.7 ± 4.13                   | 48.8 ± 3.99                 | <0.001  |
| Male gender          | 739 (49.2)          | 530 (62.4)            | 809 (72.7)                    | 446 (82.9)                  | <0.001  |
| Obesity              | 165 (11)            | 131 (15)              | 160 (14)                      | 105 (20)                    | <0.001  |
| Dyslipidemia         | 442 (29.4)          | 318 (37.5)            | 548 (49.2)                    | 345 (64.1)                  | <0.001  |
| Smoking              | 199 (13.2)          | 154 (18.1)            | 271 (24.3)                    | 195 (36.2)                  | <0.001  |
| Family history       | 221 (14.7)          | 121 (14.3)            | 182 (16.4)                    | 110 (20.4)                  | <0.001  |
| Hypertension         | 99 (6.6)            | 82 (9.7)              | 158 (14.2)                    | 120 (22.3)                  | <0.001  |
| Diabetes             | 8 (0.5)             | 14 (1.7)              | 18 (1.6)                      | 34 (6.3)                    | <0.001  |

Data are expressed as mean ± SD or n (%). Linear trend tests for categorical variables were performed by using orthogonal polynomial contrasts in logistic regression analyses. For continuous variables, an extension of the non-parametric Wilcoxon rank-sum test was used to assess trends across ordered groups.
Table S4. Analysis of the focal disease subgroup showing the most affected territories across age and gender groups (A) and risk-score range (B)

| A. Focal disease subgroup across age/gender | TOTAL 40-54 yo (n=849) | 40-44 yo (n=248) | 45-49 yo (n=174) | 50-54 yo (n=108) | 40-44 yo (n=108) | 45-49 yo (n=107) | 50-54 yo (n=54) |
|--------------------------------------------|------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Only with carotid disease (n=279)          | 33%                    | 37%              | 31%              | 23%              | 40%              | 30%              | 28%              |
| Only with CAC≥1 (n=89)                      | 11%                    | 13%              | 13%              | 19%              | 5%               | 5%               | 2%               |
| Only with aortic disease (n=139)            | 16%                    | 10%              | 13%              | 10%              | 22%              | 27%              | 31%              |
| Only with ilio-femoral disease (n=342)      | 40%                    | 40%              | 44%              | 48%              | 33%              | 38%              | 39%              |

| B. Focal disease subgroup across risk-score range | European SCORE | 10y-FHS | 30y-FHS | ASCVD <5% | 5-7.5% | ≥7.5% |
|---------------------------------------------------|----------------|---------|---------|----------|--------|-------|
|                                                   | Low (n=770)     | Mid& High (n=79) | Low (n=776) | Mid& High (n=83) | Low (n=258) | Mid& High (n=591) | <5% (n=715) | 5-7.5% (n=68) | ≥7.5% (n=51) |
| Only with carotid disease                         | 34%             | 22%     | 34%     | 23%      | 40%    | 30%    | 34%    | 32%     | 16%     |
| Only with CAC≥1                                   | 10%             | 14%     | 10%     | 13%      | 5%     | 13%    | 10%    | 9%      | 20%     |
| Only with aortic disease                          | 17%             | 14%     | 17%     | 12%      | 22%    | 14%    | 17%    | 13%     | 16%     |
| Only with ilio-femoral disease                    | 39%             | 51%     | 39%     | 52%      | 33%    | 43%    | 39%    | 46%     | 49%     |
Supplemental Figures and Figure Legends

Figure S1.
Figure S2.

FHS 10-year score & subclinical atherosclerosis by vascular territory
Figure S3.

FHS 30-year score & subclinical atherosclerosis by vascular territory

- **Carotid territory**
  - Low risk (n=1214)
  - Moderate risk (n=1401)
  - High risk (n=1387)

- **Coronary territory**
  - Low risk (n=1214)
  - Moderate risk (n=1401)
  - High risk (n=1387)

- **Aortic territory**
  - Low risk (n=1214)
  - Moderate risk (n=1401)
  - High risk (n=1387)

- **Ilio-femoral territory**
  - Low risk (n=1214)
  - Moderate risk (n=1401)
  - High risk (n=1387)
Figure S4.

10-year European SCORE & subclinical atherosclerosis by vascular territory

- Carotid territory
  - Low risk (n=3383)
  - Moderate-high risk (n=619)

- Coronary territory
  - Low risk (n=3383)
  - Moderate-high risk (n=619)

- Aortic territory
  - Low risk (n=2383)
  - Moderate-high risk (n=619)

- Ilio-femoral territory
  - Low risk (n=3383)
  - Moderate-high risk (n=619)

Legend:
- Disease
- No Disease
Figure Legends

Figure S1. Distribution of multi-territorial extent of subclinical atherosclerosis.

Figure S2. Association of subclinical atherosclerosis with the 10-year Framingham Heart Study risk score according to vascular territory.

Figure S3. Association of subclinical atherosclerosis with the 30-year Framingham Heart Study risk score according to vascular territory.

Figure S4. Association of subclinical atherosclerosis with European SCORE risk according to vascular territory.
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중년에서 무증상 족상경화증은 매우 흔하다: PESA 연구

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초록

배경
중년의 인구 집단에서 무증상 족상경화증의 발생률과 그 범위, 그리고 다혈관병에 대해서는 알려진 바가 별로 없다.

방법 및 결과
PESA(Progression of Early Subclinical Atherosclerosis) 연구는 중상이 없는 40-54세의 중년 남녀 4,184명을 대상으로 하였는데, 평균 연령은 45.8세, 남성은 63%였다. 2D/3D 초음파로 경동맥, 북부동맥, 장골-퇴퇴동맥의 족상경화증을 진단하였으며, 심장 CT(computed tomography)로 관상동맥 칼슘 수치를 측정하였다. 좌/우 경동맥, 북부동맥, 좌/우 하지동맥, 관상동맥 중 한 곳에서 진단되면 국소적(focal), 2-3곳이면 중등도(intermediate), 4-6곳은 전신성(generalized)으로 그 범위를 진단하였다. 전체 대상자의 63%에서 족상경화증이 진단되었는데, 남성에서 71%, 여성에서 48%였다. 중등도 또는 전신성 족상경화증은 41%에서 진단되었고, 하지동맥이 44%로 가장 흔하였고, 이어서 경동맥 31%, 대동맥 25%, 관상동맥 18%었다. Framingham 10년 위험도 점수가 낮은 군에서도 58%에서 족상경화증이 진단되었으며, 중등도나 전신성은 36%였다. 30년 위험도 점수로 계산하였을 때 고위험군은 83%에서 족상경화증을 보였으며, 중등도나 전신성도 66%에 달했다.

결론
중년 코호트에서 무증상 족상경화증은 흔히 관찰되었으며, 거의 절반 가까운 사람에서 중등도나 전신성이었다. 임상적으로 고위험군에서뿐 아니라 저위험군에서도 적지 않게 족상경화증이 발견되었으며, 이는 영상검사가 임상적인 위험인자에 더해 위험도 평가 및 예방에 있어 추가적인 가치가 있음을 시사한다.