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## Vascular Inflammation in Subclinical Atherosclerosis Detected by Hybrid PET/MRI

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**Brief title:** Inflammation by PET/MRI in atherosclerosis.

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## ABSTRACT

**Background:** Atherosclerosis is a chronic inflammatory disease, but data on arterial inflammation at early stages is limited.

**Objectives:** To characterize vascular inflammation by hybrid  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography/magnetic resonance imaging ( $^{18}\text{F}$ -FDG PET/MRI).

**Methods:** Carotid, aortic, and ilio-femoral  $^{18}\text{F}$ -FDG PET/MRI was performed in 755 individuals (age 40-54 years, 83.7% men) with known plaques detected by 2D/3D vascular ultrasound and/or coronary calcification in the PESA (Progression of Early Subclinical Atherosclerosis) study. We evaluated the presence, distribution, and number of arterial inflammatory foci (increased  $^{18}\text{F}$ -FDG uptake) and plaques with or without inflammation (coincident  $^{18}\text{F}$ -FDG uptake).

**Results:** Arterial inflammation was present in 48.2% of individuals (24.4% femorals, 19.3% aorta, 15.8% carotids, and 9.3% iliacs) and plaques in 90.1% (73.9% femorals, 55.8% iliacs, and 53.1% carotids).  $^{18}\text{F}$ -FDG arterial uptakes and plaques significantly increased with cardiovascular risk factors ( $p < 0.01$ ). Coincident  $^{18}\text{F}$ -FDG uptakes were present in 287/2605 (11%) plaques, and most uptakes were detected in plaque-free arterial segments (459/746; 61.5%). Plaque burden, defined by plaque presence, number, and volume, was significantly higher in individuals with arterial inflammation than in those without ( $p < 0.01$ ). The number of plaques and  $^{18}\text{F}$ -FDG uptakes showed a positive albeit weak correlation ( $r = 0.25$ ;  $p < 0.001$ ).

**Conclusion:** Arterial inflammation is highly prevalent in middle-aged individuals with known subclinical atherosclerosis. Large-scale multiterritorial PET/MRI allows characterization of atherosclerosis-related arterial inflammation and demonstrates  $^{18}\text{F}$ -FDG uptake in plaque-free arterial segments and, less frequently, within plaques. These findings suggest an arterial inflammatory state at early stages of atherosclerosis.

**Clinical Trial Registration:** <https://clinicaltrials.gov/ct2/show/NCT01410318>.

## CONDENSED ABSTRACT

Data on arterial inflammation in early atherosclerosis is limited. We characterized vascular inflammation by carotid, aortic, and ilio-femoral hybrid  $^{18}\text{F}$ -FDG PET/MRI in 755 individuals (age 40-54 years, 83.7% men) with subclinical atherosclerosis in the PESA study. Arterial inflammation was present in 48.2% of individuals, most commonly at the femoral territory. Most uptakes (61.5%) were detected in plaque-free arterial segments, and only 11% of plaques showed coincident uptake. Thus, arterial inflammation detected by multiterritorial PET/MRI is highly prevalent in middle-aged individuals with subclinical atherosclerosis, both in plaque-free arterial segments and, less frequently, within plaques, suggesting an active arterial inflammatory state.

**KEY WORDS:**  $^{18}\text{F}$ -FDG PET/MRI, subclinical atherosclerosis, arterial inflammation, plaque inflammation

## ABBREVIATIONS LIST:

CT: Computed tomography

$^{18}\text{F}$ -FDG:  $^{18}\text{F}$ -Fluorodeoxyglucose

MRI: Magnetic resonance imaging

PET: Positron emission tomography

SUV: Standardized uptake value

TBR: Target-to-background ratio

## **Introduction**

Atherosclerosis is a chronic disease in which inflammation plays an important role at all stages, from development and progression to the determination of incident clinical events (1-3). Positron emission tomography (PET) with  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) can assess arterial inflammation in vivo because uptake reflects, at least in part, the presence of invading macrophages and foam cell formation (4). Prior studies combining PET and computed tomography (CT) have shown that arterial  $^{18}\text{F}$ -FDG uptake predicts cardiovascular risk, although these studies were largely limited to a single vascular territory and/or included individuals retrospectively screened for cancer (5-8). Magnetic resonance imaging (MRI) can provide superior plaque detection and characterization, and thus hybrid  $^{18}\text{F}$ -FDG PET-MRI technology has the potential to simultaneously provide anatomical and functional information (9). However, data on vascular PET/MRI is scarce, with only small series limited to carotid atherosclerosis (10-12).

Our aim was to characterize arterial and plaque inflammation associated with early atherosclerosis by performing multiterritorial hybrid  $^{18}\text{F}$ -FDG PET/MRI in a large prospective asymptomatic cohort of middle-aged individuals with subclinical atherosclerosis. We also evaluated patient- and plaque-specific factors associated with inflammation.

## **Methods**

### *Study population*

This study was conducted in a subset of participants with known subclinical atherosclerosis from the Progression of Early Subclinical Atherosclerosis (PESA)-CNIC-Santander study (13). PESA is an observational, prospective cohort study of 4184 asymptomatic employees of the Santander Bank in Madrid. Participants were aged 40-54 years at enrollment

and were consecutively recruited between June 2010 and February 2014, with visits at baseline and at 3 and 6 years. Exclusion criteria were prior cardiovascular disease, any condition reducing life expectancy or affecting study adherence, morbid disease (body mass index  $\geq 40$  kg/m<sup>2</sup>), or chronic kidney disease (estimated glomerular filtration rate (eGFR)  $< 60$  mL/min/m<sup>2</sup>). The main objective is to characterize the presence and progression of subclinical atherosclerosis by non-invasive imaging, including carotid and ilio-femoral vascular ultrasound and non-contrast cardiac CT. A subgroup of participants with documented atherosclerosis, defined as being in the highest plaque thickness tertile on vascular ultrasound and/or having any coronary artery calcification on CT, were offered a vascular <sup>18</sup>F-FDG PET/MRI study during the baseline visit. Cardiovascular risk factors were prospectively assessed at enrollment and defined as (14) : 1) diabetes: fasting plasma glucose  $\geq 126$  mg/dL, or treatment with insulin or oral hypoglycemic medication; 2) arterial hypertension: systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg, or use of antihypertensive medication; 3) dyslipidemia: total cholesterol  $\geq 240$  mg/dL, low-density lipoprotein cholesterol  $\geq 160$  mg/dL, high-density lipoprotein cholesterol  $< 40$  mg/dL, or use of lipid-lowering drugs; 4) smoking: current smoking status, and a lifetime consumption of  $> 100$  cigarettes; 5) family history of cardiovascular disease: first degree-relative diagnosed with atherosclerosis before the age of 55 years in men and 65 in women; 6) obesity: body mass index  $\geq 30$  kg/m<sup>2</sup>. Cardiovascular risk was evaluated by the 10-year risk algorithm based on Pooled Cohort Equations (15), and cut-off values were defined as  $< 5\%$ , 5 to  $< 7.5\%$  and  $\geq 7.5\%$  risk for low, intermediate, and high risk, respectively (15). The eGFR was calculated according to the Chronic Kidney Disease Epidemiology equation (16). High sensitivity C-reactive protein (hs-CRP) was measured in venous blood collected after fasting

(13). The institutional Ethics Committee approved the study protocol and all participants provided written informed consent.

## **Hybrid PET/MRI**

### *Acquisition protocol*

Pre-scan preparation requirements included fasting for 6 hours and refraining from exercise in the preceding 24 hours. Plasma glucose levels were measured before the scan (mean concentration  $90.6 \pm 12.3$  mg/dL). Participants received a target dose of 270-300 MBq  $^{18}\text{F}$ -FDG (17) and were asked to remain at rest in a quiet room for 30 minutes after radiolabel injection. The associated radiation exposure was calculated according to the ICRP Task Group on Radiation Dose (18). Sequential whole-body PET/MRI studies were performed in a Philips Ingenuity TF PET/MR hybrid system (Philips Healthcare, Cleveland, OH). MRI was performed with a phased-array 16-channel torso XL coil for aorto-iliac and femoral arteries and a 16-channel neurovascular coil for carotid arteries, using peripheral pulse gating.

The imaging protocol is illustrated in Figure 1, and detailed MRI parameters are shown in Online Table 1. The protocol included high-resolution black-blood MRI of the carotid, iliac, and femoral arteries and co-registered PET/MRI of the carotid arteries, thoracic aorta, infrarenal abdominal aorta, iliac, and femoral arteries. Ilio-femoral MRI attenuation maps and lower-body PET were acquired at the start of the protocol. After standard localizers, iliac arteries (15 cm covering up to the aorto-iliac bifurcation) and femoral arteries (6 cm centered at the bifurcation) were first scanned using an axial double-inversion black-blood fast spin-echo T1-weighted sequence with spectral fat suppression. When plaques were visualized, additional T2-weighted images (typically 3 slices) were obtained of the largest plaque in a territory. Afterwards, an axial stack of balanced single-shot fat-saturated turbo-field echo images of the infrarenal aorta and

ilio-femoral arteries was acquired for subsequent coregistered PET/MRI analysis. Finally, a specific MRI sequence for attenuation correction was obtained with the body coil. The table was then removed from the MRI scanner and rotated 180° into the PET system (at least 90 min after <sup>18</sup>F-FDG injection). A PET scan of the infrarenal abdominal aorta and ilio-femoral territories was acquired in the cranio-caudal direction in 4 bed positions (3 minutes per bed) with 50% overlap, covering from the umbilicus to the upper portion of the leg. After a 5-minute rest off the table, the participant returned to the MRI platform for surveys and attenuation sequences of the carotid and thoracic aortic territories. This was followed by table rotation and a cranio-caudal upper-body PET in 5 bed positions (3 minutes per bed) with 50% overlap, covering from the external auditory meatus to the diaphragm (at least 120 min after <sup>18</sup>F-FDG injection). Participants were then returned to the MRI scanner, and axial balanced single-shot turbo-field echo imaging was performed of the carotid arteries and thoracic aorta, followed by carotid T1-black-blood weighted imaging (6 cm centered at the bifurcation) and selective plaque T2-weighted imaging as above.

#### *Image reconstruction and analysis*

PET scans were reconstructed in 3-dimensional mode using a blob-based, list-mode iterative algorithm with time-of-flight (TOF) information and corrections applied for attenuation, scatter, and random coincidences. Attenuation correction used MRI attenuation maps with a 3-class tissue (soft tissue, lung, and air) validated segmentation technique (19). A transverse 576-mm field of view was used and images were generated with a voxel size of 4.0 x 4.0 x 4.0 mm<sup>3</sup>. Specific templates for PET images were added to the attenuation maps to correct for attenuation effects of the scanner bed and the neurovascular coil. Similarly, truncation correction was used to compensate for the limited field of view from MRI images (20).

All images were obtained and reviewed by expert technologists, radiologists, or nuclear medicine specialists blinded to previous imaging procedures and clinical data. MRI data were analyzed with VP Diagnostics software (Seattle, USA) and PET/MRI data were analyzed with Philips Fusion Viewer V2.0. A total of 6 vascular territories per participant were analyzed in MRI: left/right carotid arteries (common and internal, excluding external), left/right iliac arteries (aorto-iliac bifurcation and common and external, excluding internal), and left/right femoral arteries (common and superficial, excluding deep). In each territory, the presence and number of plaques (1, 2, >2) was recorded as a surrogate of plaque burden. Atherosclerotic plaques were defined as focal luminal protrusions of the wall  $\geq 1.5$ mm in radial thickness on T1-weighted images, according to previous reported methodology (21) and the best discriminative cut-off within our population, using ultrasound as a reference (n=100; area under the curve [AUC]=0.80). On T1-weighted images, the inner and outer wall contours were manually traced in all sections containing plaque as well as in a proximal reference slice. Positive remodeling was defined as the ratio of maximal vessel area at the level of the plaque to the proximal reference vessel area  $\geq 1.1$  (22). We also traced plaque contours in each diseased slice to quantify plaque volume. Plaques were defined as predominantly lipid-rich if iso/hyperintense on T1- and hypointense on T2-weighted images, predominantly fibrous if iso/hyperintense on both (23), or mixed/indeterminate if combined features were present or the plaque was too small to be defined; however, analyzers were encouraged to assign plaques predominantly to the first two categories.

A total of 10 vascular territories per participant were analyzed on fused PET/MRI images, including the left/right carotid arteries, ascending/arch/descending thoracic aorta, infrarenal abdominal aorta, left/right iliac arteries, and left/right femoral arteries. Qualitative PET analysis



on each vessel was performed after adjustment of the color scale between 0 and 2 standardized uptake value (SUV) units. In each studied territory the presence and number (1, 2, >2) of arterial <sup>18</sup>F-FDG uptakes was recorded (inflammatory burden). An arterial <sup>18</sup>F-FDG uptake was defined as a localized area of increased signal intensity encompassing an artery and that could not be explained by adjacent structures such as lymph nodes or ureters (24,25). On every slice demonstrating arterial uptake, regions of interest encompassing wall and lumen were drawn to quantify maximal SUV (SUVmax, calculated as decay-corrected tissue radioactivity divided by body weight and injected dose) and target-to-background ratio (TBRmax, calculated as the ratio of SUVmax to background venous activity) (26). Venous activity was measured as mean SUV in the ipsilateral jugular veins for carotid studies, superior vena cava for the thoracic aorta, or inferior vena cava for the abdominal aorta and ilio-femoral arteries. We also assessed whether plaques visualized on T1-weighted MRI showed coincident <sup>18</sup>F-FDG uptake (plaque with inflammation) for the 6 territories with both PET and high-resolution T1-weighted MRI images (left/right carotid arteries, left/right iliac arteries, and left/right femoral arteries) and measured SUVmax and TBRmax per plaque. For plaques without coincident uptake (plaques without inflammation), we assigned the mean SUVmax and TBRmax values of the corresponding vessel in the absence of concomitant uptakes, or otherwise the contralateral vessel.

### *Statistical Analysis*

Continuous variables are expressed as mean  $\pm$  standard deviation (or median [interquartile range] if non-normally distributed) and categorical variables as n (%). Non-normal variables were log-transformed before analysis and comparisons were performed using the Student t-test and the Chi-square or Fisher exact test, as appropriate. To examine the bivariate relationships between continuous variables, we used the Spearman rank correlation with 95%

confidence intervals based on the Fisher transformation. For multivariate analysis, logistic regression models were performed. For plaque analyses, multilevel mixed models were applied to account for within-subject correlation. To evaluate arterial inflammation associations, the model was adjusted for age, sex, hypertension, smoking, diabetes, dyslipidemia, obesity, and family history of cardiovascular disease; to evaluate plaque inflammation, adjustments were made for bifurcation location, plaque volume, carotid or femoral distribution, positive remodeling, and lipid-rich or fibrotic content. Odds ratios and 95% confidence intervals are reported. For all endpoints, p values <0.05 were considered statistically significant. Statistical analyses were performed using STATA 15.0.

For reproducibility analysis, PET/MRI images of 15 participants (150 PET and 90 MRI vascular territories) were independently analyzed in a random manner by two expert PET and MRI readers. One of the readers re-analyzed the same studies after a minimum interval of 1 month. Interobserver and intraobserver agreement was assessed by intraclass correlation coefficient (ICC), with 95% confidence intervals for continuous measurements and Kappa Cohen coefficients for categorical variables. Agreement was defined as good if ICC=0.71-0.90 or Kappa=0.61-0.8, and excellent if ICC>0.90 or Kappa=0.81-1 (27,28). Reproducibility measurements were good and excellent for all endpoints (Online Table 2).

## **Results**

In PESA, we performed PET/MRI in 946 participants (78.8% of invitees) who had documented atherosclerosis detected on baseline vascular ultrasound or CT: peripheral plaques in 349 (36.9%), coronary calcification in 69 (7.3%), and both in 523 (55.3%). Mean <sup>18</sup>F-FDG dose was 292.3 ± 11.1 MBq, and radiation exposure was 5.6 ± 0.2 mSv. Mean start time after <sup>18</sup>F-FDG injection was 106.0 ± 15.0 min for lower-body PET and 132.9 ± 19.9 min for upper-

body PET. Reasons for non-completion are shown in Online Figure 1, mainly due to physical intolerance in upper-body studies (8 PETs and 51 MRIs), technical issues with the MRI attenuation maps (97 initial PETs), and poor image quality (70 iliac MRIs). Thus, complete PET/MRI studies were available in 755 (79.8%) participants.

The mean age of the PET/MRI cohort was  $49.6 \pm 4.3$  years, 632 (83.7%) were men, and all individuals were Caucasians. The most prevalent risk factor was dyslipidemia, followed by smoking, family history, obesity, hypertension, and diabetes (Table 1). Most participants had low cardiovascular risk (62.0%, versus 18.0% with intermediate risk and 20.0% with high risk). The prevalence of statin therapy in the complete PET/MRI cohort was 13.9%, with no significant differences between individuals with or without inflammation. hs-CRP was significantly elevated in individuals with arterial inflammation (**Table 1**) and positively but weakly correlated with arterial/plaque uptakes and plaque presence, volume, and composition (Online Table 3) A total of 2605 atherosclerotic plaques were detected by MRI in 680 participants (90.1%; 3 [2-5] plaques per participant), being more frequent in men. Plaque number increased with age and the presence of cardiovascular risk factors (**Figure 2**, Online Figures 2 and 3).

### **Arterial inflammation and plaque inflammation in atherosclerotic PESA participants**

Arterial inflammation, defined as increased vascular  $^{18}\text{F}$ -FDG uptake, was present in 364 participants (48.2%; total uptakes 746, 2 [1-2] per participant). The femoral territory was the most frequent location for both inflammation and plaque (**Central Illustration**). **Figure 3** shows the prevalence of plaques and inflammation according to sex and vascular territories. Participants with arterial inflammation were older and had more cardiovascular risk factors than participants without arterial inflammation. Similarly, arterial uptake number increased with age and cardiovascular risk factors, both globally and in most arterial territories (**Figure 2**, Online

Figures 2 and 3). Individuals with arterial uptakes also had increased plaque burden, as demonstrated by plaque presence, number, and volume (**Table 1**). There was a modest correlation between the number of plaques and the number of arterial uptakes ( $r=0.25$ ; 95% confidence intervals 0.19-0.32;  $p<0.001$ ). Most uptakes (459/746; 61.5%) were detected in plaque-free arterial segments. In multivariate analysis, arterial inflammation was independently associated with age, male sex, smoking, and obesity (**Figure 4**, left).

Plaque inflammation, defined as coincident  $^{18}\text{F}$ -FDG uptake in plaques, was detected in 196 participants (26.0%). Plaques with and without inflammation are compared in **Table 2**. Only 11% of plaques showed coincident uptake (287 vs 2318 without inflammation out of 2605 total plaques). Compared with plaques without inflammation, plaques with inflammation were located more frequently in the femoral territory and in bifurcations, demonstrated more positive remodeling, were larger, and more frequently had a lipid-rich composition. Also, plaques with inflammation had higher SUVmax and TBRmax values than plaques without inflammation ( $p<0.001$ ). In multivariate analysis, plaque features that significantly predicted uptake were location (carotid or femoral vs iliac) and larger volume (**Figure 4**, right). The predominant features of plaques with and without inflammation are illustrated in **Figure 5**.

Similar results for arterial inflammation and plaque inflammation were obtained in a further multivariate analysis excluding participants taking statins (Online Table 4).

## **DISCUSSION**

Vascular inflammation is a central component of atherosclerosis as supported by extensive experimental evidence, human observational data, and the recent demonstration of the potential beneficial effects of anti-inflammatory therapies in advanced atherothrombotic disease (29). Imaging early arterial inflammation in vivo can therefore help understand the pathogenesis

and natural history of atherosclerosis (30). Retrospective studies, mostly performed in individuals screened for cancer, suggest that arterial inflammation (as detected by  $^{18}\text{F}$ -FDG PET/CT) is common and heralds future events (5,6); nonetheless, prospective human data on its prevalence is limited to small series (31) and typically to single vascular territories (10).

In this PESA cohort, by far the largest ever reported using hybrid PET/MRI of multiple vascular territories,  $^{18}\text{F}$ -FDG PET/MRI prospectively detected arterial inflammation in almost 50% of middle-aged, asymptomatic, predominantly low-risk individuals with subclinical atherosclerosis. These data are comparable to those from a previous retrospective study of PET for cancer screening, in which half of the individuals aged 41 to 60 years demonstrated vascular  $^{18}\text{F}$ -FDG uptake (8). We found arterial inflammation to be most prevalent in the femoral territory, which may be related to the higher atherosclerotic burden in this territory, a site of early atherosclerosis involvement as previously demonstrated (14). To our knowledge, only one retrospective PET study, in cancer patients, has described a more frequent vascular uptake in the femoral arteries, followed by the iliac and carotid territories (8). Tahara et al (32) reported a prevalence of carotid inflammation in 29% of patients with documented carotid atherosclerosis, similar to the 24% with carotid plaques found in our cohort. In another cancer cohort (24), 16% of patients had thoracic aortic  $^{18}\text{F}$ -FDG uptake, also comparable to our study. In agreement with a previous report (33), hs-CRP levels in the PESA cohort were elevated in individuals with arterial inflammation. These findings support the existence of a pro-inflammatory state in early atherosclerosis. Our PET/MRI data were obtained in accordance with recommended standards for  $^{18}\text{F}$ -FDG circulation time and radiation exposure (26,34), showing good reproducibility comparable to previous publications (35,36). This opens the possibility of large-scale in vivo

imaging of systemic atherosclerosis-related inflammation, its study in early disease stages, and the identification of patients likely to benefit from early intervention.

In PESA, arterial inflammation increased according to the cardiovascular risk profile and was independently associated with male sex, age, smoking, and obesity. Our findings validate previous preliminary studies in small samples that suggested these associations (33,37). The predictive role of male sex for any  $^{18}\text{F}$ -FDG uptake could be related to the smaller number of women in the cohort, but may also reflect the anti-inflammatory effects of female hormones (eg, estrogen), which can attenuate arterial inflammatory responses (38). In our cohort, although the mean age of women was  $48.4 \pm 4.1$  years, most (74.8%) were premenopausal and thus exposed to the potential protective effects of estrogens. The link in our study between smoking and increased arterial  $^{18}\text{F}$ -FDG uptake is in line with published findings showing that smoking promotes immune-mediated vascular injury and accelerated atherosclerosis and is also associated with increased levels of inflammatory markers and PET activity detected with specific radiotracers (39,40). Our findings on obesity are also consistent with extensive literature showing a pro-inflammatory effect of body fat due to the release by adipocytes of proinflammatory cytokines, which play a central role in vascular inflammation (41,42).

Interestingly, inflammation was present in only 11% of plaques with most uptakes detected in plaque-free arterial walls. We found that the numbers of  $^{18}\text{F}$ -FDG uptakes and plaques were positively correlated; however, the correlation was weak, as they frequently did not coincide. This finding suggests that uptakes and plaques represents different pathophysiological or temporal phenomena in atherosclerosis (43). Regarding factors related to plaque inflammation using PET/MRI, Hyafil et al (11) found an association between high-risk plaques and inflammation in 18 patients with ischemic stroke and non-stenotic lesions. Our study, for the

first time, shows strong evidence of a plaque phenotype associated with  $^{18}\text{F}$ -FDG uptake using hybrid PET/MRI technology, based on almost 3000 plaques distributed across multiple territories and including near 300 plaques with coincident inflammation. Plaques with  $^{18}\text{F}$ -FDG uptake were more commonly located in bifurcations, lipid-rich, and positively remodeled. However, in the multivariate analysis, only plaque volume and carotid or femoral (versus iliac) distribution were independent predictors of inflamed plaques. In agreement with our findings, histological evidence shows that highly inflamed plaques tend to be larger and have more positive remodeling and larger lipid cores (44). The reason for preferential uptake in the carotid and femoral territories compared with the iliac territory requires further investigation, but may be related to local wall shear stress conditions (45), different stages of atherosclerosis development in each vascular territory, and more physiological uptake in the abdominal organs, leading to potential pitfalls in imaging interpretation (46). In future studies, other factors related to focal inflammation might be identified by the inclusion of vascular territories that were unavailable in our MRI protocol, such as the aorta. In this sense, a recent study by Joshi et al demonstrated that increased aortic vascular inflammation detected by  $^{18}\text{F}$ -FDG PET/CT in 215 psoriasis patients is associated with early coronary artery disease independently of traditional cardiovascular risk factors (47). A previous small study (n=16) indicated preferential  $^{18}\text{F}$ -FDG uptake by lipid-rich plaques (31); however, we found that this association did not persist in the multivariate analysis. This apparent contradiction might be related to a more robust adjustment in our study for potential confounders. However, it should also be acknowledged that plaque characterization was available in approximately 50% of the detected plaques in PESA, and that the plaques were relatively small; therefore, our findings in this area should be taken with caution.

### **Study limitations**

In line with recent data (43), our findings suggest that arterial inflammation may precede plaque formation; however, since this is a cross-sectional analysis, we cannot establish temporality or causation. Serial imaging in PESA, including an  $^{18}\text{F}$ -FDG PET/MRI study at 6-year follow-up, will help to define the significance of these findings. Approximately 20% of individuals invited to participate declined enrollment or had MRI contraindications; however, this proportion is comparable to similar studies (48). The high success rate (nearly 80%) of our protocol may be influenced by the relatively young age and good health of the PESA participants, and tolerability would likely have been lower in older or frail patients. Nonetheless, we used a sequential PET/MRI system and newer integrated equipment can reduce examination times significantly (49). Almost the first 100 initial PETs could not be used due to inaccuracies in MRI-based attenuation and reconstruction, which likely reflects predictable challenges when introducing new technology, but feasibility was almost 100% thereafter. Although we attempted to evaluate arterial inflammation in as many territories as possible, some could not be evaluated, in particular the coronary arteries, which present specific technical challenges (50). High-resolution black-blood MRI of the aorta was not performed in order to limit examination time; therefore, aortic plaques were not assessed. Another study limitation was the inclusion only of individuals with subclinical atherosclerosis, so that our findings may not be generalizable to populations without plaque; however, plaque-free vessels were evaluated. Experienced PET readers determined arterial and plaque uptake qualitatively, which is likely the way it would be used in clinical practice. In a post-hoc analysis (not shown), we calculated that the optimal SUVmax cutoff value for defining visually increased  $^{18}\text{F}$ -FDG plaque uptake was 1.5 (AUC=0.86), in line with previous studies (32). Also, our analysis showed a positive correlation with hs-CRP, which to some extent provides an indirect validation of our method. However, the



optimal quantitative approach to evaluate early atherosclerotic inflammation is not yet standardized, and detailed quantitative analyses in PESA are underway. Up to 13.9% of study participants were taking statin therapy, which could influence the results since statins exert anti-inflammatory effects; however, a sensitivity analysis omitting these participants yielded similar results (Online Table 4).

## **Conclusions**

Large-scale multiterritorial  $^{18}\text{F}$ -FDG PET/MRI identified arterial inflammation in 48% of middle-aged individuals with subclinical atherosclerosis, predominantly in the femoral territory. While inflammation extent correlated with plaque burden, inflammation uptakes and plaques frequently did not coincide, suggesting that they are distinct processes in atherogenesis. Age, male sex, obesity, and smoking independently predicted arterial inflammation. Inflammation was noted in only 11% of plaques and was predominantly associated with larger plaque volume and a femoral or carotid distribution. These findings demonstrate the potential for in vivo imaging of systemic atherosclerosis-related inflammation, its study at early stages, and the identification of individuals likely to benefit from early intervention.

## **CLINICAL PERSPECTIVES**

*Competency in Medical Knowledge:* Arterial inflammation can be detected by 18F-FDG PET/MRI at multiple vascular sites in asymptomatic, middle-aged individuals with subclinical atherosclerosis, but these do not necessarily correspond to plaque.

*Translational Outlook:* Future studies should investigate whether inflammation precedes plaque development and assess the value of quantifying inflammation in cardiovascular risk assessment.

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## Figure Legends

**Central Illustration. Inflammation by PET/MRI in Atherosclerosis.** Prevalence of atherosclerosis and arterial inflammation by hybrid  $^{18}\text{F}$ -FDG PET/MRI across several vascular territories in the PESA participants.  $^{18}\text{F}$ -FDG PET/MRI:  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography / magnetic resonance imaging.

**Figure 1. PESA study protocol for the assessment of multiterritorial atherosclerosis by hybrid positron emission tomography/ magnetic resonance imaging (PET/MRI).**  $^{18}\text{F}$ -FDG:  $^{18}\text{F}$ -fluorodeoxyglucose; T1w: T1-weighted; T2w: T2-weighted; SSh-TFE: Single shot turbo field echo.

**Figure 2. Relationship between  $^{18}\text{F}$ -FDG uptake and cardiovascular risk factor burden.**  $^{18}\text{F}$ -FDG:  $^{18}\text{F}$ -fluorodeoxyglucose; CVRF: cardiovascular risk factor. 0, 1, 2, or >2 CVRF in relation to diabetes, arterial hypertension, dyslipidemia, smoking, and a family history of cardiovascular disease or obesity, as defined in the main manuscript.

**Figure 3. Prevalence of atherosclerosis and arterial inflammation in men and women in PESA.** MRI: magnetic resonance imaging; PET: positron emission tomography.

**Figure 4. Multivariate logistic regression models for predicting arterial  $^{18}\text{F}$ -FDG uptake (arterial inflammation) and plaques with coincident  $^{18}\text{F}$ -FDG uptake (plaque inflammation).** Left panels show patient-related factors associated with arterial inflammation, and right panels show plaque-related characteristics associated with inflammation. The models were adjusted for all variables shown in each part of the Figure.

**Figure 5. Typical phenotypic features of plaques with or without inflammation.** Plaques with coincident  $^{18}\text{F}$ -FDG uptake are more prevalent in the femoral territory (at the bifurcation) and tend to be larger and have more positive remodeling and larger lipid cores (yellow); in

contrast, plaques without coincident  $^{18}\text{F}$ -FDG uptake tend to be smaller, lack positive remodeling, and have a fibrotic composition (pink).

**Table 1.** Characteristics of PESA study participants

	Complete PET/MRI cohort (n=755)	Individuals with arterial inflammation (n= 364)	Individuals without arterial inflammation (n= 391)	P value
<b>Demographic</b>				
Age (years)	49.6 ± 4.3	50.3 ± 4.1	48.9 ± 4.4	<0.001
Sex (male)	632 (83.7)	328 (90.1)	304 (77.7)	<0.001
10-year PCE risk	3.9 [2.2-6.5]	4.9 [3.0–7.7]	3.2 [1.6–5.4]	<0.001
Dyslipidemia	444 (58.8)	234 (64.3)	210 (53.7)	0.003
Statin therapy	105 (13.9)	59 (16.2)	46 (11.8)	0.078
Smoking*	201 (27.1)	112 (31.2)	89 (23.3)	0.016
Obesity	147 (19.5)	100 (27.5)	47 (12.0)	<0.001
Hypertension	146 (19.3)	84 (23.1)	62 (15.9)	0.012
Family history	155 (20.5)	76 (20.9)	79 (20.2)	0.819
Diabetes	36 (4.8)	23 (6.3)	13 (3.3)	0.054
eGFR (mL/min/m <sup>2</sup> )	100.5 [93.1-104.9]	100.7 [92.9-104.5]	100.2 [93.4-105.4]	0.403
hs-CRP (mg/dL)	0.11 [0.06-0.21]	0.14 [0.08-0.27]	0.09 [0.05-0.17]	<0.001
<b>MRI</b>				
Presence of plaque	680 (90.1)	343 (94.2)	337 (86.2)	<0.001
<i>Carotid</i>	401 (53.1)	218 (59.9)	183 (46.8)	<0.001
<i>Iliac</i>	421 (55.8)	223 (61.3)	198 (50.6)	0.003
<i>Femoral</i>	558 (73.9)	301 (82.7)	257 (65.7)	<0.001
N° of plaques per participant	3 [2-5]	4 [2-5]	2 [1-4]	<0.001
Volume per plaque (mm <sup>3</sup> )	95.5 [48.9-173.8]	125.3 [70.8-243.7]	92.7 [46.7-164.9]	<0.001

Values are mean ± standard deviation or median [interquartile range] for continuous variables or n (%) for categorical variables. P values relate to the comparison of the group with arterial inflammation versus the group without. eGFR: estimated glomerular filtration rate; MRI: magnetic resonance imaging; hs-CRP:

high sensitivity C-reactive protein; PCE: pooled cohort equation; PET: positron emission tomography.

\*Smoking data are available for 741 individuals.

**Table 2.** Comparison of plaques with and without inflammation

	<b>All plaques (n=2605)</b>	<b>Plaques with inflammation (n= 287)</b>	<b>Plaques without inflammation (n=2318)</b>	<b>P value</b>
<b><u>MRI</u></b>				
<b>Location</b>				
<i>Carotid</i>	630 (24.2)	85 (29.6)	545 (23.5)	0.047
<i>Iliac</i>	903 (34.7)	39 (13.6)	864 (37.3)	<0.001
<i>Femoral</i>	1,072 (41.2)	163 (56.8)	909 (39.2)	<0.001
<b>Bifurcation</b>	665 (25.5)	91 (31.7)	574 (24.8)	0.028
<b>Plaque volume (mm<sup>3</sup>)</b>	95.5 [48.9-173.8]	125.3 [70.8-243.7]	92.7 [46.7-164.9]	<0.001
<b>Positive arterial remodeling*</b>	1522 (58.4)	189 (65.8)	1333 (57.5)	0.032
<b>Plaque composition<sup>†</sup></b>				
<i>Lipid-rich</i>	519 (38.7)	92 (48.2)	427 (37.1)	0.010
<i>Fibrotic</i>	749 (55.9)	90 (47.1)	659 (57.3)	0.018
<i>Mixed /Indeterminate</i>	73 (5.4)	9 (4.7)	64 (5.6)	0.717
<b><u>PET</u></b>				
<b>SUVmax per plaque</b>	1.4 ± 0.3	1.7 ± 0.3	1.3 ± 0.3	<0.001
<b>TBRmax per plaque</b>	1.6 ± 0.4	1.9 ± 0.5	1.6 ± 0.4	<0.001

Values are mean ± standard deviation or median [interquartile range] for continuous variables and n (%) for categorical variables. MRI: magnetic resonance imaging; SUV: standardized uptakes values; TBR: target-background ratio. \*Positive arterial remodeling was calculated for 2552 plaques and SUV/TBRmax for 2284 plaques without uptake. †T2-weighted imaging was available for 1341 plaques (191 plaques with inflammation and 1150 plaques without inflammation).