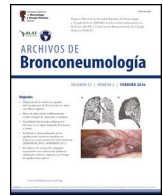




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Original Article

From Lungs to Vascular Health: Airflow Obstruction, Not Lung Function Decline, Predicts Atherosclerosis Progression Independent of Smoking Status

Mario Henríquez-Beltrán^{a,b,c,1}, Esther Gracia-Lavedan^{a,b,1}, Anna Sánchez-Cucó^a, Gerard Torres^{a,b}, Adriano D.S. Targa^{a,b}, Marcelino Bermúdez-López^{d,e}, José Manuel Valdivielso^d, Reinald Pamplona^{e,f}, Dídac Mauricio^{g,h}, Eva Castro-Boqué^d, Elvira Fernández^d, Albert Lecube^{h,i}, Jordi de Batlle^{a,b}, Ferrán Barbé^{a,b}, Jessica González^{a,b,*}, on behalf of the ILERVAS project collaborators

^a Group of Translational Research in Respiratory Medicine, IRBLeida, Hospital Universitari Arnau de Vilanova i Santa Maria, Lleida, Spain

^b CIBER of Respiratory Diseases (CIBERES), Institute of Health Carlos III, Madrid, Spain

^c Núcleo de Investigación en Ciencias de la Salud, Universidad Adventista de Chile, Chillán, Chile

^d Vascular and Renal Translational Research Group, Institute for Research in Biomedicine of Lleida (IRBLeida), Renal Research Network (RICORS2040, ISCIII), Lleida, Spain

^e Department of Experimental Medicine, University of Lleida, Spain

^f Metabolic Pathophysiology Group, Institute for Research in Biomedicine of Lleida (IRBLeida), Lleida, Spain

^g Department of Endocrinology & Nutrition, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

^h CIBERDEM, IR Sant Pau, Barcelona, Spain

ⁱ Department Endocrinology and Nutrition, University Hospital Vall d'Hebron, Diabetes and Metabolism Research Group, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain

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ABSTRACT

Objectives: To prospectively evaluate the relationship between 4-year changes in lung function and the progression of subclinical atherosclerosis among 1623 middle-aged adults with at least one cardiovascular risk factor participating in ILERVAS, and to determine whether individuals who develop airflow obstruction (AO) are especially susceptible to accelerated atherosclerosis progression.

Methods: This prospective cohort study included 1623 middle-aged adults from the ILERVAS cohort, recruited in primary care centers in the province of Lleida (Catalonia, Spain), with baseline assessments conducted between 2015 and 2018 and follow-up visits between 2019 and 2021 (mean follow-up, 3.99 [SD, 0.22] years). Pulmonary function was assessed by spirometry at baseline and at 4-year follow-up. Subclinical atherosclerosis was evaluated using vascular ultrasound of 12 carotid and femoral territories at baseline and at follow-up, with total plaque area quantified. Associations were analyzed using multi-variable linear regression models, adjusting for clinical variables and baseline plaque burden. Analyses were stratified by smoking status.

Results: Median annual declines were -95 mL (-2.04%) for FVC and -78 mL (-2.00%) for FEV₁. Categorization of annual pulmonary function decline by tertiles showed no significant association with plaque progression. In contrast, incident AO was associated with greater annual FEV₁ decline (-146.73 vs -74.90 mL; $P < .001$) and with greater plaque burden, reflected by an increase in affected vascular territories (0.26 [IQR, $0.00-0.75$]; $P < .001$). Multivariable models confirmed larger annual increases in total (4.40 mm²; $P < .001$), carotid (2.33 mm²; $P < .001$), and femoral (1.99 mm²; $P = .031$) plaque areas among participants with incident AO, with consistent results across smoking strata. Sensitivity analyses using a lower limit of normal-based definition of AO showed similar findings, with effect estimates consistent with the primary fixed-ratio analyses.

Conclusions: In this two-time-point analysis, lung function decline was not independently associated with subclinical atherosclerosis progression. In contrast, incident AO was consistently associated with greater plaque progression across smoking strata. These findings support incident AO as a spirometric marker associated with vascular risk.

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* Corresponding author.

E-mail address: jgonzalezgutierrez88@gmail.com (J. González).

¹ Mario Henríquez-Beltrán and Esther Gracia-Lavedan contributed equally to this work and share first authorship.

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Introduction

Pulmonary function is a key marker of respiratory and systemic health, reflecting not only ventilatory capacity but also the interaction between pulmonary, cardiovascular, and metabolic systems [1,2]. Although gradual declines are expected with aging, environmental exposures, such as tobacco smoke and air pollution, can accelerate this deterioration [3–6]. Beyond respiratory consequences, reduced pulmonary function has been associated with adverse cardiovascular events [7–11], suggesting that it may serve as an early indicator of systemic vascular damage and dysfunction.

Several studies have reported an association between lung function impairment and subclinical atherosclerosis in the general population [12–15]. This relationship is particularly relevant in individuals with airflow obstruction (AO) or clinically defined chronic obstructive pulmonary disease (COPD) [16], who often exhibit a greater atherosclerotic burden [17,18]. These findings suggest a shared pathophysiological mechanism between early vascular dysfunction and lung function impairment [14,19]. In this context, systemic inflammation and endothelial dysfunction associated with lung function impairment may promote a proatherogenic environment, thereby contributing to vascular pathology [18].

Although the association between lung function impairment and subclinical atherosclerosis has been explored in various epidemiological and cross-sectional studies [8,12,17,20,21], well-characterized longitudinal studies assessing the parallel progression of both conditions in asymptomatic individuals, including non-smokers, are lacking. Therefore, the main objective of this study was to prospectively evaluate the relationship between changes in lung function and the progression of subclinical atherosclerosis over a 4-year follow-up period in 1623 middle-aged individuals with at least one cardiovascular risk factor participating in the ILERVAS project [22]. Additionally, we explored whether individuals who develop AO are particularly susceptible to the progression of subclinical atherosclerosis.

Methods

Study design and objectives

This study corresponds to a sub-study of the ILERVAS project (NCT03228459) [22], a prospective, multicenter, longitudinal cohort conducted in primary care centers across the province of Lleida (Catalonia, Spain) between 2015 and 2018. The overarching objective of the ILERVAS project was to characterize the prevalence of subclinical atheromatous disease and previously undiagnosed chronic kidney disease in a population with low to moderate cardiovascular risk.

The primary objective of our study was to prospectively evaluate the relationship between changes in lung function, categorized by tertiles, and the progression of subclinical atherosclerosis over a 4-year follow-up period. The secondary objective was to determine whether the development of AO during the 4-year follow-up period was specifically associated with the progression of subclinical atherosclerosis.

Study population

This was an observational longitudinal study using data from the ILERVAS cohort [22]. Baseline assessments were conducted between 2015 and 2018, and follow-up visits took place approximately 4 years later, between 2019 and 2021, with a mean follow-up duration of 3.99 (SD, 0.22) years. The inclusion criteria for this sub-study were: (1) women aged 50–70 years and men

aged 45–65 years; and (2) presence of at least one cardiovascular risk factor (such as hypertension, dyslipidemia, obesity, smoking history, or a first-degree family history of premature cardiovascular disease), with no previous clinical history of cardiovascular disease, diabetes, chronic kidney disease, active neoplasia, or a life expectancy of less than 18 months.

Among 8330 individuals initially enrolled in the ILERVAS cohort, 1743 had both baseline and follow-up spirometry available for longitudinal analyses. Extreme pulmonary function values were identified using symmetric trimming at the ≤ 0.5 th and ≥ 99.5 th percentiles. All spirometric values meeting these criteria were individually reviewed by a pulmonologist, who confirmed that they were not physiologically plausible and were most consistent with technical artifacts or nonreproducible maneuvers. Fifty participants were excluded at this stage, resulting in 1693 individuals.

Subsequently, extreme values in annual change of total atheromatous plaque area were identified using the same symmetric trimming approach (≤ 0.5 th and ≥ 99.5 th percentiles). Seventy additional participants were excluded based on this criterion, yielding a final analytic sample of 1623 participants (Fig. 1).

Within this final analytic sample, participants with AO at baseline were excluded from incident analyses. According to the primary fixed-ratio definition ($FEV_1/FVC < 0.70$), 194 individuals (12%) met criteria for baseline obstruction and were therefore not eligible for incident evaluation. The remaining 1429 participants were eligible for incident analysis. During follow-up, 160 developed incident AO, whereas 1269 remained nonobstructed.

In predefined sensitivity analyses using the lower limit of normal (LLN) definition (FEV_1/FVC z-score < -1.645), incident AO was assessed among participants without baseline LLN-defined obstruction. Under this alternative definition, 1517 individuals were eligible for incident evaluation, of whom 116 (7.65%) developed AO during follow-up.

The ILERVAS study protocol was approved by the Ethics Committee of the *Hospital Universitario Arnau de Vilanova* (CEIC-1410; CEIC-2015), and all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Sample size calculation

No formal sample size calculation was performed for this ancillary analysis; all eligible participants from the ILERVAS cohort meeting the inclusion criteria were included.

Sociodemographic evaluation

In the current study, sociodemographic and anthropometric variables were collected, including sex, age, and body mass index (BMI, in kg/m^2). Comorbidities such as hypertension, dyslipidemia, obesity, and COPD (based on self-report of a prior clinical diagnosis) were documented, as well as lifestyle factors, including tobacco use. In addition, capillary blood parameters and pharmacotherapy data were collected.

Pulmonary function

Forced spirometry was performed using a portable ultrasonic spirometer (Datospir©, Sibelmed, Barcelona, Spain) by certified pulmonary technicians, following the standards established by the European Respiratory Society (ERS) and the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) [23,24]. Each participant completed at least three acceptable and reproducible maneuvers, and the highest values of forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) were selected for analysis. Postbronchodilator testing was not performed. FVC and FEV_1 were

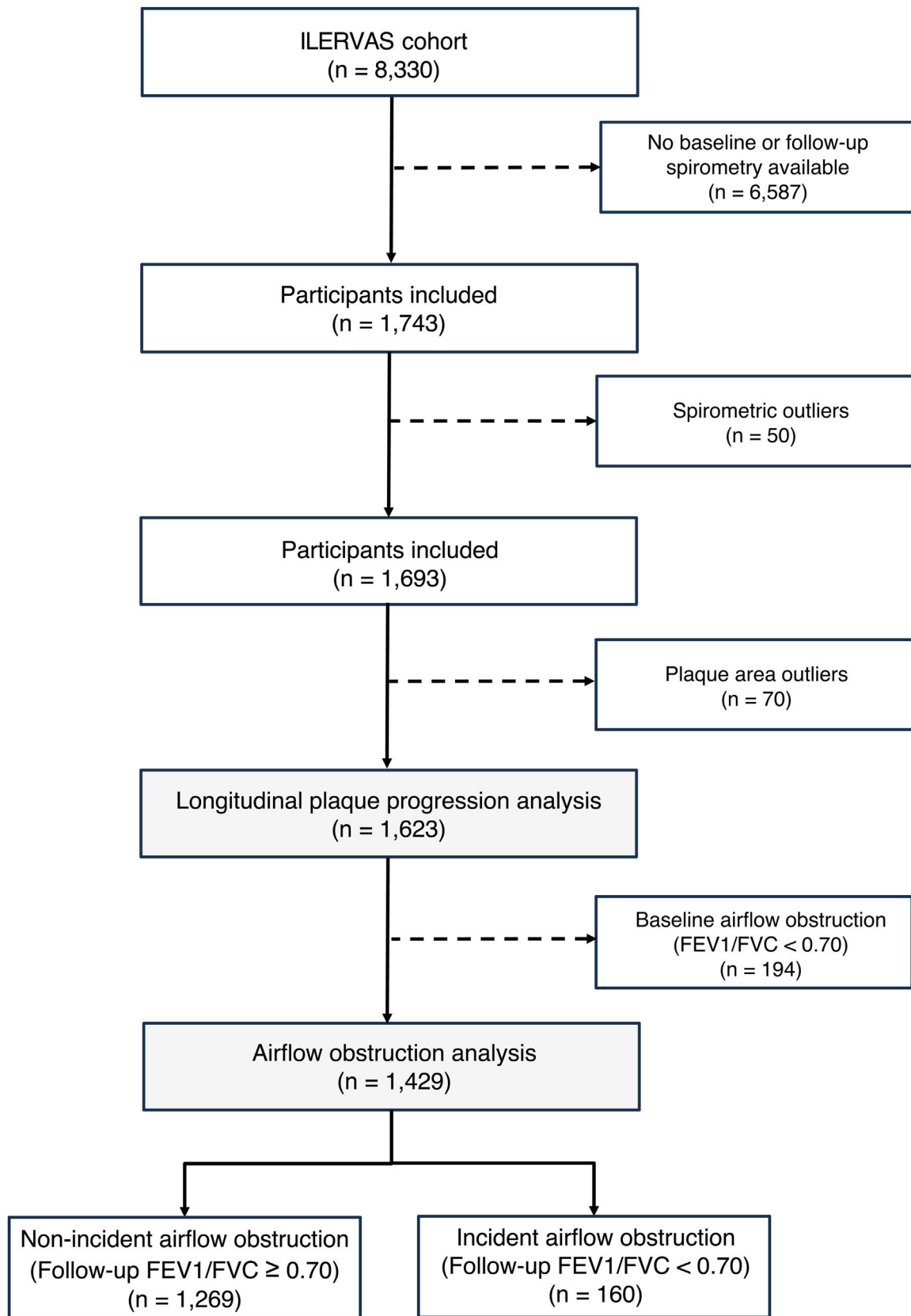


Fig. 1. Flowchart of longitudinal cohort and incident airflow obstruction analyses.

recorded in absolute values (mL) and expressed as a percentage of predicted values based on ERS reference equations, as well as z-scores derived from Global Lung Function Initiative (GLI) reference equations.

Groups defined by pulmonary function trajectory

AO was defined primarily using a fixed FEV₁/FVC ratio <0.70, in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [16]. For sensitivity analyses, AO was alternatively defined using the LLN, corresponding to an FEV₁/FVC z-score < -1.645 derived from GLI reference equations [25].

Pulmonary function trajectories were examined first by tertiles of annual FVC and FEV₁ change, and subsequently according to the FEV₁/FVC ratio at baseline and at follow-up. Two groups were defined: (1) incident AO group: participants with FEV₁/FVC ≥0.70 at baseline who declined to <0.70 at follow-up; and (2) nonincident AO group: participants who maintained FEV₁/FVC ≥0.70 at both time points.

Vascular ultrasound method for atheromatous plaque evaluation

Arterial ultrasound was performed in 12 vascular territories: both carotid arteries (common, bifurcation, internal, and external) and femoral arteries (common and superficial) [26]. Trained sonographers acquired the images using a VIVID-i ultrasound system (BT09 model, GE Healthcare, Waukesha, WI, USA), equipped with a 12L-RS linear broadband probe (6–13 MHz) and pulsed Doppler capabilities to assess hemodynamic abnormalities. Standardized and validated scanning and reading protocols were followed to minimize interoperator variability and type II errors. All readings were performed by blinded evaluators with no access to participants' clinical data.

Subclinical atherosclerosis was defined as the presence of at least one plaque in any of the 12 assessed regions. According to the Mannheim consensus, a plaque was defined as a focal thickening of the intima-media complex protruding into the lumen ≥1.5 mm [27]. The total plaque area (mm²) was measured for all identified plaques [20,28].

For the purpose of the study, the primary outcome was the annual change in total plaque area (carotid and femoral territories).

Follow-up assessments

At the 4-year follow-up visit, participants underwent repeated evaluations of sociodemographic and anthropometric characteristics, pulmonary function (spirometry), and subclinical atheromatous plaque burden through vascular ultrasound.

Statistical analysis

Baseline characteristics were summarized for all individuals and separately by study groups (incident AO group and nonincident AO group). Continuous variables were described as means (SD), or medians (IQR), according to their distribution, while categorical variables were expressed as frequencies (percentages). Group comparisons were performed using the Student *t* test or the Mann–Whitney *U* test for continuous variables, as appropriate. The Mann–Whitney *U* test evaluates differences in the overall distribution of values rather than differences in medians alone. Categorical variables were compared using χ^2 tests. Pulmonary function and atheromatous plaque data (affected vascular territories and plaque area) were also summarized at baseline and as annual change for all individuals and by study group using the same descriptive approach.

To evaluate the association between annual change in pulmonary function or incident airflow obstruction and annual change in total atheromatous plaque area (total, carotid, and femoral territories), multivariable linear regression models were fitted. Although baseline plaque area measures are right-skewed, annual change in total atheromatous plaque area is a continuous variable that can assume both positive and negative values, supporting the use of linear regression to obtain clinically interpretable effect estimates.

All models were adjusted for potential confounders, including age, sex, systolic and diastolic blood pressure, total cholesterol, body mass index (BMI), waist circumference, smoking status, pack-years of smoking, antihypertensive treatment, statin therapy, glycated hemoglobin (HbA1c), and baseline total plaque area. Medication variables were defined at baseline.

Analyses were additionally stratified by smoking status, defined as non-smokers (never and former smokers combined) versus current smokers.

A sensitivity analysis was performed by rerunning the fully adjusted main models without percentile trimming of extreme annual plaque-change values, using the same model specifications, to assess the robustness of the findings to the inclusion of extreme values.

Further sensitivity analyses were conducted using the LLN-based definition of incident AO to explore its association with annual change in total atheromatous plaque area (total, carotid, and femoral territories), applying the same multivariable linear regression approach and adjustments.

Multicollinearity was assessed using variance inflation factors (VIF). Model assumptions were evaluated through residual diagnostics, with particular attention to heteroscedasticity. All analyses were conducted using heteroscedasticity-robust (Huber–White) standard errors. Adjusted estimates with 95%CI were reported.

All analyses were performed using R (version 4.4; R Foundation for Statistical Computing, Vienna, Austria). A 2-sided *P* < .05 was considered statistically significant.

Results

Baseline characteristics of the overall cohort and their association with annual changes in pulmonary function and atheromatous plaque progression

Baseline characteristics of the cohort (*N* = 1623) are summarized in Table 1. Women represented 52.5% of participants, with a mean age of 57.4 (SD, 6.27) years. The most prevalent comorbidities were dyslipidemia (51.6%) and hypertension (39.2%); 25.5% were current smokers and 39.9% were never smokers.

Median annual changes in pulmonary function were -95.39 mL (IQR, -172.19 to -24.76) and -2.04% (IQR, -4.19 to 0.24) for FVC, and -77.82 mL (IQR, -136.43 to -22.60) and -2.00% (IQR, -4.20 to 0.13) for FEV₁ (e-Table 1, in supplementary material). Regarding atheromatous plaque burden, the annual median change was 0.25 (IQR, 0.00–0.50) affected territories, 6.20 mm² (IQR, 1.00–15.3) for total plaque area, and 1.44 mm² (IQR, 0.00–10.8) for carotid plaque area (e-Table 2, in supplementary material).

Groups defined by tertiles of annual FVC and FEV₁ change were generally comparable at baseline (e-Table 3, in supplementary material). A modest difference was noted in the proportion of female participants across FEV₁ tertiles (*P* = .041). Across FVC tertiles, greater declines in pulmonary function were significantly associated with a higher atherosclerotic burden, with the third tertile showing more territories with plaque (2.0 [0.0–3.0] vs 1.0 [0.0–3.0]; *P* = .019) and larger carotid plaque area (25.0 mm² [0.0–72.5] vs 17.0 mm² [0.0–60.0]; *P* = .018). For FEV₁, differences

Table 1
Baseline characteristics of the overall study population.

	Global N = 1623
<i>Sociodemographic and anthropometric data</i>	
Sex, female	852 (52.5%)
Age, years	57.4 (SD, 6.27)
Body mass index, kg/m ²	28.9 (SD, 4.84)
<i>Comorbidities</i>	
Dyslipidemia	837 (51.6%)
Hypertension	636 (39.2%)
Obesity	462 (28.5%)
COPD	41 (2.53%)
<i>Habits</i>	
Tobacco	
Never-smoker	647 (39.9%)
Former smoker	562 (34.6%)
Current smoker	414 (25.5%)
Pack-years	12.4 (SD, 16.2)
<i>Capillary blood-related information</i>	
HbA1c (glycated hemoglobin)	
<5.7% (normoglycemia)	1177 (72.6%)
5.7–6.4% (prediabetes)	433 (26.7%)
≥6.5% (diabetes)	12 (0.74%)
Serum creatinine	0.78 (SD, 0.18)
Glomerular filtration rate	92.9 (SD, 13.6)
Uric acid	5.35 (SD, 1.49)
Total cholesterol, mg/dL	206 (SD, 36.2)
<i>Pharmacotherapy</i>	
Angiotensin II receptor blockers	128 (7.89%)
Diuretics	237 (14.6%)
Angiotensin-converting enzyme inhibitors	258 (15.9%)
Statins	249 (15.3%)

Data are presented as mean (SD), or No. (%). Abbreviation: COPD, chronic obstructive pulmonary disease.

were less marked but suggested greater plaque involvement and larger carotid burden with steeper declines.

After adjustment for potential confounders (sex, age, systolic blood pressure, diastolic blood pressure, total cholesterol, BMI, waist circumference, smoking status, pack-years of smoking, anti-hypertensive treatment, statin therapy, HbA1c, and baseline plaque burden), annual changes in pulmonary function categorized by tertiles were not significantly associated with plaque progression (e-Fig. 1, in supplementary material).

Baseline characteristics according to incident airflow obstruction and association with atheromatous plaque progression

Of the 1623 participants included in the longitudinal analyses, 1429 had a normal FEV₁/FVC ratio at baseline and were eligible for the incident AO analysis. At follow-up, 160 participants (11.2%) developed AO. They were slightly older (58.7 [SD, 6.33] vs 56.9 [SD, 6.18] years; $P = .001$) and more frequently women (61.9% vs 51.4%; $P = .015$) compared with those who did not. No significant differences in cardiometabolic comorbidities or smoking status were observed between groups (Table 2).

At baseline, FEV₁ (mL) and the FEV₁/FVC ratio were lower in the incident AO group, whereas FVC (mL) was similar. Percent-predicted FVC was slightly higher in this group, with no difference in percent-predicted FEV₁. Longitudinally, incident AO was associated with a greater annual decline in FEV₁ (−146.73 vs −74.90 mL; $P < .001$) and percent-predicted FEV₁ (−4.69% vs −1.84%; $P < .001$). In contrast, annual FVC decline (both absolute and percent-predicted values) was greater in the nonincident AO group (−97.14 vs −72.08 mL and −2.07% vs −1.21%, respectively). The FEV₁/FVC ratio declined significantly in the incident AO group (−2.50; $P < .001$) but remained stable in the nonincident AO group (Table 3).

Baseline plaque burden was comparable between both groups. However, over the follow-up period, the incident AO group showed a greater annual increase in plaque extent, with more affected vascular territories (0.26 [IQR, 0.00–0.75] vs 0.25 [IQR, 0.00–0.50]; $P < .001$), greater involvement of carotid territories (0.25 [IQR, 0.00–0.50] vs 0.00 [IQR, 0.00–0.25]; $P = .001$), and higher carotid plaque burden (2.50 mm² [IQR, 0.00–8.78] vs 1.24 mm² [IQR, 0.00–4.48]; $P < .001$), as well as a larger increase in total plaque area across carotid and femoral territories (7.62 mm² [IQR, 2.00–19.0] vs 5.27 mm² [IQR, 0.48–13.7]) (Table 4). Although median values appeared similar in some comparisons, the Mann–Whitney U test indicated a shift in the overall distribution of plaque progression toward higher values in the incident AO group.

After adjustment for key confounders (sex, age, systolic blood pressure, diastolic blood pressure, total cholesterol, BMI, waist circumference, smoking status, pack-years of smoking, anti-hypertensive treatment, statin therapy, HbA1c, and baseline atheromatous plaque), incident AO remained significantly associated with greater annual increases in total (4.40 mm²; $P < .001$), carotid (2.33 mm²; $P < .001$), and femoral (1.99 mm²; $P = .031$) plaque area (Fig. 2).

In sensitivity analyses without percentile trimming of annual plaque change, the results of the fully adjusted models were materially unchanged, with effect estimates of similar magnitude and direction and no meaningful differences in statistical significance compared with the primary analysis (e-Fig. 2, in supplementary material).

In sensitivity analyses using an LLN-based definition of AO (FEV₁/FVC z-score < −1.645), 116 (7.6%) of 1517 participants without airflow obstruction at baseline (FEV₁/FVC z-score ≥ −1.645) developed incident obstruction at follow-up. In fully adjusted models, effect estimates were of similar magnitude and direction compared with the primary fixed-ratio analyses (e-Table 4 and e-Fig. 3, in supplementary material).

Analysis stratified according to smoking status between the incident AO and nonincident AO groups

Baseline characteristics by smoking status are presented in e-Table 5, in supplementary material. Among non-smokers, those with incident AO were older, had lower diastolic blood pressure, a distinct lipid profile, and greater statin use. In adjusted analyses, incident AO was associated with greater annual progression of total and carotid plaque in both non-smokers and smokers (e-Fig. 4, in supplementary material).

Discussion

In this large cohort of 1623 middle-aged individuals with cardiovascular risk factors, lung function decline assessed using a 2-time-point, tertile-based approach was not independently associated with atherosclerotic plaque progression over 4 years. In contrast, participants who developed AO during follow-up experienced both steeper pulmonary decline and greater increases in atherosclerotic burden. Multivariable-adjusted models confirmed that incident AO was independently associated with faster annual growth in total, carotid, and femoral plaque areas, with consistent results across smoking strata.

The magnitude of pulmonary decline in our cohort was substantially greater than previously reported [8,29]. Participants lost on average −95 mL (−2.04%) of FVC and −78 mL (−2.00%) of FEV₁ annually. In the Framingham Heart Study [29], declines were considerably smaller, reflecting a healthier baseline population. By contrast, in the ARIC study [8], the highest quartile of FEV₁ decline averaged approximately −120 mL/year and was associated

Table 2
Baseline characteristics of the study population by group.

	Global N = 1429	Nonincident AO group N = 1269	Incident AO group N = 160	P value
<i>Sociodemographic and anthropometric data</i>				
Sex, female	751 (52.6%)	652 (51.4%)	99 (61.9%)	.015
Age, years	57.1 (SD, 6.22)	56.9 (SD, 6.18)	58.7 (SD, 6.33)	.001
Body mass index, kg/m ²	29.0 (SD, 4.75)	29.1 (SD, 4.71)	28.5 (SD, 5.05)	.147
<i>Comorbidities</i>				
Hypertension	578 (40.4%)	510 (40.2%)	68 (42.5%)	.634
Dyslipidemia	736 (51.5%)	656 (51.7%)	80 (50.0%)	.749
Obesity	424 (29.7%)	381 (30.0%)	43 (26.9%)	.466
COPD	23 (1.61%)	19 (1.50%)	4 (2.50%)	.315
<i>Habits</i>				
Tobacco				.190
Never-smoker	603 (42.2%)	539 (42.5%)	64 (40.0%)	
Former smoker	496 (34.7%)	446 (35.1%)	50 (31.2%)	
Current smoker	330 (23.1%)	284 (22.4%)	46 (28.7%)	
Pack-years	10.8 (SD, 14.9)	10.6 (SD, 14.4)	12.9 (SD, 18.0)	.127
<i>Capillary blood-related information</i>				
Glycated hemoglobin				.892
<5.7% (normoglycemia)	1039 (72.8%)	920 (72.6%)	119 (74.4%)	
5.7–6.4% (prediabetes)	377 (26.4%)	337 (26.6%)	40 (25.0%)	
≥6.5% (diabetes)	12 (0.84%)	11 (0.87%)	1 (0.62%)	
Serum creatinine	0.78 (SD, 0.19)	0.78 (SD, 0.18)	0.73 (SD, 0.19)	<.001
Glomerular filtration rate	93.1 (SD, 13.6)	92.9 (SD, 13.7)	94.8 (SD, 13.0)	.085
Uric acid	5.37 (SD, 1.47)	5.41 (SD, 1.46)	5.04 (SD, 1.53)	.004
Total cholesterol, mg/dL	206 (SD, 35.7)	207 (SD, 36.2)	202 (SD, 31.9)	.055
<i>Pharmacotherapy</i>				
Angiotensin II receptor blockers	113 (7.91%)	95 (7.49%)	18 (11.2%)	.132
Diuretics	216 (15.1%)	181 (14.3%)	35 (21.9%)	.016
Angiotensin-converting enzyme inhibitors	234 (16.4%)	205 (16.2%)	29 (18.1%)	.602
Statins	223 (15.6%)	190 (15.0%)	33 (20.6%)	.082

Data are presented as mean (SD), or No. (%). Abbreviations: AO, airflow obstruction; COPD, chronic obstructive pulmonary disease.

Table 3
Pulmonary function at baseline and annual change by study group.

	Baseline nonincident AO group N = 1269	Baseline incident AO group N = 160	P value	Annual change nonincident AO group N = 1269	Annual change incident AO group N = 160	P value
<i>Pulmonary function data</i>						
FVC, mL	3550 (IQR, 2960–4350)	3480 (IQR, 2918–4252)	.385	−97.14 (IQR, −167.27 to −26.70)	−72.08 (IQR, −186.15 to 2.51)	.048
FVC, % predicted	101 (IQR, 89.8–111)	104 (IQR, 93.1–117)	.019	−2.07 (IQR, −4.08 to 0.12)	−1.21 (IQR, −4.26 to 1.31)	.023
FEV ₁ , mL	2820 (IQR, 2340–3470)	2720 (IQR, 2222–3200)	.006	−74.90 (IQR, −129.98 to −22.47)	−146.73 (IQR, −265.24 to −81.89)	<.001
FEV ₁ , % predicted	102 (IQR, 90.1–112)	99.3 (IQR, 88.5–114)	.431	−1.84 (IQR, −3.88 to 0.11)	−4.69 (IQR, −9.03 to −2.01)	<.001
FEV ₁ /FVC	79.5 (IQR, 76.2–82.9)	75.5 (IQR, 72.3–78.3)	<.001	0.04 (IQR, −0.65 to 0.72)	−2.50 (IQR, −4.30 to −1.77)	<.001

Data are presented as median (IQR). Abbreviations: AO, airflow obstruction; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second.

Table 4
Atheromatous plaque at baseline and change between visits by study group.

	Baseline nonincident AO group N = 1269	Baseline incident AO group N = 160	P value	Annual change nonincident AO group N = 1269	Annual change incident AO group N = 160	P value
<i>Presence of atheromatous plaque by territories</i>						
12 total explored territories	823 (64.9%)	111 (69.4%)	.296	–	–	–
8 explored carotid territories	536 (42.2%)	77 (48.1%)	.183	–	–	–
4 explored femoral territories	634 (50.0%)	80 (50.0%)	>.99	–	–	–
<i>Extent of atheromatous plaque</i>						
Total number of territories with plaque	1.00 (IQR, 0.00–3.00)	1.00 (IQR, 0.00–3.00)	.478	0.25 (IQR, 0.00–0.50)	0.26 (IQR, 0.00–0.75)	<.001
Number of carotid territories with plaque	0.00 (IQR, 0.00–1.00)	0.00 (IQR, 0.00–1.25)	.194	0.00 (IQR, 0.00–0.25)	0.25 (IQR, 0.00–0.50)	.001
Number of femoral territories with plaque	0.00 (IQR, 0.00–2.00)	0.50 (IQR, 0.00–2.00)	.972	0.00 (IQR, 0.00–0.25)	0.00 (IQR, 0.00–0.25)	.002
<i>Atheromatous plaque burden area, mm²</i>						
Total carotid and femoral plaque	19.0 (IQR, 0.00–61.0)	17.0 (IQR, 0.00–62.8)	.723	5.27 (IQR, 0.48–13.7)	7.62 (IQR, 2.00–19.0)	.003
Total carotid plaque	0.00 (IQR, 0.00–14.0)	0.00 (IQR, 0.00–16.2)	.144	1.24 (IQR, 0.00–4.48)	2.50 (IQR, 0.00–8.78)	<.001
Total femoral plaque	0.00 (IQR, 0.00–48.0)	2.50 (IQR, 0.00–42.0)	.724	2.91 (IQR, 0.00–9.78)	4.00 (IQR, 0.00–11.3)	.073

Data are presented as No. (%) or median (IQR,). Abbreviation: AO, airflow obstruction.

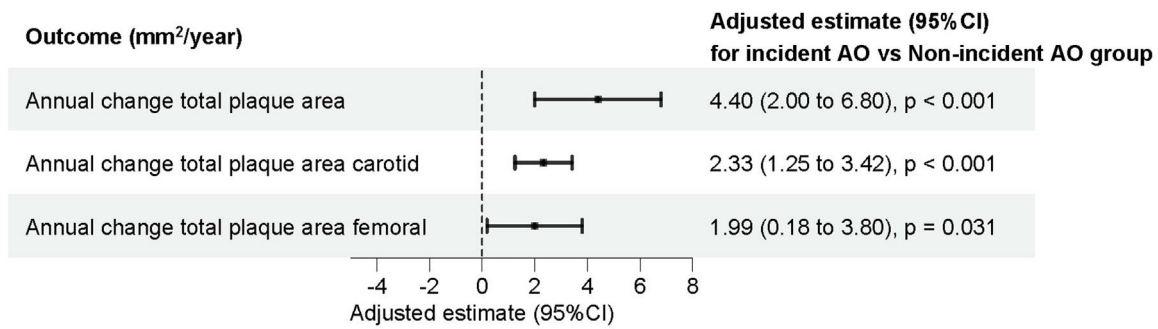


Fig. 2. Association between incident airflow obstruction and annual progression of atheromatous plaque area. Multivariable linear regression models assessed the association between Incident AO group (vs. Non-incident AO) and annual change in total atheromatous plaque area (carotid and femoral, mm²/year), with estimates and 95% robust confidence intervals (CI). Models were adjusted for sex, age, systolic and diastolic blood pressure, total cholesterol, body mass index, waist circumference, smoking status, pack-years of smoking, antihypertensive treatment, statin treatment, glycated hemoglobin (HbA1c) and baseline total atheromatous plaque area.

with increased cardiovascular risk [8]. Similarly, the CARDIA study defined rapid decline as >−52 mL/year [30], and smoker-specific trajectories reported by Backman et al. [31] described declines of approximately −72 mL/year. These comparisons suggest that the ILERVAS cohort more closely resembles high-risk trajectories described in populations with clustered cardiometabolic burden rather than normative reference cohorts. Differences in age distribution, risk-factor clustering, and baseline cardiovascular vulnerability likely contributed to the accelerated decline observed.

Despite these marked declines, stratification by tertiles of annual pulmonary function loss did not predict plaque progression. This contrasts with evidence from younger populations and from the UK Biobank [30,32], where accelerated decline was linked to clinical cardiovascular events. One possible explanation is that our vascular endpoint—quantitative progression of subclinical atherosclerotic plaque—may reflect biological pathways distinct from those underlying overt cardiovascular disease. The absence of systemic inflammatory biomarkers also precluded evaluation of proposed mechanistic links.

The relatively high incidence of AO observed during follow-up (11.2% over 4 years) should be interpreted within the methodological framework of this study [6,8,30]. AO was defined using a fixed prebronchodilator FEV₁/FVC threshold (<0.70), and age-related physiological decline in this ratio may increase transitions across the diagnostic cutoff [25,33]. Accordingly, incident AO represents a spirometric transition rather than a definitive clinical diagnosis. Sensitivity analyses using an LLN-based definition yielded consistent associations with plaque progression, suggesting that the findings are unlikely to be solely attributable to age-related misclassification. Moreover, only a small proportion of participants who developed incident spirometric obstruction had a prior clinical diagnosis of COPD, consistent with the well-recognized underdiagnosis of COPD in population-based studies [34]. In this cohort, COPD status was self-reported and not confirmed by postbronchodilator testing, further emphasizing the distinction between spirometric airflow obstruction and clinically established COPD.

Beyond these methodological considerations, the association between incident AO and plaque progression was robust, persisting after multivariable adjustment and across smoking strata. These findings align with prior reports linking obstructive spirometric patterns to subclinical carotid atherosclerosis [17] and to greater coronary plaque burden [35]. AO is associated with systemic inflammation, oxidative stress, endothelial dysfunction, and vascular remodeling, all of which are well-established contributors to atherogenesis [19,36]. Thus, incident AO may represent not only a pulmonary phenotype but also a systemic marker of heightened vascular risk within this high-risk population.

Notably, the association between AO and plaque progression was observed in both smokers and non-smokers. This indicates

that smoking, while an important risk factor, is not the sole driver of vascular pathology in airflow limitation [37–39]. Alternative mechanisms—such as chronic airway inflammation, environmental exposures, or genetic predisposition—may link pulmonary impairment with atherosclerotic remodeling [40]. Large cohorts of never-smokers have shown that both restrictive and obstructive patterns are associated with increased risks of coronary artery disease and heart failure [39]. Similarly, the AGES-Reykjavik study [37] found that AO was independently related to higher atherosclerotic burden even after adjustment for cardiovascular risk factors and inflammatory markers. Taken together, these observations underscore that airflow limitation itself, irrespective of smoking status, may contribute to vascular disease.

Strengths and limitations of the study

The strengths of this study include its large, well-characterized cohort, longitudinal design, repeated high-quality spirometry, and objective quantification of carotid and femoral plaque by trained personnel. The inclusion of participants with cardiometabolic risk factors enhances the clinical relevance of the findings, and the comprehensive multivariable adjustment strengthens the robustness of the observed associations. Several limitations should be acknowledged. First, spirometry was performed without postbronchodilator testing; therefore, airflow obstruction was defined using a prebronchodilator FEV₁/FVC ratio <0.70, precluding differentiation between persistent and reversible airflow limitation. Although the fixed-ratio definition is age dependent, sensitivity analyses using an LLN-based definition yielded consistent results. Second, lung function decline was assessed using only 2 spirometric measurements and categorized into tertiles, which does not allow estimation of true longitudinal slopes and may limit the ability to distinguish real decline from measurement variability or regression to the mean. Third, mechanistic biomarkers were not available, preventing direct evaluation of biological pathways linking pulmonary impairment and atherosclerotic progression. Finally, recruitment from a predominantly rural population may limit generalizability, and analyses were restricted to participants with complete follow-up data, which may introduce selection or survivor bias.

Clinical implications and future research

These findings have several clinical implications. First, spirometry—and particularly the detection of AO—may provide incremental value for cardiovascular risk stratification. Second, early pulmonary assessment could help identify individuals at elevated vascular risk, including those without a smoking history or overt cardiopulmonary symptoms. Finally, integrating pulmonary function testing into cardiovascular prevention strategies may

support more personalized risk assessment, targeting patients with overlapping respiratory and vascular vulnerability.

In summary, in middle-aged individuals with cardiovascular risk factors, lung function decline assessed using a 2-time-point analytical approach was not independently associated with plaque progression, whereas the development of incident AO was consistently associated with greater atherosclerotic plaque progression, including in non-smokers. These findings extend prior evidence linking obstructive impairment with cardiovascular risk and suggest that airflow limitation may represent a spirometric marker associated with vascular disease. Early identification of AO could therefore contribute to integrated cardiopulmonary risk stratification, although further longitudinal and mechanistic studies are needed to clarify causal pathways.

Authors' contributions

MHB, EGL: Conceptualization, data curation, writing-original draft; EGL: Methodology, formal analysis, writing-review & editing; GT: Conceptualization, supervision, writing-review & editing; ADST: Formal analysis, visualization, writing-review & editing; ASC: Methodology, writing-review & editing, investigation; MBL: Investigation, data collection, writing-review & editing; JMV: Methodology, resources, writing-review & editing; RP: Methodology, writing-review & editing, supervision; DM: Methodology, writing-review & editing, supervision; ECB: Investigation, data collection, writing-review & editing; EF: Methodology, writing-review & editing, investigation; AL: Methodology, writing-review & editing, investigation; JdB: Formal analysis, visualization, writing-review & editing; FB: Conceptualization, project administration, writing-review & editing supervision; JG: Conceptualization, project administration, supervision, guarantor, writing-review & editing. All authors approved the final manuscript.

Other contributions

We thank the ILERVAS study participants for their invaluable collaboration and the technical staff for their assistance in data collection and quality control.

Data sharing statement

The datasets generated for this study are available on request to the corresponding author.

Clinical trial registration

The ILERVAS project protocol was approved by the Ethics Committee of the Arnau de Vilanova University Hospital (First visit: CEIC-1410, 19/12/2014; Follow-up: CEIC-2015, 20/12/2018). ClinicalTrials.gov identifier: NCT03228459.

Artificial intelligence involvement

During the preparation of this work, the author(s) used ChatGPT in order to assist with improving the writing and use of English. After using this tool/service, the author(s) reviewed and edited the content as needed and takes full responsibility for the content of the published article.

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Conflict of interests

The authors declare not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.arbres.2026.04.012](https://doi.org/10.1016/j.arbres.2026.04.012).

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