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Lung Function Impairment Is Related to Subclinical Atherosclerosis Only in Active Smokers

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Abstract: Background: Although an association between lung function and subclinical atherosclerosis has been reported, it remains unclear whether this association is only driven by tobacco smoking. We aimed to assess this in a population with at least one cardiovascular risk factor. Methods: We recruited 6209 subjects aged between 45 and 70 years with at least one cardiovascular risk factor (excluding diabetes mellitus) participating in the ILERVAS project 2015–2018. Lung function was determined by spirometry. Subclinical atherosclerosis was assessed with the ankle–brachial index (ABI) and the presence of carotid and femoral plaques measured by ultrasound. Results: A total of 5927 subjects were included: 49% male, median (p25–p75) age 57 years (52–62). Plaques were found in 4337 (73.2%) of the subjects. The patients with atherosclerosis showed worse lung function: median forced expiratory volume in one second (FEV_1) 95% and forced vital capacity (FVC) 94% in the patients with plaques vs. 99% and 98% in the other patients ($p < 0.001$). Adjusted models stratified by smoking status showed that being in the lower quartiles of FEV_1 % was associated with carotid and femoral plaques (OR 1.599, $p = 0.005$; and OR 1.654, $p = 0.006$), whereas FVC % was inversely associated with carotid plaques (OR 0.967, $p = 0.041$). A pathological ABI was associated with worse FEV_1 (OR 1.971, $p = 0.038$) and the presence of airway obstruction (OR 1.658, $p = 0.015$). However, these differences were restricted to current smokers. Conclusions: Lung function impairment was correlated with subclinical atherosclerosis only in current smokers. This highlights the unique role of smoking-related vascular and pulmonary dysfunction in early stages of pulmonary and cardiovascular afflictions.

Keywords: subclinical atherosclerosis; lung function; smoking

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1. Introduction

Impaired lung function, represented by the forced expiratory volume in one second (FEV_1) or forced vital capacity (FVC), is related to an increased incidence of and mortality from cardiovascular disease (CVD) and all-cause mortality [1–7]. The mechanisms underlying this relationship are uncertain, and, given the association among the never smokers [1,8,9], it is unlikely that tobacco smoking could be the only responsible factor. Most studies attempting to understand this relationship have focused on the clinical outcomes. However, subclinical atherosclerosis is a well-established risk factor for ischemic CVD. Numerous large cohorts with long follow-up periods have shown a clear association between the presence of subclinical atheromatous plaques in the carotid arteries and the risk of a coronary or cerebrovascular event [10–12].

The measurement of subclinical atherosclerosis offers a distinct approach to assessing the underlying mechanisms linking lung dysfunction and CVDs. The literature regarding the relationship between subclinical atherosclerosis and lung function is not limited [13–20], but shows inconsistent results. Some of the studies have found an inverse correlation between lung function and subclinical atherosclerosis [13,14,20], but not others [15,18,19,21]. Although the differences exist in the characteristics of the studied populations and the tools used to assess subclinical atherosclerosis, the key factors explaining the conflicting results may be the matching for potential confounding variables and, most importantly, the inclusion of a never smoker control group. Therefore, given the overlapping mechanisms linking tobacco, lung function and subclinical atherosclerosis, this relationship must be studied in a large cohort of well-characterized subjects, including the never smokers.

The current study aimed to clarify the relationship between lung function impairment and subclinical carotid and femoral atherosclerosis, as measured by the ankle–brachial index (ABI) and the ultrasound-confirmed presence of carotid and femoral plaques, in a population of subjects with at least one cardiovascular risk factor.

2. Material and Methods

2.1. Study Population

This is an ancillary study of the ILERVAS project (clinicaltrials.gov identifier: NCT03228459), approved by the Ethics and Clinical Research Committee of the University Hospital Arnau de Vilanova de Lleida, 2 June 2015. ILERVAS is a randomized interventional study aiming, among other objectives, to assess the impact of the early diagnosis of atherosclerosis on cardiovascular morbidity and mortality and to detect potential biomarkers that could improve the cardiovascular risk predictions. The ILERVAS intervention group (subjects participating in the early diagnosis program) comprises 8330 subjects aged between 45 and 65 years (men) or 50 and 70 years (women) with the following characteristics: at least one CVD risk factor (hypertension, dyslipidemia, obesity, smoking habit, or first-degree family history of early CVD); no prior medical history of CVD (angina, myocardial infarction, stroke, peripheral arterial disease, intestinal ischemia, or carotid surgery), diabetes, chronic kidney disease or active neoplasm; not institutionalized or receiving long-term home care; and a life expectancy greater than or equal to 18 months. The current study focused on 6209 consecutive subjects who completed lung function tests (spirometry). All of the participants were recruited in the province of Lleida (Catalonia, Spain) between 2015 and 2018. The ILERVAS protocol and study design are described elsewhere [22]. The project was approved by the ethics committee of the University Hospital Arnau de Vilanova with code CEIC-1410.

2.2. Clinical and Demographic Data

At the baseline, some of the sociodemographic data were collected from an electronic database (Information System for the Development of Research in Primary Care, SIDIAP) [23]. Important information, such as age, sex, weight, height, waist circumference, body mass index (BMI), office blood pressure and tobacco habits (active smoker,

former smoker (at least one month without tobacco) or never smoker; total pack-years) was collected in the face-to-face interview and physical examination on the ILERVAS bus.

2.3. Biochemical Measures

Using dried capillary blood testing (fingertip puncture) and the REFLOTRON® Plus system (Roche), the creatinine (mg/dL) and total cholesterol (mg/dL) levels were obtained. The subjects with a total cholesterol greater than 200 mg/dL after 6 h of fasting or when the total cholesterol was ≥250 mg/dL regardless of the fasting hours were considered eligible to perform the complete lipid profile determinations: HDL cholesterol; LDL cholesterol and triglycerides. Additionally, the glycated hemoglobin (HbA1c) level was analyzed using the same system. Prediabetes was diagnosed if the value of the glycated hemoglobin was between 5.7% and 6.4%. Based on the creatinine levels and considering ethnicity and sex, the CKD-EPI glomerular filtration rate of each subject was determined [24].

2.4. Carotid Ultrasound

Ultrasound imaging was performed on both the carotid (common artery, bifurcation, internal and external) and femoral (common and superficial) arteries. The images were obtained by trained sonographers, using the Doppler Ultrasound Vivid-I (General Electric Healthcare, Waukesha, WI, USA) equipped with a linear-transducer broadband linear 12 L-RS that operates at frequencies between 6 and 13 MHz [22]. Standardized and validated scanning and reading protocols were used to decrease inter-operator variability and type 2 errors [25]. Intra-observer reliability assessment showed a k-coefficient of one, with two repeated measurements and 1007 observations. The overall inter-rater reliability for all of the raters showed a k-coefficient of 0.915 (95% CI: 0.892–0.944; 959 observations), demonstrating excellent reliability. The readers were unaware of the patients' clinical histories.

As previously described, subclinical atherosclerosis was defined as the presence of at least one plaque in any of the 12 assessed areas [26,27]. A plaque was defined as a focal intima-media thickness ≥1.5 mm protruding in the lumen [26,27].

2.5. Lung Function

To assess lung function, forced spirometry was performed using a portable ultrasonic spirometer (Datospir©; Sibelmed, Barcelona, Spain). The pulmonary function tests were performed by trained and certified pulmonary experts, following the guidelines of the Spanish Respiratory Society (SEPAR) [28]. Using this test, the forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and the ratio between FEV_1 and FVC (FEV_1/FVC) were measured in ml and expressed as percentages of the predicted values [29]. A bronchodilator test was not included in the pulmonary evaluation. Airway obstruction (AO) was defined as an FEV_1/FVC < 70%, using the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [30].

2.6. Ankle-Brachial Index (ABI)

The ABI, defined as the ratio of the ankle to arm systolic blood pressure, is commonly used to assess lower extremity arterial disease in clinical practice and epidemiologic studies [31]. The ABI was measured using a continuous Doppler (Hadecco ES100X MiniDop), sphygmomanometer and blood pressure cuffs (Riester minimus III). The systolic blood pressure was measured in the brachial artery, posterior tibial artery and dorsalis pedis artery in both limbs in the prone position. The ratios between the tibial and pedal systolic blood pressure in each leg and higher brachial blood pressure were calculated. The final value for each limb was the lower value of those obtained between the tibial and pedal blood pressure. An ankle–brachial index value ≤0.9 suggested stenosis and was classified as pathologic. The values greater than 1.4 were excluded and suggested arterial rigidity or calcified arterial walls [22].

2.7. Statistical Analysis

A descriptive analysis of the participants' characteristics was performed for the presence/absence of atheromatous plaques. The categorical variables were described using percentages, and the continuous variables were described using medians and the 25th and 75th percentiles. Chi-squared test and the Wilcoxon rank-sum test were used to evaluate the differences for the categorical and continuous variables, respectively. The association of lung function with the presence of carotid plaques, femoral plaques and pathologic ABI was evaluated, using multivariate unconditional logistic regression models. The models were adjusted for the following important risk factors: sex, age, blood pressure, cholesterol, BMI, waist circumference, smoking habit, pack-years, prediabetes, hypertension and hypolipidemic treatment. An analysis was also performed after stratifying by smoking habit (never, former and current smokers). Finally, as a supplemental analysis, the impact of smoking cessation on lung function was assessed, using multivariate linear regression models. The statistical analyses were conducted using R: A language and environment for statistical computing, version 3.6 (R Core Team, 2019, Vienna, Austria).

3. Results

Among the 6209 consecutive subjects with available lung function, we excluded 33 subjects with missing, invalid or nonreproducible data; 96 subjects diagnosed with diabetes; and, 153 with renal failure (eGFR (estimated glomerular) filtration rate of <60% mL/min/1.73 m^2). Finally, 5927 subjects were included in the analyses.

The characteristics of the study population according to the presence of the atheromatous plaques are displayed in Table 1. Briefly, the participants had a median (p25–p75) age of 57 (52–62) years and a median BMI of 28.4 (25.5–31.6) kg/m^2. Sex was distributed equally (50.6% female and 49.4% male). The patients with atheromatous plaques were more likely to be the current smokers (33.5%), with twice as much accumulated exposure to tobacco (23.5 vs. 12.8 pack-years). The cardiovascular risk factors were more prevalent in the patients with plaques, including higher levels of cholesterol, triglycerides, systolic pressure and diastolic pressure. The patients with plaques showed higher proportions of antihypertensive drug use (33.2% vs. 27.7%) and pathological ABI (6.36% vs. 3.99%) and worse lung function as defined by FEV_1 % (95% vs. 99%) and FVC % (94% vs. 98%).

Table 1. Study population: clinical and demographic data based on the presence of atheromatous plaques.

Variables	Presence of Atheromatous Plaques			
	ALL *n* **= 5927**	**No Plaques** *n* **= 1590**	**Plaques** *n* **= 4337**	***p* Value** [a]
Age, years, median (p25;p75)	57.0 (52.0;62.0)	55.0 (51.0;60.0)	58.0 (53.0;63.0)	<0.001
Gender, Male, *n* (%)	2928 (49.4)	569 (35.7)	2359 (54.4)	<0.001
BMI, kg/m^2, median (p25;p75)	28.4 (25.5;31.6)	28.4 (25.3;31.7)	28.4 (25.5;31.6)	0.974
Waist circumference, *n* (%)				0.003
Male <102 cm; Female <88 cm	1861 (31.4)	451 (28.4)	1410 (32.5)	
Male ≥102 cm; Female ≥88 cm	4065 (68.6)	1139 (71.6)	2926 (67.5%)	
Smoking history, *n* (%)				
Never Smoker	2215 (37.4)	767 (48.2)	1448 (33.4)	<0.001
Current	1760 (29.7)	308 (19.4)	1452 (33.5)	
Former	1952 (32.9)	515 (32.4)	1437 (33.1)	
Pack-years of smoking, median (p25;p75)	20.8 (10.3;33.5)	12.8 (5.6;22.5)	23.5 (12.3;35.0)	<0.001
Cholesterol, mg/dL, median (p25;p75)	203 (180;229)	200 (178;227)	203 (181;230)	0.013
Cholesterol				
<200 mg/dL	2754 (46.5)	785 (49.4)	1969 (45.4)	0.006
≥200 mg/dL	3173 (53.5)	805 (50.6)	2368 (54.6)	
LDL *, mg/dL, median (p25;p75)	142 (127;159)	140 (126;157)	143 (128;159)	0.062
HDL *, mg/dL, median (p25;p75)	55.0 (46.0;66.0)	57.5 (49.0;68.0)	54.0 (46.0;66.0)	<0.001
Triglycerides, mg/dL, median (p25;p75)	132 (100;178)	123 (94.0;167)	135 (101;183)	<0.001
Systolic blood pressure, mmHg, median (p25;p75)	131 (120;142)	127 (117;138)	132 (121;144)	<0.001
Diastolic blood pressure, mmHg, median (p25;p75)	82.0 (75.7;88.0)	80.0 (74.0;87.0)	82.0 (76.0;88.7)	<0.001
Hypolipidemic treatment, *n* (%)	1001 (16.9)	212 (13.3)	789 (18.2)	<0.001
Antihypertensive treatment, *n* (%)	1882 (31.8)	440 (27.7)	1442 (33.2)	<0.001

Table 1. *Cont.*

Variables	Presence of Atheromatous Plaques			
	ALL ***n* = 5927**	**No Plaques** ***n* = 1590**	**Plaques** ***n* = 4337**	***p* Value** [a]
FEV_1 %, median (p25;p75)	96.0 (84.0;108)	99.0 (88.0;111)	95.0 (83.0;106)	<0.001
FVC %, median (p25;p75)	95.0 (84.0;106)	98.0 (87.0;109)	94.0 (84.0;105)	<0.001
ABI PTA pathologic, *n* (%)	337 (5.72%)	63 (3.99%)	274 (6.36%)	0.001

Median (25th percentile; 75th percentile) [a] Wilcoxon rank-sum test for continuous variables and Pearson's chi-squared test for categorical variables. * Lipid profile only available for participants with total cholesterol higher than 200 mg/dL. FEV_1 % = forced expiratory volume-one second percentage; FVC % = forced vital capacity percentage; BMI = body mass index; LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol; ABI PTA = ankle–brachial index posterior tibial artery.

Table 2 shows the prevalence of the atheromatous plaques and pathological ABI according to lung function in the never smokers, former smokers and current smokers. Overall, the prevalence of subclinical atherosclerosis was higher among the patients with worse lung function, as represented by the quartiles of FEV_1 and FVC impairment. Although the current smoker participants with worse lung function showed a higher prevalence of carotid and femoral plaques (prevalence of carotid plaques: Q1 vs. Q4 FEV_1: 48% vs. 65%, $p < 0.001$; prevalence of femoral plaques: Q1 vs. Q4 FEV_1: 57% vs. 79%, $p < 0.001$), in the former smokers, this relationship held only for the carotid plaques (prevalence of carotid plaques: Q1 vs. Q4 FEV_1: 48% vs. 61%, $p < 0.001$; prevalence of femoral plaques: Q1 vs. Q4 FEV_1: 54% vs. 63%, $p = 0.050$) and was almost nonexistent among the never smokers (prevalence of carotid plaques: Q1 vs. Q4 FEV_1: 46% vs. 53%, $p = 0.047$; prevalence of femoral plaques: Q1 vs. Q4 FEV_1: 41% vs. 42%, $p = 0.811$). When considering ABI, statistically significant differences were only found in the current smoker group.

Table 2. Prevalence of carotid/femoral atheromatous plaques and pathologic ABI in relation to tobacco consumption and lung function.

Variables	Presence of CAROTID Plaque							
	ALL	***p* Value**	**Never Smokers**	***p* Value**	**Former Smokers**	***p* Value**	**Current Smokers**	***p* Value**
	n = 5927		*n* = 2215		*n* = 1952		*n* = 1760	
FEV_1 %, quartiles								
108–157	649/1383 (47%)	<0.001	297/650 (46%)	0.047	218/452 (48%)	<0.001	134/281 (48%)	<0.001
96–108	747/1488 (50%)		311/621 (50%)		231/478 (48%)		205/389 (53%)	
84–96	823/1524 (54%)		273/519 (53%)		272/518 (53%)		278/487 (57%)	
22–84	920/1532 (60%)		226/425 (53%)		305/504 (61%)		389/603 (65%)	
FVC % ≥80%	2563/4968 (52%)	<0.001	928/1880 (49%)	0.189	833/1643 (51%)	<0.001	802/1445 (56%)	0.003
<80%	576/959 (60%)		179/335 (53%)		193/309 (62%)		204/315 (65%)	
FEV_1/FVC ≥70%	2636/5129 (51%)	<0.001	996/2026 (49%)	0.015	869/1707 (51%)	<0.001	771/1396 (55%)	0.002
<70%	503/798 (63%)		111/189 (59%)		157/245 (64%)		235/364 (65%)	
Variables	**Presence of FEMORAL Plaque**							
	ALL	***p* Value**	**Never Smokers**	***p* Value**	**Former Smokers**	***p* Value**	**Current Smokers**	***p* Value**
	***n* = 5927**		***n* = 2215**		***n* = 1952**		***n* = 1760**	
FEV_1 %, quartiles								
108–157	672/1383 (49%)	<0.001	267/650 (41%)	0.811	244/452 (54%)	0.05	161/281 (57%)	<0.001
96–108	788/1488 (53%)		248/621 (40%)		278/478 (58%)		262/389 (67%)	
84–96	889/1524 (58%)		221/519 (43%)		310/518 (60%)		358/487 (74%)	
22–84	969/1532 (63%)		179/425 (42%)		316/504 (63%)		474/603 (79%)	
FVC % ≥80%	2735/4968 (55%)	0.001	779/1880 (41%)	0.82	953/1643 (58%)	0.108	1003/1445 (69%)	<0.001
<80%	583/959 (61%)		136/335 (41%)		195/309 (63%)		252/315 (80%)	
FEV_1/FVC ≥70%	2776/5129 (54%)	<0.001	829/2026 (41%)	0.251	983/1707 (58%)	0.005	964/1396 (69%)	<0.001
<70%	542/798 (68%)		86/189 (46%)		165/245 (67%)		291/364 (80%)	

Table 2. *Cont.*

Variables	Pathologic ABI							
	ALL	*p* Value	Never Smokers	*p* Value	Former Smokers	*p* Value	Current Smokers	*p* Value
	n = 5887		*n* = 2195		*n* = 1938		*n* = 1754	
FEV_1 %, quartiles								
108–157	57/1375 (4%)	<0.001	29/648 (4%)	0.933	13/447 (3%)	0.318	15/280 (5%)	0.002
96–108	75/1475 (5%)		31/613 (5%)		21/473 (4%)		23/389 (6%)	
84–96	88/1515 (6%)		22/513 (4%)		23/515 (4%)		43/487 (9%)	
22–84	117/1522 (8%)		20/421 (5%)		27/503 (5%)		70/598 (12%)	
FVC % ≥80%	275/4936 (6%)	0.282	92/1864 (5%)	0.167	72/1629 (4%)	0.785	111/1443 (8%)	0.005
<80%	62/951 (7%)		10/331 (3%)		12/309 (4%)		40/311 (13%)	
FEV_1/FVC ≥70%	260/5095 (5%)	<0.001	92/2008 (5%)	0.769	64/1695 (4%)	0.003	104/1392 (7%)	0.001
<70%	77/792 (10%)		10/187 (5%)		20/243 (8%)		47/362 (13%)	

FEV_1 % = forced expiratory volume-one second percentage; FVC % = forced vital capacity percentage; ABI PTA = ankle–brachial index posterior tibial artery.

Only the presence of airway obstruction (OR: 1.23, $p = 0.015$) and being in the worse quartiles of FEV_1 % (Q3 OR: 1.17, $p = 0.048$; and Q4 OR: 1.27, $p < 0.004$) were associated with the presence of carotid plaques after adjustment (Table 3). By contrast, an impaired FVC (<80%) was not associated with subclinical carotid atherosclerosis. No significant associations were found between the lung function and femoral plaques. Finally, being in the worse quartile of FEV_1 % (OR: 1.43, CI 1.00–2.04, $p = 0.046$) and having airway obstruction (OR: 1.54, CI 1.15–2.05, $p = 0.004$) were associated with having pathological ABI.

Table 3. Adjusted logistic regression model of pulmonary function and the presence of carotid and femoral atheromatous plaques.

Variables	Presence of Carotid Plaques		
	OR	95% CI	*p* Value
FEV_1 % (5-unit % change)	0.974	0.959–0.989	0.001
FEV_1 %, quartiles			
(108,157)	1		
(96,108)	1.073	0.917–1.256	0.377
(84,96)	1.174	1.002–1.375	0.048
(22,84)	1.27	1.079–1.494	0.004
FVC % (5-unit % change)	0.984	0.968–1	0.055
FVC %:			
≥80%	1		
<80%	1.097	0.941–1.279	0.236
FEV_1/FVC:			
≥70%	1		
<70%	1.231	1.041–1.457	0.015
Variables	**Presence of Femoral Plaques**		
	OR	**95% CI**	***p* Value**
FEV_1 % (5-unit % change)	0.995	0.979–1.012	0.561
FEV_1 %, quartiles			
(108,157)	1		
(96,108)	1.018	0.865–1.199	0.828
(84,96)	1.097	0.93–1.294	0.271
(22,84)	1.009	0.85–1.197	0.922
FVC % (5-unit % change)	1.008	0.991–1.025	0.367
FVC %:			
≥80%	1		
<80%	0.908	0.772–1.069	0.248
FEV_1/FVC:			
≥70%	1		
<70%	1.172	0.978–1.405	0.086

Table 3. *Cont.*

Variables	Pathologic ABI		
	OR	**95% CI**	***p* Value**
FEV_1 % (5-unit % change)	0.97	0.94–1.001	0.057
FEV_1 %, quartiles			
(108,157)	1		
(96,108)	1.194	0.828–1.721	0.343
(84,96)	1.315	0.92–1.879	0.133
(22,84)	1.435	1.007–2.045	0.046
FVC % (5-unit % change)	0.998	0.965–1.032	0.920
FVC %:			
≥80%	1		
<80%	0.902	0.661–1.23	0.514
FEV_1/FVC:			
≥70%	1		
<70%	1.54	1.153–2.057	0.004

Adjusted by sex, age, blood pressure, cholesterol, BMI, waist circumference, smoking habit, pack-years, prediabetes and hypertension and hypolipidemic treatment. FEV_1 % = forced expiratory volume-one second percentage; FVC % = forced vital capacity percentage.

Table 4 shows the adjusted logistic regression models for the relationship between lung function and the presence of carotid plaques, femoral plaques and pathologic ABI, stratified by the smoking status. In the current smokers, both FEV_1 % and FVC % were associated with carotid plaques and pathological ABI, while only FEV_1 % was associated with femoral plaques. By contrast, the association between the AO and femoral plaques was only found in the former smokers, and no associations were found in the never smokers.

Table 4. Adjusted logistic regression model of pulmonary function and the presence of carotid/femoral atheromatous plaques stratified by smoking status.

Variables	Presence of Carotid Plaques					
	Never Smokers	***p* Value**	**Former Smokers**	***p* Value**	**Current Smokers**	***p* Value**
FEV_1 % (5-unit % change)	0.978 (0.955–1.002)	0.073	0.986 (0.958–1.015)	0.332	0.953 (0.925–0.982)	0.002
FEV_1 %, quartiles						
(108,157)	1		1		1	
(96,108)	1.186 (0.943–1.492)	0.145	0.884 (0.667–1.172)	0.391	1.191 (0.845–1.681)	0.318
(84,96)	1.246 (0.977–1.588)	0.076	0.942 (0.711–1.246)	0.674	1.429 (1.026–1.991)	0.035
(22,84)	1.211 (0.935–1.567)	0.146	1.095 (0.818–1.465)	0.543	1.599 (1.151–2.22)	0.005
FVC % (5-unit % change)	0.983 (0.959–1.008)	0.171	1.003 (0.972–1.034)	0.861	0.967 (0.937–0.999)	0.041
FVC %:						
80%	1		1		1	
<80%	1.042 (0.815–1.331)	0.743	1.146 (0.868–1.514)	0.336	1.11 (0.835–1.476)	0.472
FEV_1/FVC:						
≥70%	1		1		1	
<70%	1.218 (0.887–1.671)	0.223	1.39 (1.025–1.886)	0.034	1.143 (0.873–1.495)	0.331
Variables	**Presence of Femoral Plaques**					
	Never Smokers	***p* Value**	**Former Smokers**	***p* Value**	**Current Smokers**	***p* Value**
FEV_1 % (5-unit % change)	1.008 (0.983–1.033)	0.538	1.01 (0.981–1.041)	0.492	0.95 (0.918–0.984)	0.004
FEV_1 %, quartiles						
(108,157)	1		1		1	
(96,108)	0.925 (0.73–1.172)	0.519	1.039 (0.778–1.388)	0.796	1.269 (0.879–1.833)	0.203
(84,96)	0.985 (0.769–1.261)	0.903	0.991 (0.742–1.323)	0.951	1.64 (1.146–2.345)	0.007
(22,84)	0.899 (0.69–1.171)	0.428	0.829 (0.614–1.12)	0.222	1.654 (1.158–2.362)	0.006
FVC % (5-unit % change)	1.016 (0.99–1.042)	0.233	1.029 (0.997–1.062)	0.077	0.969 (0.935–1.004)	0.079
FVC %:						
≥80%	1		1		1	
<80%	0.85 (0.66–1.093)	0.206	0.857 (0.643–1.142)	0.292	1.15 (0.819–1.614)	0.420
FEV_1/FVC:						
≥70%	1		1		1	
<70%	0.96 (0.699–1.318)	0.801	1.218 (0.886–1.674)	0.225	1.355 (0.985–1.864)	0.062

Table 4. *Cont.*

Variables	Pathologic ABI					
	Never Smokers	*p* Value	Former Smokers	*p* Value	Current Smokers	*p* Value
FEV_1 % (5-unit % change)	1.02 (0.965–1.077)	0.485	0.98 (0.919–1.045)	0.534	0.928 (0.882–0.975)	0.003
FEV_1 %, quartiles						
(108,157)	1		1		1	
(96,108)	1.087 (0.643–1.841)	0.755	1.63 (0.785–3.385)	0.190	1.081 (0.52–2.247)	0.836
(84,96)	0.969 (0.543–1.727)	0.915	1.542 (0.746–3.189)	0.243	1.718 (0.891–3.312)	0.106
(22,84)	1.006 (0.554–1.827)	0.983	1.44 (0.685–3.028)	0.337	1.971 (1.039–3.741)	0.038
FVC % (5-unit % change)	1.028 (0.972–1.088)	0.333	1.039 (0.969–1.114)	0.282	0.951 (0.9–1.004)	0.068
FVC %:						
≥80%	1		1		1	
<80%	0.552 (0.281–1.085)	0.085	0.545 (0.264–1.123)	0.100	1.4 (0.913–2.145)	0.123
FEV_1/FVC:						
≥70%	1		1		1	
<70%	1.124 (0.566–2.231)	0.738	1.59 (0.896–2.821)	0.113	1.648 (1.102–2.464)	0.015

Adjusted by sex, age, blood pressure, cholesterol, BMI, waist circumference, prediabetes and hypertension and hypolipidemic treatment. Former and current smokers also adjusted by pack-years. FEV_1 % = forced expiratory volume-one second percentage; FVC % = forced vital capacity percentage.

Finally, as a supplemental analysis, Table 5 explores the impact of smoking cessation on lung function, showing that the current smokers have significantly worse lung function than the former smokers.

Table 5. Linear regression model exploring the differences between former and current smoking in relation to lung function (FEV_1 and FVC), adjusted by age, sex, BMI and waist circumference.

Variables	FEV_1 %			FEV_1/FVC		
	Linear Regression Coefficient (β)	95% CI	*p* Value	Linear Regression Coefficient (β)	95% CI	*p* Value
Former smoker	Ref			Ref		
Current smoker	−5.34	−6.54 to −4.14	<0.001	−2.13	−2.64 to −1.62	<0.001
Age	−0.42	−0.52 to −0.31	<0.001	−0.27	−0.31 to −0.22	<0.001
Sex, female	7.07	5.71 to 8.43	<0.001	0.41	−0.16 to 0.99	0.160
BMI	−0.12	−0.27 to 0.02	0.096	0.14	0.08 to 0.21	<0.001
High waist circumference (Male ≥102 cm Female ≥88 cm)	−3.19	−4.77 to −1.61	<0.001	0.33	−0.34 to 1.00	0.332

FEV_1 % = forced expiratory volume-one second percentage; FEV_1/FVC = forced expiratory volume-one second to forced vital capacity ratio; BMI = body mass index.

4. Discussions

Our main finding is that in the subjects with at least one cardiovascular risk factor, lung function impairment expressed as a lower FEV_1, even in the normal range, is correlated with subclinical atherosclerosis, but only in the current smokers. These findings highlight the critical role of smoking in the relationship between lung function and subclinical atherosclerosis.

The relationship between lung function and subclinical atherosclerosis has been analyzed in various epidemiological cohorts [13–20]. Based on the data from the British Regional Heart Study, Ebrahim et al. [15] reported a significant age-adjusted association between FEV_1 and carotid intima-media thickness (IMT) in 800 subjects. However, they did not adjust for smoking status, cholesterol, hypertension or other important variables. More recently, a close association was revealed between subclinical atherosclerosis (including the ABI) and pulmonary function (FEV_1 % and FVC %) in 3775 middle-aged smokers at risk of early atherosclerosis [20]. Additionally, the study of a prospective cohort of 656 volunteers aged 50–71 years found that reduced peak expiratory flow (PEF) was related to the development of carotid plaques after adjustment [14]. Thus, our results agree with this previous study, but extend the findings by considering the population of the never smokers. Furthermore, the inclusion of additional potential confounding variables not assessed in some

previous studies (such as waist circumference, prediabetes and the use of hypertensive or hypolipidemic drugs) contributes to the appropriateness of the current research.

Given the potentially strong confounding by tobacco use in the relationship between lung function and subclinical atherosclerosis, an adjustment by tobacco use was insufficient to control for this factor, and a substantial degree of residual confounding could not be disregarded. Therefore, exploring the relationship stratified by smoking status was performed, including the never smokers. The first study to explore this issue [19], comprising 14,000 subjects with 54% of the never smokers, showed that the existing association between both the IMT and the ABI and FEV_1 was attenuated after adjustment for the CVD risk factors and disappeared in the group of the never smokers. Regarding the presence of carotid plaques, a small association was observed with lung function that again disappeared in the never smokers. Our results agree with those findings and provide added information concerning femoral plaques, with a significant relationship between the worse quartiles of FEV_1 and the presence of both carotid and femoral plaques, although only in the current smokers. Moreover, the reported differences in lung function after smoking cessation (regardless of potential biases related with the cause of smoking cessation) combined with the finding of lung function impairment being associated with subclinical atherosclerosis only in the current smokers, highlights the public health relevance of promoting smoking cessation.

In our study, the patients with worse lung function (represented by the quartiles of FEV_1 and FVC impairment), presented a higher prevalence of subclinical atherosclerosis. Several existing hypotheses can explain the association between impaired lung function and cardiovascular health [8], including the role of the lungs in the capture and elimination of external toxic agents [32,33], ventilation/perfusion mismatch associated with impaired lung function [8], a systemic inflammatory response [34,35] and oxidative stress [36]. However, regarding the results of the present study, the cause of lung function impairment and its specific inflammatory mechanisms may be the determinant of the subclinical atherosclerosis in the ultrasound examinations. In other words, only the lung function impairment mediated by active tobacco exposure can explain the presence of the subclinical atherosclerosis. This finding may be that cigarette smoking is one of the strongest sources of oxidative stress and inflammatory products, causing both vascular and pulmonary damage [37,38].

The current study has several strengths that should be disclosed. The large number of middle-aged subjects included, combined with their cardiovascular risk profile, makes our study population well suited for answering the research questions posed in the manuscript. Additionally, the subclinical atherosclerosis was assessed by experienced personnel using ultrasound and covering key arterial territories. Finally, the inclusion of a significant proportion of never smokers was paramount. Several potential limitations should also be considered. First, additional information on the cardiovascular factors would have been helpful (e.g., the time since hypertension or dyslipidemia diagnostics and its degree of control with medications). However, their inclusion in the analysis would not have significantly affected the results, because the already large number of cardiovascular-risk-related variables used in the adjusted models should suffice for the appropriate control of confounding. Next, the lack of postbronchodilator spirometry precluded the characterization of the airway hyper-responsiveness of the included COPD patients. This information would be valuable, given the potential differences in the inflammatory profiles of the patients and the relationship of these profiles with the formation of atheromatous plaques. Next, our study population was based in a rural area, implying low exposure to air pollution and its reported airway effects. However, this limitation could also be seen as a strength, because the rural areas are frequently under-represented in research studies. Finally, a more precise characterization of the participants, including genetic profiling, measures of arterial stiffness (Pulse Wave Velocity) or oxidized LDL receptor could have provided more insight on the potential mechanisms behind the reported associations.

5. Conclusions

In conclusion, the finding of a relationship between lung function (represented by FEV_1) and subclinical carotid and femoral atherosclerosis only in the current smokers suggests that the lung function could be used to measure the cardiovascular health status of such individuals. Thus, we recommend performing spirometry testing in all of the smoking patients and providing them with smoking cessation advice to improve both pulmonary and cardiovascular health.

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