High prevalence of interstitial lung abnormalities in middle-aged never-smokers

Ida Pesonen[1,2], Fredrik Johansson[3], Åse Johnsson[4,5], Anders Blomberg[6], Marianne Boijsen[4,5], John Brandberg[4,5], Kerstin Cederlund[7], Arne Egesten[8], Össur Ingi Emilsson[9,10], Jan E. Engvall[11,12], Andreas Frølich[6], Emil Hagström[13,14], Eva Lindberg[10], Andrei Malinovschi[15], Nikolai Stenfors[6], Eva Swahn[16], Hanan Tanash[17], Raquel Themudo[18,19], Kjell Torén[20,21], Lowie E.G.W. Vanfleteren[22,23], Per Wollmer[24], Suneela Zaigham[15,25], Carl Johan Östgren[11,26] and C. Magnus Sköld[1,2]

[1]Respiratory Medicine Unit, Department of Medicine Solna and Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden. [2]Department of Respiratory Medicine and Allergy, Karolinska University Hospital, Stockholm, Sweden. [3]Medical Library, Danderyd Hospital, Stockholm, Sweden. [4]Region Västra Götaland, Sahlgrenska University Hospital, Department of Radiology, Gothenburg, Sweden. [5]Department of Radiology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. [6]Department of Public Health and Clinical Medicine, Section of Medicine, Umeå University, Umeå, Sweden. [7]Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, Sweden. [8]Respiratory Medicine, Allergology, and Palliative Medicine, Department of Clinical Sciences Lund, Lund University and Skåne University Hospital, Lund, Sweden. [9]Faculty of Medicine, University of Iceland, Reykjavik, Iceland. [10]Department of Medical Sciences, Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden. [11]CMIV, Centre of Medical Image Science and Visualization, Linköping University, Linköping, Sweden. [12]Department of Clinical Physiology, and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden. [13]Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden. [14]Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden. [15]Department of Medical Sciences, Clinical Physiology, Uppsala University, Sweden. [16]Department of Cardiology and Department of Health, Medicine, and Caring Sciences, Linköping University, Linköping, Sweden. [17]Department of Respiratory Medicine, Skåne University Hospital, Lund University, Malmö, Sweden. [18]Department of Clinical Science, Intervention and Technology at Karolinska Institute, Division of Medical Imaging and Technology, Stockholm, Sweden. [19]Department of Radiology, Karolinska University Hospital in Huddinge, Stockholm, Sweden. [20]Section of Occupational and Environmental Medicine, School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. [21]Department of Occupational and Environmental Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden. [22]COPD Center, Department of Respiratory Medicine and Allergology, Sahlgrenska University Hospital, Gothenburg, Sweden. [23]Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. [24]Department of Translational Medicine, Lund University, Lund, Sweden. [25]Department of Clinical Sciences in Malmö, Lund University, Malmö, Sweden. [26]Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden.

Corresponding author: Ida Pesonen (Ida.pesonen@ki.se)

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Interstitial lung abnormalities are common among never-smokers (7.9%) and associated with older age, low-grade inflammation, a restrictive spirometric pattern and impaired diffusing capacity for carbon monoxide https://bit.ly/3K5uuNO

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Abstract

Background Interstitial lung abnormalities (ILA) are incidental findings on chest computed tomography (CT). These patterns can present at an early stage of fibrotic lung disease. Our aim was to estimate the prevalence of ILA in the Swedish population, in particular in never-smokers, and find out its association with demographics, comorbidities and symptoms.

Methods Participants were recruited to the Swedish CArdioPulmonary BioImage Study (SCAPIS), a population-based survey including men and women aged 50–64 years performed at six university hospitals in Sweden. CT scan, spirometry and questionnaires were performed. ILA were defined as cysts, ground-glass opacities, reticular abnormality, bronchiectasis and honeycombing.

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Findings Out of 29 521 participants, 14 487 were never-smokers and 14 380 were men. In the whole population, 2870 (9.7%) had ILA of which 134 (0.5%) were fibrotic. In never-smokers, the prevalence was 7.9% of which 0.3% were fibrotic. In the whole population, age, smoking history, chronic bronchitis, cancer, coronary artery calcium score and high-sensitive C-reactive protein were associated with ILA. Both ILA and fibrotic ILA were associated with restrictive spirometric pattern and impaired diffusing capacity of the lung for carbon monoxide. However, individuals with ILA did not report more symptoms compared with individuals without ILA.

Interpretation ILA are common in a middle-aged Swedish population including never-smokers. ILA may be at risk of being underdiagnosed among never-smokers since they are not a target for screening.

Introduction

Interstitial lung abnormalities (ILA) are interstitial changes visible on computed tomography (CT). These abnormalities include ground-glass opacities, centrilobular nodules, non-emphysematous cysts, reticular pattern, honeycombing and traction bronchiectasis affecting >5% of any lung zone [1–3]. ILA can be an early stage of fibrotic lung diseases such as idiopathic pulmonary fibrosis (IPF) or other pulmonary diseases [2, 4].

There are associations between ILA, in particular those with honeycombing and traction bronchiectasis, and increased mortality [5–7]. The prevalence of these findings is mostly estimated in smokers [5], and there are still limited data among never-smokers and in the general population. Another important question is whether screening of risk groups could be cost-effective in the future [8, 9]. However, questions regarding assessment of ILA, whether they need a follow-up and with what frequency remain to be answered [3, 4].

Detection of ILA may result in a diagnosis of fibrotic lung disease, giving opportunities to treat patients at an earlier stage of the disease, including referral to lung transplantation. Also, early diagnosis may prevent patients from being treated with possibly harmful medications due to misdiagnosis. The diagnosis of IPF and other fibrotic lung diseases is not always straightforward, and the median diagnostic delay from onset of symptoms varies between 7 months and 2 years, which may have potentially detrimental effects on prognosis [10, 11].

In this cross-sectional population-based cohort study, we aimed to estimate the prevalence of ILA in Sweden in never-smokers and smokers and to study its association with demographics, symptoms, comorbidities and lung function. Our main hypothesis was that individuals with ILA in the Swedish population have impaired lung function, especially restrictive spirometric pattern, and more airway symptoms compared to individuals without ILA. Our second hypothesis was that the prevalence of ILA is higher in older individuals, men and smokers.

Methods

Study population

Study participants were recruited to the population-based Swedish CArdioPulmonary BioImage Study (SCAPIS) [12]. The SCAPIS cohort consists of 30 154 randomly contacted individuals from the general population aged between 50 and 64 years. The enrolment was performed by six Swedish University Hospitals (Uppsala, Umeå, Linköping, Malmö/Lund, Gothenburg and Stockholm) between November 2013 and November 2018. Detailed examination was done on two or three occasions within a 2-week period. Individuals unable to understand written and spoken Swedish for consent were excluded. Inclusion criteria for this study required individuals to have undergone a chest CT with a complete evaluation of interstitial patterns.

Questionnaires

Demographic binary, categorical or continuous variables were collected through a questionnaire: sex, age, smoking status (current, former or never), pack-years, data on lung diseases (asthma, chronic bronchitis, COPD or emphysema) and rheumatic diseases (rheumatoid arthritis, Bechterew disease, psoriasis arthritis, systemic lupus erythematosus, Sjögren's syndrome), comorbidities (heart failure, hypertension, diabetes, tuberculosis, obstructive sleep apnoea, any cancer), and airway symptoms – chronic bronchitis (cough almost every day for at least 3 months per year for >2 years) and dyspnoea (converted to a modified Medical Research Council (mMRC) dyspnoea scale). Main occupation during professional life was coded and converted to a job exposure matrix-assigned occupational exposure to vapour, gas, dust, and fumes developed in Gothenburg [13].

Other measurements

Weight and height were measured at baseline and body mass index (BMI) was calculated. Plasma high-sensitivity C-reactive protein (hs-CRP) and haemoglobin were analysed in a venous blood sample taken after an overnight fast at the participating hospital central labs. These blood tests were used to assess the grade of general inflammation.

Lung function

Lung function test was performed by dynamic spirometry 15 min after inhalation of 400 µg salbutamol. Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were recorded. Diffusing capacity of the lung for carbon monoxide (D_{LCO}) was measured using a single-breath carbon monoxide diffusion test. Both tests were performed by a Jaeger MasterScreen PFT (Vyaire, Mettawa, IL, USA) according to American Thoracic Society (ATS)/European Respiratory Society (ERS) standards [14–16]. Predicted values for FEV_1 and FVC were calculated according to Global Lung Function Initiative (GLI) reference values [17]. Chronic airflow limitation was presented based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) with a cut-off FEV_1/FVC <0.7 and as <lower limit of normality (LLN) according to SCAPIS reference values. A restrictive spirometric pattern (RSP) was defined as FVC <80% of predicted and FEV_1/FVC ⩾0.7 [18] according to GLI reference values or FVC <LLN SCAPIS and FEV_1/FVC ⩾LLN SCAPIS [19]. D_{LCO} was presented as per cent of predicted and LLN according to reference values generated from a reference population in the SCAPIS cohort (personal communication).

CT of the lung

Study participants were examined through a dual-source CT scanner equipped with a Stellar Detector (Somatom Definition Flash, Siemens Healthineers, Erlangen, Germany) [12]. Images were interpreted by expert radiologists at each radiology department and recorded in an electronic case report form. Consensus meetings were held before the start of the study to improve the consistency of interpretation across radiologists. Radiologists were blinded to participant characteristics collected in the framework of this study but were able to review previous CTs while making the interpretation of the CT.

Terminology previously published by the Fleischner Society was used [20]. Binary variables (yes or no) on ILA patterns (cysts, ground-glass opacities, reticular abnormality, bronchiectasis and honeycombing) were determined. In addition, emphysema was reported. For the aims of this study, ILA was defined as presence of any ILA pattern. The severity of ILA was further evaluated based on the type and combination of different patterns using the definitions from the Fleischner Society as a reference [3]: nonfibrotic ILA pattern was defined as presence of ground-glass opacities, cysts and/or reticular pattern without bronchiectasis; fibrotic ILA pattern was defined as presence of honeycombing and/or reticular pattern with bronchiectasis. To distinguish between bronchiectasis and traction bronchiectasis we only used the variable bronchiectasis if it coexisted with a reticular pattern and assumed that reticular pattern coexisted with traction bronchiectasis.

Coronary artery calcification score

Before undergoing coronary CT angiography, a non-contrast calcium scoring exam was performed and coronary artery calcification score (CACS) was summed according to Agatston and international standards [21]. CACS was chosen to represent an indicator of atherosclerosis and categorised in groups with increasing risk for cardiovascular disease according to guidelines as following: CACS 0 = no CAC, very low risk; CACS 1–99 = mild CAC, mildly increased risk; CACS 100–299 = moderate CAC, moderately increased risk; CACS ⩾300 = moderate to severely increased risk [22].

Statistical analysis

Independent, continuous data on demographics, biochemistry, symptoms, lung function and D_{LCO} were presented as mean±$_{SD}$ for normally distributed variables and as median (interquartile range) for variables where the assumption of normal distribution failed. We compared individuals with and without ILA with independent-samples t-test or Mann–Whitney U-test, when appropriate. Binary data were presented as number in the sample and per cent and compared between individuals with and without ILA with Chi-square test or Fischer's exact test, when appropriate.

The point prevalence of ILA patterns was compiled in the study population, and the distribution of ILA in each age group (50–54, 55–59 and 60–64 years) according to sex and smoking status was presented.

The association between independent variables and ILA patterns was explored using multivariable logistic regression analysis. The multivariable regression analyses were adjusted for potential confounders: sex,

age, BMI, pack-years of smoking, occupational exposure, CACS, chronic bronchitis, rheumatic disease, cancer and hs-CRP.

Additional models were made to explore the association of ILA patterns with RSP, impaired D_{LCO} and dyspnoea (mMRC ⩾2). The model for RSP was adjusted for sex, age, BMI, pack-years of smoking, chronic bronchitis, rheumatic disease, cancer and occupational exposure. For the analyses of impaired D_{LCO} and dyspnoea, additional adjustments were made by adding CACS and emphysema to the D_{LCO} model and CACS and RSP to the dyspnoea model, respectively.

We used Benjamini–Hochberg correction to control for multiple testing. All tests were two-tailed, and the adjusted significance level was set at $p<0.05$. SPSS version 28.0 (IBM Corp, Armonk, NY, USA) was used for the analyses.

Ethics

The study was conducted in accordance with the ethical standards of the 1964 Helsinki Declaration. The study was approved by the Ethical Review Boards of Umeå (Dnr 2010-228-31M) and Gothenburg (Dnr 173-18, 2020-03592). The participants signed a written informed consent before inclusion in the study.

Role of the funding source

The funding sources had no part in the writing of this article and the decision to submit it.

Results

Study population

Of the 30 154 participants in the SCAPIS cohort, 29 521 met the inclusion criteria (figure 1). About half of them (n=14 380; 48.7%) were men, and the median age was 57.4 with a range between 50.1 and 65.8 years. The number of current smokers was 3636 (12.7%) and 14 487 (50.8%) were never-smokers (table 1). Information regarding smoking status was missing from 976 individuals.

Prevalence of ILA in the entire cohort

The prevalence of ILA for the entire cohort was 2870 (9.7%). Furthermore, the prevalence of nonfibrotic and fibrotic ILA was 2736 (9.3%) and 134 (0.5%) respectively (figure 1, table 1). The prevalence of ILA was higher in older age groups and among former and current smokers compared with never-smokers. However, there was no difference between men and women (supplementary figure S1). The prevalence of fibrotic ILA in the population was 0.5% among former smokers and 0.8% among current smokers.

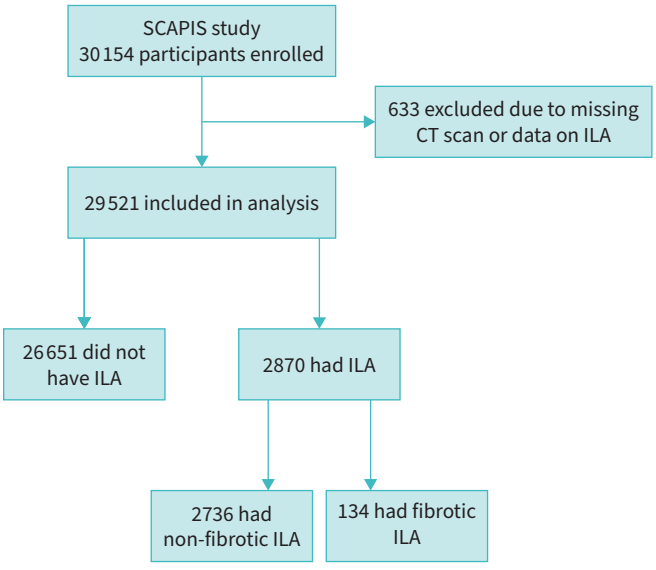

FIGURE 1 Participant flow for the Swedish CardioPulmonary BioImage Study. ILA: interstitial lung abnormalities; CT: computed tomography.

TABLE 1 Baseline characteristics of the study population

	All	No ILA	ILA[#]		p-value no ILA *versus* ILA
			Nonfibrotic ILA	Fibrotic ILA	
Participants	29 521 (100)	26 651 (90.3)	2736 (9.3)	134 (0.5)	
Sex, male	14 380 (48.7)	13 019 (48.8)	1281 (46.8)	80 (59.7)	0.15
Age years	57.5±4.3	57.4±4.3	58.4±4.3	60.0±4.1	**<0.001**[¶]
BMI kg·m^{-2}	27.0±4.5	27.0±4.5	27.0±4.4	27.4±4.9	0.96
Smoking status					**<0.001**[+]
Current	3636 (12.7)	3157 (12.2)	451 (17.1)	28 (22.0)	
Former	10 422 (36.5)	9283 (36.0)	1087 (41.2)	52 (40.9)	
Never	14 487 (50.8)	13 (51.7)	1102 (41.7)	47 (37.0)	
Pack-years	15.7±13.1	15.4±12.9	18.1±14.2	20.0±17.1	**<0.001**
Occupational exposure					0.068[+]
Low	24 946 (88.7)	22 (88.9)	2264 (87.7)	106 (84.1)	
Moderate	2584 (9.2)	2312 (9.1)	257 (9.9)	15 (11.9)	
High	579 (2.1)	512 (2.0)	62 (2.4)	5 (4.0)	
Medical history[§] (self-reported)					
Asthma[§]	2366 (8.3)	2127 (8.3)	226 (8.6)	13 (10.2)	0.45
Chronic bronchitis	1458 (5.1)	1265 (4.9)	177 (6.8)	16 (12.8)	**<0.001**
Emphysema	1683 (5.7)	1358 (5.1)	300 (11.0)	25 (18.7)	**<0.001**
COPD, CB or emphysema[§]	350 (1.2)	300 (1.2)	44 (1.7)	6 (4.7)	**0.003**
Rheumatic disease[§]	1063 (3.7)	928 (3.6)	128 (4.9)	7 (5.5)	**<0.001**
Heart failure[§]	145 (0.5)	127 (0.5)	16 (0.6)	2 (1.6)	0.26
Hypertension[§]	6515 (22.8)	5799 (22.5)	682 (25.9)	34 (26.8)	**<0.001**
Diabetes	2223 (7.5)	1986 (7.5)	221 (8.1)	16 (11.9)	0.12
TBC[§]	74 (0.3)	68 (0.3)	5 (0.2)	1 (0.8)	0.65
OSA[§]	1267 (4.4)	1133 (4.4)	123 (4.7)	11 (8.7)	0.26
Any cancer[§]	1700 (6.0)	1468 (5.7)	218 (8.3)	14 (11.0)	**<0.001**
Reflux[§]	6529 (23.0)	5884 (23.0)	618 (23.7)	27 (21.3)	0.47
CACS					**<0.001**
Score 0	17 034 (59.1)	15 543 (59.7)	1440 (54.2)	51 (40.8)	
Score 1–99	8226 (28.5)	7371 (28.3)	809 (30.4)	46 (36.8)	
Score 100–299	2079 (7.2)	1847 (7.1)	218 (8.2)	14 (11.2)	
Score ⩾300	1486 (5.2)	1282 (4.9)	190 (7.2)	14 (11.2)	
Biochemistry, median (IQR)					
hs-CRP mg·L^{-1}	1.0 (1.6)	1.0 (1.5)	1.2 (1.9)	1.8 (2.8)	**<0.001**[f]
Hb g·L^{-1} (male)	149 (13)	149 (13)	149 (14)	145 (15.5)	0.66
Hb g·L^{-1} (female)	134 (11)	134 (11)	135 (12)	135.5 (13.25)	0.11
Lung function					
FEV_1 % predicted	102.1±13.9	102.4±13.8	99.9±14.9	97.6±16.8	**<0.001**
FVC % predicted	102.7±13.0	102.8±12.9	101.6±13.3	99.3±17.7	**<0.001**
FEV_1/FVC	0.78±0.06	0.78±0.06	0.77±0.07	0.77±0.08	**<0.001**
D_{LCO} % predicted SCAPIS	97.9±14.4	98.2±14.2	95.2±15.0	86.3±20.5	**<0.001**
CAL GOLD	2524 (8.6)	2162 (8.2)	342 (12.7)	20 (14.9)	**<0.001**
CAL LLN SCAPIS	2848 (9.7)	2442 (9.2)	384 (14.2)	22 (16.4)	**<0.001**
RSP	994 (3.4)	862 (3.3)	110 (4.1)	22 (16.4)	**<0.001**
RSP SCAPIS	1615 (5.5)	1418 (5.4)	172 (6.4)	25 (18.7)	**<0.001**
Symptoms					
mMRC high (⩾2)	497 (1.8)	426 (1.7)	63 (2.4)	8 (6.4)	**<0.001**

Data are presented as n (%) or mean±SD, unless otherwise stated. Statistically significant p-values are in bold type. Occupational exposure: exposure to vapour, gas, dust and fumes. ILA: interstitial lung abnormalities; BMI: body mass index; CB: chronic bronchitis; TBC: history of tuberculosis; OSA: obstructive sleep apnoea; Reflux: gastro-oesophageal reflux; CACS: coronary artery calcium score; hs-CRP: high-sensitivity C-reactive protein; Hb: haemoglobin; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO} % predicted SCAPIS: diffusing capacity of the lung for carbon monoxide, % of predicted; CAL: chronic airway limitation, defined by FEV_1/FVC <0.7 or <LLN SCAPIS; LLN: lower limit of normal; IQR: interquartile range; RSP: restrictive spirometric pattern defined by FVC <80% of predicted and FEV_1/FVC ⩾0.7 or FVC <LLN SCAPIS and FEV_1/FVC ⩾LLN SCAPIS; mMRC: modified Medical Research Council dyspnoea scale. [#]: n=2870 (9.7%); [¶]: independent samples t-test; [+]: Chi-square test. [§]: self-reported by participant; [f]: Mann–Whitney U-test.

ILA in never-smokers

The prevalence of ILA among never-smokers was 1149 (7.9%): nonfibrotic (7.6%) and fibrotic (0.3%) ILA (supplementary table S1). Never-smoking individuals with ILA were older compared to those without ILA (p<0.001) (supplementary table S1) and had a higher incidence of emphysema and cancer, higher CACS, higher hs-CRP, lower lung function and lower D_{LCO} compared with individuals without ILA (supplementary table S1).

Associations to demographics

Individuals with ILA were generally older than individuals without ILA (p<0.001) (table 1). Furthermore, individuals with ILA were more likely to be current and former smokers, had smoked more pack-years, were more likely to have comorbidities, and had higher CACS, higher hs-CRP, lower lung function and more symptoms compared to individuals without ILA (table 1). The comorbidities included chronic bronchitis, COPD, emphysema, rheumatic disease, hypertension and cancer.

In the multivariable logistic regression model, age, smoking, comorbidities (chronic bronchitis and cancer), CACS and hs-CRP were associated with ILA. There was an interaction between sex and CACS; male sex together with CACS was inversely associated with ILA but the p-value was not statistically significant after Benjamini–Hochberg adjustment (p-value for interaction between CACS and sex 0.038). Occupational exposure was not associated with ILA (figure 2a).

The multivariable logistic regression analysis of association between demographics and fibrotic ILA pattern is presented in figure 2b. Age, smoking and chronic bronchitis, but not sex, were associated with a fibrotic ILA pattern.

In a subgroup analysis for never-smokers, age and hs-CRP were associated with ILA and age was associated with fibrotic ILA (supplementary table S1, figure 3a and b).

Association to lung function and symptoms

Both ILA and fibrotic ILA patterns were associated with a RSP and impaired D_{LCO} (table 2). The odds for RSP was 1.33 times higher and for impaired D_{LCO} 1.49 times higher for individuals with ILA compared with individuals without ILA (p<0.001 for both). In fibrotic ILA, the association was even stronger: 3.61 times higher odds for RSP and 3.30 times higher odds for impaired D_{LCO} (p<0.001 for both). However, there was no significant association between ILA, fibrotic ILA and dyspnoea measured by mMRC; individuals with higher scores for mMRC smoked more and had more chronic bronchitis, higher CACS and a higher proportion of RSP compared with individuals with lower mMRC.

Among never-smokers, fibrotic ILA was associated with RSP. Individuals with fibrotic ILA had 2.76 higher odds of having RSP (p=0.017) compared with individuals without ILA. Both ILA and fibrotic ILA were associated with impaired D_{LCO} (p=0.003 and p=0.013, respectively). There was no significant association between ILA, fibrotic ILA and dyspnoea (table 3).

Discussion

ILA were common among never-smokers in this middle-aged population with a prevalence of 7.9%. Age and hs-CRP were associated with ILA. Even though ILA and fibrotic ILA were not associated with dyspnoea, both patterns were associated with impaired D_{LCO}. Furthermore, fibrotic ILA was associated with RSP. These findings suggest that individuals with ILA or preclinical interstitial lung disease (ILD) may not be symptomatic although an impairment in lung function and D_{LCO} is already detectable.

As screening for lung cancer is becoming more common in a target population of older former and current smokers, individuals with ILA and potential preclinical ILD are likely to be picked up also. In our study, the prevalence of ILA was 13.2% among current smokers indicating that potentially more than one in eight screened individuals would need to be evaluated for the risk of developing an ILD. The management of ILA has been an active topic of discussion and concern since several studies have shown an association between fibrotic type of ILA and rapid progression [6, 23]. Thus, according to expert opinions, it has been agreed that the presence of honeycombing and traction bronchiectasis on lung cancer screening should always lead to a referral to an expert in pulmonology [9]. In our study, the prevalence of fibrotic ILA with honeycombing and reticular pattern with bronchiectasis was 0.5% among former smokers and 0.8% among current smokers. These findings differ from previous studies, partly due to different definitions and ages of the study populations. A study from Iceland where the median age for the ILA groups ranged from 75 to 79 years (range was 66 to 94 years for the whole cohort) found the prevalence of severe traction bronchiectasis and/or honeycombing to be 0.2% among former smokers and 0.08% among current

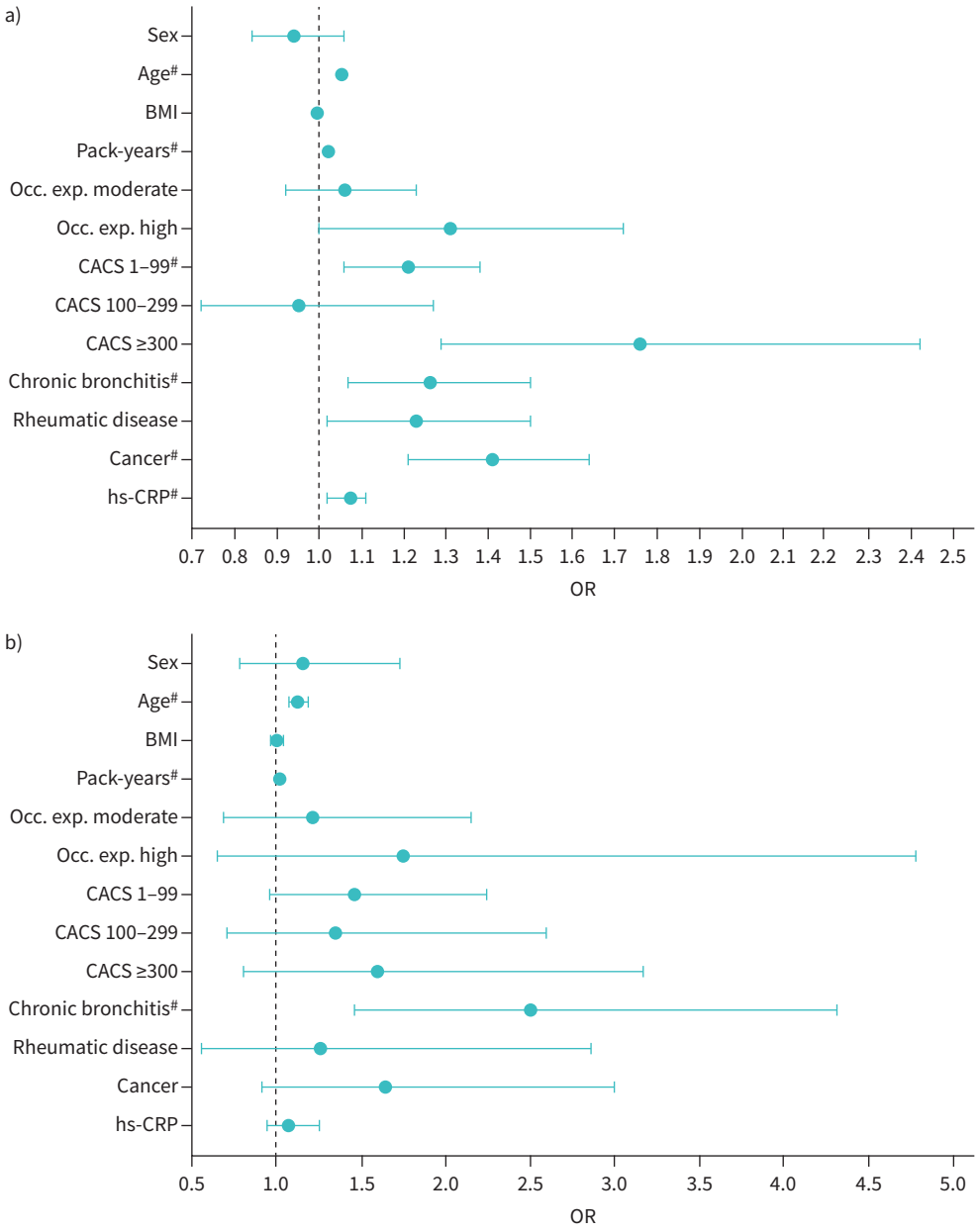

FIGURE 2 Multivariable logistic regression to assess factors associated with interstitial lung abnormalities (ILA) comparing a) ILA with no ILA and b) fibrotic ILA with no ILA. Sex: OR is for comparison of male with female. Age: OR is for each additional year older. BMI: OR is for 1 $kg \cdot m^{-2}$ increase in BMI. Pack-years: OR is for each additional pack-year smoked. Occ. exp: OR is for comparison of moderate and high exposure with low exposure. CACS: OR is for comparison of the three groups with CACS=0. Chronic bronchitis: OR is for comparison of chronic bronchitis with no chronic bronchitis. Rheumatic disease: OR is for comparison of rheumatic disease with no rheumatic disease. Cancer: OR is for comparison of cancer with no cancer. hs-CRP: OR is for each 5-unit increase in hs-CRP. BMI: body mass index; CACS: coronary artery calcium score; hs-CRP: high-sensitivity C-reactive protein ($mg \cdot L^{-1}$); Occ. exp.: occupational exposure to vapour, gas, dust and fumes. #: significant factors after Benjamini–Hochberg correction.

smokers [7]. A Danish study with an age range of 50 to 70 years found the prevalence of honeycombing to be 0.6% among participants with a history of smoking [5]. Never-smokers are not a target population for lung cancer screening, which may result in underdiagnosis, and these individuals are only diagnosed when they have more severe, symptomatic disease.

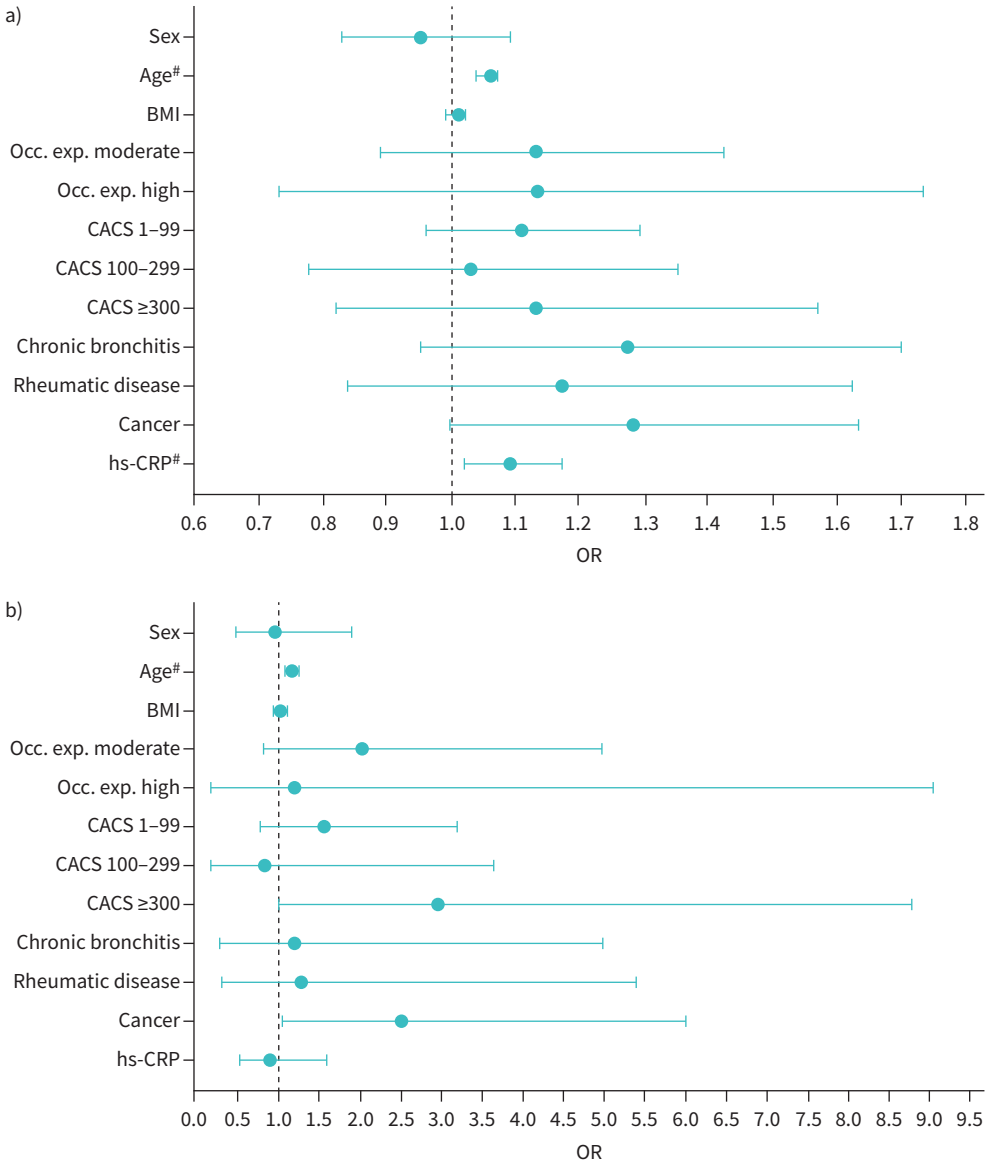

FIGURE 3 Multivariable logistic regression to assess factors associated with interstitial lung abnormalities (ILA) comparing a) ILA with no ILA and b) fibrotic ILA with no ILA among never-smokers. Sex: OR is for comparison of male with female. Age: OR is for each additional year older. BMI: OR is for 1 $kg \cdot m^{-2}$ increase in BMI. Occ. exp: OR is for comparison of moderate and high exposure with low exposure. CACS: OR is for comparison of the three groups with CACS=0. Chronic bronchitis: OR is for comparison of chronic bronchitis with no chronic bronchitis. Rheumatic disease: OR is for comparison of rheumatic disease with no rheumatic disease. Cancer: OR is for comparison of cancer with no cancer. hs-CRP: OR is for each 5-unit increase in hs-CRP. BMI: body mass index; CACS: coronary artery calcium score; hs-CRP: high-sensitivity C-reactive protein ($mg \cdot L^{-1}$); Occ. exp.: occupational exposure to vapour, gas, dust and fumes. #: significant factors after Benjamini–Hochberg correction.

Across the whole cohort, ILA were associated with age, smoking, comorbidities and low-grade inflammation. Even if we could not find an association between sex and ILA, there was a tendency for male sex to be more common among individuals with fibrotic ILA. However, the association did not appear to be significant in multivariable models, probably because of the small number of individuals with fibrotic ILA.

Both ILA and fibrotic ILA were associated with RSP and impaired D_{LCO}, but neither ILA nor fibrotic ILA were associated with dyspnoea in multivariable models. However, individuals with ILA and fibrotic ILA reported more dyspnoea, which is in line with a previous study [24]. A higher prevalence of chronic

TABLE 2 Univariable and multivariable logistic regression analyses of the association between ILA pattern and RSP, D_{LCO} or mMRC

	RSP		D_{LCO} <LLN SCAPIS		mMRC ⩾2	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Unadjusted						
ILA	1.32 (1.13–1.53)	**0.001**	1.98 (1.77–2.22)	**<0.001**	1.57 (1.22–2.03)	**<0.001**
Fibrotic ILA	4.04 (2.61–6.26)	**<0.001**	5.13 (3.53–7.49)	**<0.001**	4.02 (1.95–8.28)	**<0.001**
Adjusted						
ILA	1.33 (1.13–1.57)[#]	**<0.001**	1.49 (1.30–1.70)[¶]	**<0.001**	1.07 (0.78–1.48)[+]	0.67
Fibrotic ILA	3.61 (2.24–5.82)[#]	**<0.001**	3.30 (2.06–5.29)[¶]	**<0.001**	1.90 (0.78–4.59)[+]	0.16

Statistically significant p-values are in bold type. ILA: interstitial lung abnormalities; RSP: restrictive spirometric pattern defined by FVC<LLN SCAPIS and FEV_1/FVC⩾LLN SCAPIS; D_{LCO}: diffusing capacity of the lung for carbon monoxide; mMRC: modified Medical Research Council dyspnoea scale; LLN: lower limit of normal; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: multivariable model for RSP was adjusted for sex, age, body mass index (BMI), pack-years of smoking, comorbidities (chronic bronchitis, rheumatic disease, cancer) and occupational exposure (exposure to vapour, gas, dust and fumes); [¶]: multivariable model for D_{LCO} was adjusted for sex, age, BMI, pack-years of smoking, comorbidities (chronic bronchitis, rheumatic disease, cancer), occupational exposure (exposure to vapour, gas, dust and fumes), coronary artery calcium score (CACS) and emphysema; [+]: multivariable model for mMRC was adjusted for sex, age, BMI, pack-years of smoking, comorbidities (chronic bronchitis, rheumatic disease, cancer), occupational exposure (exposure to vapour, gas, dust and fumes), CACS and RSP.

bronchitis, higher CACS and a higher prevalence of RSP outweighed the association between ILA and high mMRC score in multivariable models. The association between ILA, fibrotic ILA and impaired D_{LCO} was not explained by emphysema.

A high CACS, which represents coronary atherosclerosis, was associated with ILA. This finding suggests that atherosclerosis coexists with ILA and is a known comorbidity in IPF [25].

Although occupational exposure is a well-known risk factor for ILD [26], we were not able to detect any associations between occupational exposure and ILA. Similar results were seen in a population-based study from the USA [27], where only subgroup analysis including individuals under 65 years currently employed with exposure to vapours/gas showed an association between occupational exposure and ILA.

TABLE 3 Univariable and multivariable logistic regression analyses of the association between ILA pattern and RSP, D_{LCO} or mMRC among never-smokers

	RSP		D_{LCO} <LLN SCAPIS		mMRC ⩾2	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Unadjusted						
ILA	1.24 (0.97–1.57)	0.085	1.60 (1.27–2.02)	**<0.001**	1.43 (0.88–2.31)	0.15
Fibrotic ILA	2.93 (1.31–6.56)	**0.009**	4.41 (2.13–9.16)	**<0.001**	1.81 (0.25–13.23)	0.56
Adjusted						
ILA	1.23 (0.96–1.59)[#]	0.10	1.47 (1.14–1.89)[¶]	**0.003**	1.08 (0.59–1.98)[+]	0.81
Fibrotic ILA	2.76 (1.20–6.35)[#]	**0.017**	3.04 (1.26–7.35)[¶]	**0.013**	0.88 (0.08–9.53)[+]	0.91

Statistically significant p-values in bold type. ILA: interstitial lung abnormalities; RSP: restrictive spirometric pattern defined by FVC<LLN SCAPIS and FEV_1/FVC⩾LLN SCAPIS; D_{LCO}: diffusing capacity of the lung for carbon monoxide; mMRC: modified Medical Research Council dyspnoea scale; LLN: lower limit of normal; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: multivariable model for RSP was adjusted for sex, age, body mass index (BMI), comorbidities (chronic bronchitis, rheumatic disease, cancer) and occupational exposure (exposure to vapour, gas, dust and fumes); [¶]: multivariable model for D_{LCO} was adjusted for sex, age, BMI, comorbidities (chronic bronchitis, rheumatic disease, cancer), occupational exposure (exposure to vapour, gas, dust and fumes), coronary artery calcium score (CACS) and emphysema; [+]: multivariable model for mMRC was adjusted for sex, age, BMI, comorbidities (chronic bronchitis, rheumatic disease, cancer), occupational exposure (exposure to vapour, gas, dust and fumes), CACS and RSP.

As far as we know this is the largest population-based study on ILA. Another population-based study from Iceland included 5320 participants with a mean age of 78 years and found ILA in 7% [28, 29]. The difference in prevalence between this and our study could be explained by differences in the methodologies in the studies; the Icelandic study defined ILA as changes affecting >5% of the lung while in our study, as proposed by the Fleischner guidelines [3], we were not able to interpret the extent of ILA, which may have led to overreporting. Most studies employing pulmonary CT scans included only smokers, while in the present study, almost half of the study population were never-smokers. One large study including never-smokers was carried out in China but was not a random sample. In that study (mean age of participants was 46 years), the prevalence of ILA was only 2.1% and 58.8% of these were never-smokers [30]. In another cohort study from the USA including 1867 participants, 22% of whom were never-smokers, the prevalence of ILA was 3% and of indeterminate ILA was 44% at the first evaluation. At 6 years follow-up, the prevalence was 7% and 41% for ILA and indeterminate ILA, respectively [31]. In that study, the definition of ILA also included centrilobular nodules, which was later removed from the Fleischner position paper definitions due to its strong association with smoking-related respiratory bronchiolitis but not with ILD [3].

The large number of participants strengthens the external validity of the study. The participants underwent detailed investigations regarding health status and lung function and CT imaging of the lungs and heart was obtained, which enabled a thorough characterisation of the population. There are, however, some limitations. Firstly, we were not able to interpret the distribution, extent of or exact location of ILA, which could lead to misclassification of ILA patterns. Furthermore, the lack of information about the extent of ILA potentially leads to overreporting of ILA and makes comparison with other studies difficult since the ILA definition used is not in complete alignment with the Fleischner position paper. Since SCAPIS is a population-based study with the aim of investigating the general middle-aged population, the inclusion criteria were few. Thus, it is possible that a minority of included participants had an existing ILD diagnosis. However, we believe that this does not change the overall results in this large population-based cohort. Also, many comorbidities were self-reported, which could be underestimated due to recall bias. Unfortunately, we were not able to interpret the self-reported cancer type to make more conclusions about the association.

Conclusions

ILA were common findings in survey participants, including in never-smokers. Never-smokers may be at risk of being underdiagnosed since they are not in general a target for lung cancer screening. Individuals with ILA have underlying diseases with suggested shared mechanisms, *e.g.* chronic inflammation. Individuals with ILA are mostly asymptomatic but, especially with the fibrotic type, show impairments in lung function and D_{LCO}, which confirms the importance of follow-up of these individuals. Thus, potential screening for ILD in the future should not be done according to smoking status but instead by focusing on other risk factors, *e.g.*, age, comorbidities (cardiovascular disease) and overall inflammatory status.

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Conflict of interest: I. Pesonen reports fees from Boehringer Ingelheim for lectures and participation on advisory boards. A. Egeston reports consulting fees from BioCryst, payment/honoraria from AstraZeneca and an unrestricted research grant from CSL-Behring. Ö.I. Emilsson reports payment from study work from Boehringer Ingelheim, unrelated to this publication. E. Hagström reports payments to institution from Pfizer and Amgen, small personal fees from Amgen, NovoNordisk, Bayer and AstraZeneca, and a small personal fee from Amarin AB for participation on an advisory board. He is the co-chair of the Swedish secondary prevention registry and the national coordinator for the trials DalCore DAL301 DalGne, Regeneron R1500-CL-1643 and Aegis II/Perfuse. L.E.G.W. Vanfleteren reports grants paid to his institution from the Swedish Heart and Lung Foundation and the family Kamprad foundation, and payments/honoraria from AstraZeneca, GSK, Boehringer, Novartis, Chiesi, Pulmonx for lectures and presentations. He also reports personal payments for participation on a data safety monitoring board or advisory board for AstraZeneca. He was member of the board for the Swedish National Airway registry. He is as associate editor of this journal. P. Wollmer received fees for lectures from Chiesi Pharma outside the scope of the study. He also has a patent issued for a device and method for pulmonary function measurement outside the

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