EU PAS Abstract

Title	Epidemiology of interstitial lung diseases and their progressive-fibrosing behaviour in six mid-size European countries: the PERSEIDS study
Keywords	Interstitial lung diseases, progressive-fibrosing, incidence, prevalence
Rationale and background	Among fibrosing interstitial lung diseases (F-ILDs), idiopathic pulmonary fibrosis (IPF) is the most frequent. It is characterized by a progressive-fibrosing behaviour and a usual interstitial pneumonia (UIP) pattern. IPF remains the ILD with the worst prognosis, but other subtypes of F-ILD (non-IPF F-ILDs) may have a similar prognosis when a progressive-fibrosing behaviour and/or UIP pattern are present. Of these subtypes, systemic sclerosis-related ILD (SSc-ILD) is of particular interest as it is the leading cause of death related to SSc. Despite their associated mortality, few studies have addressed the epidemiology of ILDs and their progressive-fibrosing behaviour in Europe. Overall in Europe, data on the epidemiology of the different ILD are scarce or outdated.
Research question and objectives	Estimate incidence and prevalence of ILDs, F-ILDs, IPF, non-IPF F-ILDs and SSc-ILD; and to further characterize non-IPF F-ILDs in terms of progressive-fibrosing behaviour and UIP pattern.
Study design	Non-interventional, epidemiological, retrospective, two-phase, database study, using aggregate data for the 2014-2018 period. In Phase 1, an algorithm based on codes/keywords was used to search the source databases and identify incident/prevalent cases of ILDs for each year of the study period, and crude incidence/prevalence was estimated for each country based on its total adult population. In Phase 2, a subset of the non-IPF F-ILD cases identified at each centre were manually reviewed to determine the percentages of UIP pattern and progressive-fibrosing behaviour. For the latter, a weighted mean percentage was calculated for each country, and used to extrapolate incidence/prevalence of progressive-fibrosing ILDs. This review also delivered the algorithm's positive predictive value (PPV), which was used to adjust incidence/prevalence estimates obtained in both phases.
Setting	Pulmonary and/or Rheumatology departments at 14 centres in Belgium, Denmark, Finland, Norway, Greece and Portugal; of these, 13 participated in Phase 1 and 10 in Phase 2.
Subjects and study size	Phase 1: all adults listed in source databases during 2014-2018. Phase 2: first 100 patients at each database with a code/keyword for any non-IPF F-ILD from 2016.
Variables and data sources	Primary outcomes were crude incidence/prevalence of ILDs, F-ILDs, IPF, non-IPF F-ILDs, and SSc-ILD in each country, annually and for the study period (Phase 1) and percentages of each non-IPF F-ILD subtype with progressive-fibrosing behaviour, UIP pattern, both or none, overall for all countries (Phase 2). Secondary outcomes of Phase 2 included PPV of the algorithm by centre and country; crude incidence/prevalence of progressive-fibrosing ILDs in each country, annually and for the study period; and adjusted incidence/prevalence estimates for both phases.
Results	The PPVs of the search algorithm are shown in Table 1. In the latest year assessed (2018), incidences per 10^5 person-years in the participating countries ranged between 9.4-83.6 (ILDs), 7.7-76.2 (F-ILDs), 0.4-10.3 (IPF), 6.6-71.7 (non-IPF F-ILDs) and 0.3-1.5 (SSc-ILD). In the same year, prevalences per 10^5 persons ranged from 33.6-247.4 (ILDs), 26.7-236.8 (F-ILDs), 2.8-31.0 (IPF), 22.3-205.8 (non-IPF F-ILDs) and 1.4-10.1 (SSc-ILD) (Table 2).

	The percentage of progressive-fibrosing behaviour ranged between 10.4-50.0%, and of UIP pattern between 6.7-70.2%. The extrapolated incidences of progressive-fibrosing ILDs ranged between 2.1-14.5 per 10^5 person-years, and the prevalences between 6.9-78.0 per 10^5 persons (Table 3).
Discussion	In general, the algorithm used to identify ILD cases showed a high PPV. The incidence and prevalence of the ILDs assessed (including progressive-fibrosing ILDs) was relatively stable in all countries throughout the study period. The prevalence of IPF, SSc-ILD and progressive-fibrosing ILDs is below the threshold number (50 per 10^5 persons) defined by the European Union for an orphan disease. Overall, approximately a third of non-IPF F-ILDs showed a progressive-fibrosing behaviour. The non-IPF F-ILD subtype most prone to progression was hypersensitivity pneumonitis.
Marketing authorization holder	Not applicable.
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Table 1. PPV of the search algorithm used in Phase 1, by centre and country

	Centre 1	Centre 2	Centre 3	Country
Belgium	0.75			0.75
Denmark	0.73			0.73
Finland	0.49			0.49
Greece	0.64	0.93	0.80	0.79
Norway	0.75			0.75
Portugal	0.68	0.77		0.73

Belgium: Centre 1 –Ghent University Hospital. This was a reference centre for SSc-ILD, and only provided data for this condition. The participating unit did not perform a systematic search. Instead, they retrieved SSc-ILD cases from a pre-existing departmental database which captured all patients with SSc-lLD presenting for assessment each year. As a result, the PPV for this centre was 1.00. As this could lead to overestimation, a conservative approach was chosen, and the PPV used was the average for the rest of countries (0.75).
Denmark: Centre 1 (Vejle Hospital).
Finland: Centre 1(Turku University Hospital)
Greece: Centre 1 (University Hospital of Larissa), Centre 2 (General Hospital of Thessaloniki), Centre 3 (Athens Medical Centre).
Norway: Centre 1 (Oslo University Hospital, Rikshospitalet).
Portugal: Centre 1 (Centro Hospitalar Universitário de Sao Joao), Centre 2 (Hospital Beatriz Angelo).
Abbreviations: PPV, positive predictive value; SSc-ILD, systemic sclerosis-associated ILD.

Table 2. Incidence (A) and prevalence (B) of ILD, F-ILD, IPF, non-IPF F-ILD, and SSc-ILD in each country, annually and for the study period

(A) Incidence per 10^5 person-years (95% CI)

			Study period	2014	2015	2016	2017	2018
ILD	Belgium	Min	17.9 (16.9,18.9)	14.0 (12.3,16.0)	17.5 (15.4,19.9)	17.2 (15.1,19.5)	21.0 (18.7,23.7)	20.5 (18.1,23.1)
		Max	71.1 (67.7,74.7)	55.3 (49.3,62.1)	63.5 (56.8,71.1)	71.4 (63.9,79.7)	86.9 (78.4,96.3)	83.6 (75.2,93.0)
	Denmark	Min	41.3 (40.5,42.1)	41.0 (39.1,42.9)	43.8 (41.9,45.8)	43.1 (41.2,45.0)	38.5 (36.8,40.4)	40.1 (38.3,42.0)
		Max	56.9 (56.0,57.9)	56.5 (54.3,58.8)	60.4 (58.2,62.8)	59.4 (57.2,61.7)	53.1 (51.0,55.3)	55.3 (53.2,57.5)
	Finland	Min	26.2 (24.1,28.6)	36.7 (31.2,43.3)	20.8 (16.7,25.9)	22.6 (18.3,27.8)	24.8 (20.3,30.2)	26.3 (21.7,31.9)
		Max	53.5 (50.4,56.9)	75.0 (66.8,84.1)	42.4 (36.4,49.4)	46.1 (39.8,53.3)	50.6 (44.0,58.2)	53.7 (46.9,61.4)
	Greece	Min	10.6 (10.1,11.1)	5.8 (5.1,6.6)	10.0 (9.0,11.1)	11.4 (10.3,12.6)	13.3 (12.1,14.5)	12.5 (11.4,13.7)
		Max	24.1 (23.2,25.1)	20.2 (18.1,22.5)	21.7 (19.8,23.8)	23.2 (21.3,25.4)	29.2 (27.0,31.7)	25.2 (23.2,27.5)
	Norway	Min	12.4 (11.8,13.1)	NA	12.3 (11.0,13.7)	16.6 (15.2,18.2)	11.1 (10.0,12.4)	9.9 (8.8,11.1)
		Max	31.8 (30.4,33.2)	NA	31.4 (28.6,34.5)	43.2 (39.9,46.7)	29.4 (26.7,32.3)	24.2 (21.9,26.7)
	Portugal	Min	8.0 (7.6,8.5)	6.3 (5.3,7.3)	8.2 (7.1,9.4)	7.3 (6.3,8.4)	8.7 (7.6,9.9)	9.4 (8.3,10.5)
		Max	11.1 (10.5,11.7)	8.6 (7.5,9.9)	11.3 (10.1,12.7)	10.1 (8.9,11.4)	11.9 (10.7,13.4)	12.9 (11.7,14.2)
F-ILD	Belgium	Min	16.7 (15.8,17.7)	13.3 (11.6,15.2)	16.4 (14.4,18.7)	16.0 (14.0,18.2)	19.9 (17.6,22.5)	18.7 (16.5,21.2)
		Max	66.4 (63.1,69.8)	52.3 (46.5,58.8)	59.5 (53.0,66.7)	66.3 (59.2,74.3)	82.2 (74.1,91.3)	76.2 (68.3,85.1)
	Denmark	Min	40.2 (39.4,41.1)	40.0 (38.2,41.9)	42.8 (40.9,44.8)	42.0 (40.1,43.9)	37.5 (35.7,39.3)	39.1 (37.3,40.9)
		Max	55.5 (54.5,56.5)	55.1 (53.0,57.4)	59.0 (56.8,61.3)	57.9 (55.7,60.1)	51.7 (49.6,53.8)	53.9 (51.8,56.0)

			Study period	2014	2015	2016	2017	2018
	Finland	Min	22.4 (20.4,24.6)	33.1 (27.8,39.3)	18.3 (14.5,23.1)	18.2 (14.4,23.0)	21.3 (17.2,26.4)	21.5 (17.4,26.6)
		Max	45.8 (42.9,48.9)	67.5 (59.8,76.2)	37.3 (31.7,43.9)	37.1 (31.6,43.7)	43.5 (37.4,50.5)	43.8 (37.8,50.9)
	Greece	Min	9.8 (9.4,10.3)	5.3 (4.6,6.1)	9.4 (8.5,10.5)	10.6 (9.6,11.7)	12.3 (11.2,13.5)	11.5 (10.4,12.7)
		Max	22.4 (21.5,23.4)	18.9 (16.9,21.1)	20.4 (18.6,22.5)	21.6 (19.7,23.7)	27.2 (25.1,29.6)	23.1 (21.1,25.2)
	Norway	Min	11.2 (10.6,11.8)	NA	11.0 (9.8,12.4)	14.5 (13.2,16.0)	10.1 (9.0,11.4)	9.1 (8.1,10.2)
		Max	28.5 (27.2,29.9)	NA	28.2 (25.6,31.1)	37.7 (34.7,41.0)	26.8 (24.3,29.6)	22.2 (20.1,24.6)
	Portugal	Min	6.3 (5.8,6.7)	4.6 (3.9,5.6)	6.0 (5.1,7.1)	5.4 (4.5,6.4)	7.2 (6.2,8.3)	7.7 (6.8,8.7)
		Max	8.6 (8.1,9.2)	6.4 (5.5,7.5)	8.3 (7.2,9.5)	7.4 (6.4,8.6)	9.9 (8.7,11.2)	10.6 (9.5,11.8)
IPF	Belgium	Min	0.9 (0.7,1.3)	0.7 (0.3,1.5)	1.1 (0.6,2.1)	0.6 (0.3,1.4)	1.2 (0.7,2.2)	1.1 (0.6,2.1)
		Max	3.8 (2.9,4.9)	2.7 (1.4,5.5)	4.1 (2.4,7.0)	2.5 (1.2,5.3)	5.0 (3.0,8.4)	4.6 (2.7,7.9)
	Denmark	Min	0.4 (0.4,0.5)	0.4 (0.4,0.5)	0.5 (0.5,0.6)	0.4 (0.4,0.5)	0.4 (0.3,0.4)	0.4 (0.4,0.5)
		Max	10.6 (10.2,11.1)	10.3 (9.4,11.3)	11.4 (10.4,12.4)	11.4 (10.5,12.4)	9.8 (8.9,10.7)	10.3 (9.4,11.2)
	Finland	Min	3.5 (2.7,4.4)	4.2 (2.6,6.8)	3.5 (2.1,6.0)	3.0 (1.7,5.3)	3.5 (2.1,5.9)	3.2 (1.9,5.6)
		Max	7.1 (6.0,8.4)	8.5 (6.1,12.0)	7.2 (5.0,10.4)	6.1 (4.1,9.2)	7.1 (4.9,10.3)	6.6 (4.5,9.7)
	Greece	Min	3.5 (3.3,3.8)	1.5 (1.2,2.0)	3.5 (3.0,4.2)	3.8 (3.2,4.5)	4.3 (3.6,5.0)	4.5 (3.9,5.3)
		Max	8.0 (7.4,8.5)	4.3 (3.4,5.4)	7.6 (6.5,8.9)	8.2 (7.0,9.5)	9.2 (8.0,10.6)	9.7 (8.5,11.2)
	Norway	Min	2.2 (1.9,2.5)	NA	2.1 (1.6,2.7)	2.4 (1.9,3.0)	2.2 (1.7,2.8)	2.0 (1.6,2.6)
		Max	5.5 (5.0,6.2)	NA	5.3 (4.2,6.6)	6.2 (5.0,7.6)	5.8 (4.7,7.2)	4.9 (4.0,6.2)
	Portugal	Min	0.9 (0.7,1.1)	0.7 (0.4,1.1)	0.7 (0.4,1.1)	0.6 (0.4,1.0)	1.2 (0.9,1.8)	1.1 (0.8,1.5)

			Study period	2014	2015	2016	2017	2018
		Max	1.2 (1.0,1.4)	1.0 (0.7,1.5)	0.9 (0.6,1.4)	0.9 (0.6,1.3)	1.7 (1.3,2.3)	1.5 (1.1,2.0)
Non-IPF F-ILD	Belgium	Min	15.8 (14.9,16.7)	12.6 (11.0,14.4)	15.3 (13.3,17.5)	15.4 (13.5,17.5)	18.7 (16.6,21.2)	17.6 (15.4,20.0)
		Max	62.6 (59.5,65.9)	49.5 (43.9,55.8)	55.4 (49.3,62.3)	63.8 (56.9,71.6)	77.2 (69.4,86.0)	71.7 (64.1,80.1)
	Denmark	Min	32.5 (31.8,33.3)	32.5 (30.8,34.2)	34.6 (32.9,36.3)	33.7 (32.0,35.4)	30.4 (28.8,32.0)	31.6 (30.0,33.3)
		Max	54.9 (53.9,55.9)	54.6 (52.4,56.8)	58.3 (56.1,60.6)	57.3 (55.1,59.6)	51.1 (49.1,53.3)	53.3 (51.2,55.4)
	Finland	Min	19.0 (17.1,21.0)	28.9 (24.0,34.8)	14.7 (11.4,19.1)	15.2 (11.8,19.6)	17.8 (14.1,22.5)	18.2 (14.5,23.0)
		Max	38.7 (36.0,41.5)	58.9 (51.8,67.1)	30.1 (25.1,36.1)	31.0 (25.9,37.0)	36.4 (30.9,42.8)	37.2 (31.7,43.8)
	Greece	Min	6.3 (5.9,6.7)	3.8 (3.2,4.5)	5.9 (5.1,6.7)	6.8 (6.0,7.7)	8.0 (7.2,9.0)	6.9 (6.1,7.9)
		Max	15.5 (14.8,16.3)	15.2 (13.4,17.2)	13.5 (12.0,15.2)	14.4 (12.9,16.1)	19.6 (17.8,21.6)	14.8 (13.3,16.6)
	Norway	Min	9.0 (8.5,9.6)	NA	9.0 (7.9,10.2)	12.1 (10.9,13.5)	7.9 (7.0,9.0)	7.1 (6.2,8.1)
		Max	23.0 (21.8,24.2)	NA	22.9 (20.6,25.6)	31.5 (28.8,34.6)	21.0 (18.8,23.5)	17.3 (15.4,19.4)
	Portugal	Min	5.4 (5.0,5.8)	3.9 (3.2,4.8)	5.3 (4.5,6.3)	4.7 (4.0,5.7)	5.9 (5.0,7.0)	6.6 (5.7,7.6)
		Max	7.4 (7.0,7.9)	5.4 (4.6,6.4)	7.4 (6.4,8.5)	6.5 (5.6,7.6)	8.2 (7.1,9.4)	9.1 (8.1,10.2)
SSc-ILD	Belgium	Min	0.9 (0.7,1.0)	0.4 (0.2,0.8)	1.1 (0.8,1.6)	1.1 (0.8,1.6)	0.7 (0.4,1.1)	1.0 (0.6,1.4)
		Max	1.1 (1.0,1.4)	0.5 (0.3,0.9)	1.5 (1.1,2.0)	1.5 (1.1,2.1)	1.0 (0.6,1.4)	1.3 (0.9,1.8)
	Denmark	Min	0.5 (0.4,0.6)	0.5 (0.3,0.7)	0.5 (0.3,0.7)	0.4 (0.3,0.7)	0.5 (0.3,0.7)	0.5 (0.3,0.7)
		Max	0.6 (0.5,0.7)	0.7 (0.5,1.0)	0.6 (0.4,0.9)	0.6 (0.4,0.8)	0.6 (0.4,0.9)	0.6 (0.4,0.9)
	Finland	Min	0.3 (0.1,0.7)	0.4 (0.1,1.9)	0.1 (0.0,2.1)	0.4 (0.1,1.9)	0.2 (0.0,1.8)	0.5 (0.1,2.0)
		Max	0.7 (0.4,1.1)	0.8 (0.3,2.4)	0.3 (0.0,1.8)	0.8 (0.2,2.4)	0.5 (0.1,2.0)	1.0 (0.4,2.7)

		Study period	2014	2015	2016	2017	2018
Greece	Min	0.4 (0.3,0.5)	0.4 (0.2,0.6)	0.4 (0.2,0.6)	0.4 (0.2,0.6)	0.5 (0.3,0.8)	0.4 (0.3,0.7)
	Max	1.1 (0.9,1.4)	1.4 (0.9,2.1)	1.0 (0.6,1.5)	0.7 (0.4,1.2)	1.7 (1.2,2.3)	1.0 (0.7,1.5)
Norway	Min	0.9 (0.7,1.1)	NA	0.7 (0.4,1.1)	1.5 (1.1,2.0)	0.7 (0.5,1.1)	0.6 (0.4,1.0)
	Max	2.2 (1.9,2.6)	NA	1.8 (1.2,2.6)	3.8 (2.9,5.0)	1.9 (1.3,2.8)	1.5 (1.0,2.2)
Portugal	Min	0.3 (0.3,0.5)	0.3 (0.1,0.6)	0.5 (0.3,0.9)	0.3 (0.1,0.6)	0.3 (0.1,0.6)	0.3 (0.2,0.6)
	Max	0.5 (0.4,0.6)	0.4 (0.2,0.7)	0.7 (0.5,1.2)	0.4 (0.2,0.8)	0.4 (0.2,0.8)	0.5 (0.3,0.8)

(B) Prevalence per 10^5 persons (95% CI)

			Study period	2014	2015	2016	2017	2018
ILD	Belgium	Min	49.8 (46.7,53.0)	37.5 (34.9,40.1)	45.5 (42.5,48.5)	52.0 (48.8,55.3)	55.4 (52.0,58.9)	61.4 (57.8,65.1)
		Max	195.1 (184.3,205.8)	145.4 (136.7,154.2)	163.3 (154.1,172.6)	213.1 (201.5,224.6)	225.4 (213.4,237.5)	247.4 (234.6,260.1)
	Denmark	Min	132.2 (128.9,135.6)	130.8 (127.4,134.2)	141.1 (137.6,144.6)	128.5 (125.2,131.8)	121.7 (118.5,124.9)	139.2 (135.7,142.6)
		Max	182.4 (178.5,186.3)	180.4 (176.5,184.4)	194.7 (190.6,198.7)	177.2 (173.3,181.1)	167.9 (164.1,171.6)	191.9 (187.9,195.9)
	Finland	Min	90.9 (81.4,100.3)	90.8 (81.3,100.3)	85.8 (76.6,95.0)	87.8 (78.5,97.1)	90.7 (81.3,100.1)	99.0 (89.2,108.8)
		Max	185.4 (172.0,198.9)	185.3 (171.8,198.9)	175.1 (162.0,188.3)	179.2 (166.0,192.5)	185.2 (171.7,198.6)	202.1 (188.1,216.1)
	Greece	Min	23.8 (21.0,26.6)	16.3 (14.0,18.6)	17.5 (15.1,19.8)	23.0 (20.3,25.8)	28.5 (25.4,31.5)	33.6 (30.3,36.9)
		Max	93.3 (85.0,101.5)	67.7 (60.7,74.7)	67.4 (60.4,74.4)	90.3 (82.2,98.4)	113.0 (103.9,122.1)	128.3 (118.6,138.0)
	Norway	Min	55.8 (53.0,58.5)	48.2 (45.5,50.8)	49.5 (46.8,52.1)	59.9 (57.0,62.7)	63.4 (60.5,66.3)	56.8 (54.1,59.5)
		Max	142.1 (136.0,148.2)	121.1 (115.3,126.9)	126.5 (120.6,132.4)	155.6 (149.1,162.0)	167.4 (160.8,174.0)	138.8 (133.1,144.5)

			Study period	2014	2015	2016	2017	2018
	Portugal	Min	31.3 (28.1,34.4)	NA	NA	NA	NA	35.4 (32.1,38.8)
		Max	52.4 (47.9,56.9)	35.9 (32.2,39.5)	45.9 (41.8,49.9)	51.8 (47.5,56.2)	58.0 (53.4,62.6)	76.7 (70.6,82.9)
F-ILD	Belgium	Min	48.3 (45.2,51.4)	36.6 (34.1,39.2)	44.3 (41.4,47.2)	50.3 (47.2,53.5)	53.9 (50.5,57.2)	58.9 (55.3,62.4)
		Max	189.0 (178.5,199.5)	142.0 (133.4,150.6)	159.0 (149.9,168.0)	205.9 (194.6,217.1)	219.0 (207.2,230.8)	236.8 (224.5,249.1)
	Denmark	Min	129.7 (126.3,133.0)	128.1 (124.8,131.4)	138.6 (135.2,142.1)	125.9 (122.7,129.2)	119.2 (116.0,122.3)	136.6 (133.2,139.9)
		Max	178.8 (175.0,182.7)	176.7 (172.8,180.6)	191.2 (187.2,195.3)	173.7 (169.9,177.5)	164.4 (160.7,168.1)	188.3 (184.4,192.3)
	Finland	Min	83.0 (73.9,92.0)	84.3 (75.2,93.5)	79.9 (71.0,88.8)	79.3 (70.5,88.1)	82.3 (73.3,91.2)	89.0 (79.7,98.3)
		Max	169.3 (156.4,182.2)	172.1 (159.1,185.2)	163.1 (150.4,175.7)	161.8 (149.2,174.4)	167.9 (155.1,180.7)	181.6 (168.3,194.9)
	Greece	Min	22.7 (20.0,25.4)	15.7 (13.4,17.9)	16.8 (14.4,19.1)	22.1 (19.4,24.8)	27.1 (24.1,30.0)	31.7 (28.5,35.0)
		Max	89.5 (81.4,97.6)	65.5 (58.6,72.3)	65.2 (58.3,72.1)	87.2 (79.2,95.2)	108.3 (99.4,117.2)	121.6 (112.1,131.0)
	Norway	Min	50.9 (48.3,53.5)	44.0 (41.4,46.5)	44.8 (42.2,47.3)	53.1 (50.4,55.8)	58.6 (55.8,61.4)	52.9 (50.2,55.5)
		Max	129.7 (123.9,135.5)	110.6 (105.1,116.2)	114.4 (108.8,120.0)	138.0 (131.9,144.1)	154.8 (148.5,161.2)	129.2 (123.7,134.7)
	Portugal	Min	20.3 (17.8,22.8)	NA	NA	NA	NA	26.7 (23.8,29.6)
		Max	34.0 (30.4,37.6)	21.0 (18.2,23.7)	28.4 (25.1,31.6)	32.2 (28.8,35.6)	36.9 (33.2,40.5)	57.9 (52.5,63.2)
IPF	Belgium	Min	4.4 (3.0,5.8)	0.9 (0.3,1.6)	2.9 (1.8,4.0)	4.9 (3.5,6.4)	5.8 (4.2,7.4)	7.5 (5.7,9.3)
		Max	17.8 (12.9,22.6)	3.8 (1.5,6.0)	10.6 (7.0,14.2)	20.9 (15.5,26.2)	24.2 (18.5,30.0)	31.0 (24.5,37.4)
	Denmark	Min	2.7 (2.2,3.1)	2.6 (2.2,3.1)	2.8 (2.3,3.3)	2.7 (2.2,3.2)	2.3 (1.9,2.7)	2.8 (2.4,3.3)
		Max	27.7 (26.2,29.3)	25.9 (24.4,27.4)	29.3 (27.8,30.9)	27.4 (25.9,28.9)	25.7 (24.2,27.1)	30.4 (28.8,32.0)
	Finland	Min	11.2 (7.8,14.5)	8.5 (5.6,11.4)	10.5 (7.2,13.7)	11.3 (8.0,14.6)	12.5 (9.0,16.0)	13.0 (9.5,16.6)

			Study period	2014	2015	2016	2017	2018
		Max	22.8 (18.0,27.5)	17.3 (13.2,21.5)	21.3 (16.8,25.9)	23.0 (18.3,27.8)	25.4 (20.4,30.4)	26.6 (21.5,31.7)
	Greece	Min	6.2 (4.8,7.7)	2.9 (1.9,3.9)	4.1 (2.9,5.2)	5.9 (4.5,7.3)	8.0 (6.4,9.6)	10.3 (8.4,12.1)
		Max	17.8 (14.2,21.4)	8.2 (5.8,10.7)	11.7 (8.8,14.6)	16.9 (13.4,20.5)	23.0 (18.9,27.1)	29.3 (24.7,33.9)
	Norway	Min	8.1 (7.1,9.2)	8.1 (7.0,9.2)	6.5 (5.5,7.4)	8.1 (7.0,9.1)	8.7 (7.6,9.8)	9.0 (7.9,10.1)
		Max	20.7 (18.3,23.0)	20.5 (18.1,22.8)	16.5 (14.4,18.7)	21.0 (18.6,23.4)	22.9 (20.5,25.4)	22.0 (19.7,24.3)
	Portugal	Min	2.8 (1.9,3.7)	NA	NA	NA	NA	3.1 (2.1,4.1)
		Max	4.7 (3.4,6.0)	2.8 (1.8,3.8)	4.1 (2.9,5.3)	4.9 (3.6,6.3)	5.5 (4.1,6.9)	6.8 (4.9,8.6)
Non-IPF F-ILD	Belgium	Min	44.2 (41.3,47.0)	35.7 (33.2,38.2)	41.4 (38.7,44.2)	45.4 (42.5,48.3)	48.1 (45.0,51.2)	51.4 (48.2,54.6)
		Max	172.4 (162.6,182.1)	138.2 (129.8,146.6)	148.4 (139.8,157.0)	185.0 (174.6,195.3)	194.8 (184.0,205.6)	205.8 (194.8,216.9)
	Denmark	Min	109.6 (106.6,112.7)	109.3 (106.2,112.4)	117.7 (114.5,120.9)	106.3 (103.3,109.3)	100.3 (97.4,103.3)	114.7 (111.6,117.8)
		Max	175.3 (171.5,179.2)	173.0 (169.1,176.9)	187.8 (183.7,191.8)	170.2 (166.4,174.0)	160.9 (157.2,164.6)	184.8 (180.8,188.7)
	Finland	Min	71.8 (63.4,80.2)	75.9 (67.2,84.5)	69.4 (61.2,77.7)	68.0 (59.8,76.2)	69.8 (61.5,78.0)	75.9 (67.4,84.5)
		Max	146.5 (134.6,158.5)	154.8 (142.4,167.2)	141.7 (129.9,153.5)	138.8 (127.1,150.5)	142.4 (130.6,154.2)	155.0 (142.7,167.3)
	Greece	Min	17.2 (14.9,19.6)	13.7 (11.6,15.8)	13.4 (11.3,15.5)	16.9 (14.6,19.3)	19.8 (17.3,22.4)	22.3 (19.6,25.0)
		Max	69.0 (61.9,76.1)	55.5 (49.2,61.8)	51.9 (45.7,58.0)	67.8 (60.8,74.9)	82.1 (74.3,89.8)	88.1 (80.0,96.1)
	Norway	Min	42.8 (40.4,45.2)	35.9 (33.6,38.2)	38.3 (35.9,40.6)	45.0 (42.5,47.5)	49.9 (47.4,52.5)	43.9 (41.5,46.2)
		Max	109.0 (103.7,114.4)	90.2 (85.1,95.2)	97.9 (92.7,103.0)	117.0 (111.4,122.6)	131.9 (126.0,137.8)	107.2 (102.2,112.2)
	Portugal	Min	17.5 (15.1,19.8)	NA	NA	NA	NA	23.6 (20.8,26.3)
		Max	29.3 (25.9,32.6)	18.2 (15.6,20.8)	24.3 (21.3,27.3)	27.3 (24.1,30.4)	31.4 (28.0,34.7)	51.1 (46.1,56.1)

			Study period	2014	2015	2016	2017	2018
SSc-ILD	Belgium	Min	4.1 (3.0,5.3)	3.0 (2.0,4.0)	3.7 (2.6,4.8)	4.5 (3.3,5.7)	4.4 (3.3,5.6)	4.9 (3.7,6.2)
		Max	5.5 (4.2,6.8)	4.0 (2.9,5.1)	4.9 (3.7,6.2)	6.0 (4.6,7.4)	5.9 (4.5,7.3)	6.5 (5.1,8.0)
	Denmark	Min	2.2 (1.8,2.7)	2.5 (2.1,3.0)	2.6 (2.1,3.0)	2.3 (1.8,2.7)	1.6 (1.3,2.0)	2.3 (1.8,2.7)
		Max	3.1 (2.6,3.6)	3.5 (2.9,4.0)	3.5 (3.0,4.1)	3.1 (2.6,3.6)	2.2 (1.8,2.7)	3.1 (2.6,3.6)
	Finland	Min	2.0 (0.6,3.4)	1.6 (0.4,2.9)	1.9 (0.5,3.3)	2.0 (0.6,3.4)	1.9 (0.5,3.2)	2.6 (1.0,4.2)
		Max	4.1 (2.1,6.1)	3.4 (1.5,5.2)	3.9 (1.9,5.8)	4.1 (2.1,6.1)	3.8 (1.9,5.7)	5.3 (3.0,7.6)
	Greece	Min	1.3 (0.7,2.0)	1.2 (0.6,1.8)	1.1 (0.5,1.7)	1.3 (0.6,1.9)	1.5 (0.8,2.3)	1.6 (0.9,2.4)
		Max	4.1 (2.4,5.9)	2.0 (0.8,3.2)	2.7 (1.3,4.2)	3.9 (2.2,5.6)	5.8 (3.7,7.8)	6.2 (4.1,8.4)
	Norway	Min	5.3 (4.4,6.1)	4.9 (4.0,5.7)	4.3 (3.5,5.0)	6.1 (5.2,7.0)	6.9 (5.9,7.8)	4.2 (3.4,4.9)
		Max	13.4 (11.5,15.3)	12.3 (10.4,14.1)	10.9 (9.1,12.6)	15.8 (13.7,17.9)	18.2 (16.0,20.4)	10.1 (8.6,11.7)
	Portugal	Min	1.3 (0.7,2.0)	NA	NA	NA	NA	1.4 (0.8,2.1)
		Max	2.3 (1.3,3.2)	1.4 (0.7,2.1)	2.1 (1.2,3.0)	2.3 (1.4,3.2)	2.6 (1.6,3.6)	3.1 (1.9,4.3)

The ILD category includes F-ILD; the F-ILD category includes IPF and non-IPF F-ILD; and the non-IPF F-ILD category includes SSc-ILD.

For the participating centres receiving referrals from other (satellite) centres, there was uncertainty over the most valid population to be used as denominator for incidence/prevalence estimates. To address this, both maximum and minimum estimates were obtained using as denominator, respectively, each centre's reference population and extended population (for the latter, the satellite centres' reference population was added). In Denmark and Finland there was a single participating centre, which searched a national or regional database (respectively) instead of the centre's own database. Therefore, the distinction between reference and extended population was not applicable, and only single crude and adjusted estimates were obtained (not minimum-maximum for each).

For convenience, the table shows the maximum range of estimates obtained in the analysis: minimum adjusted (by the corresponding PPV shown in Table 1) and maximum crude. For Denmark and Finland, the single adjusted and the single crude estimate are shown. Minimum adjusted incidences for all ILD subtypes in Portugal and for Scc-ILD in Belgium could not be obtained, so maximum adjusted values are reported instead.

Abbreviations: CI, confidence interval; F-ILD, fibrosing interstitial lung disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NA, not available; SSc-ILD, systemic sclerosis-associated interstitial lung disease; PPV, positive predictive value.

Table 3. Incidence (A) and prevalence (B) of progressive-fibrosing ILDs in each country, annually and for the study period

(A) Incidence per 10^5 person-years (95% CI)

		Study period	2014	2015	2016	2017	2018
Belgium	Min	5.8 (5.5,6.1)	4.6 (4.1,5.2)	5.6 (5.0,6.4)	5.7 (5.1,6.4)	6.9 (6.2,7.7)	6.5 (5.8,7.3)
	Max	13.7 (13.0,14.6)	12.0 (10.5,13.8)	12.8 (11.2,14.6)	13.7 (12.0,15.6)	15.9 (14.0,18.0)	14.5 (12.7,16.5)
Denmark	Min	8.5 (8.3,8.5)	8.5 (7.9,8.9)	9.1 (8.5,9.4)	8.8 (8.2,9.2)	8.0 (7.4,8.3)	8.3 (7.7,8.6)
	Max	14.4 (13.9,14.9)	14.3 (13.2,15.5)	15.3 (14.2,16.5)	15.0 (14.0,16.2)	13.4 (12.4,14.5)	14.0 (12.9,15.1)
Finland	Min	5.0 (4.5,4.5)	7.6 (6.3,7.5)	3.9 (3.0,4.1)	4.0 (3.1,4.2)	4.7 (3.7,4.9)	4.8 (3.8,5.0)
	Max	10.1 (8.8,11.6)	15.4 (12.0,19.9)	7.9 (5.5,11.2)	8.1 (5.7,11.5)	9.5 (6.9,13.1)	9.7 (7.1,13.4)
Greece	Min	2.1 (1.9,1.9)	1.3 (1.0,1.5)	2.0 (1.6,2.0)	2.3 (1.9,2.2)	2.7 (2.3,2.6)	2.3 (2.0,2.3)
	Max	5.2 (4.8,5.7)	5.1 (4.1,6.3)	4.5 (3.7,5.5)	4.8 (4.0,5.9)	6.6 (5.6,7.8)	5.0 (4.1,6.0)
Norway	Min	2.7 (2.5,2.9)	NA	2.7 (2.2,3.2)	3.6 (3.1,4.2)	2.4 (2.0,2.8)	2.1 (1.8,2.6)
	Max	6.8 (6.2,7.5)	NA	6.8 (5.6,8.3)	9.4 (7.9,11.1)	6.2 (5.1,7.7)	5.2 (4.2,6.4)
Portugal	Min	2.1 (1.9,2.9)	1.5 (1.2,2.5)	2.1 (1.7,3.2)	1.8 (1.5,2.8)	2.3 (1.9,3.4)	2.6 (2.2,3.6)
	Max	2.9 (2.6,3.2)	2.1 (1.6,2.8)	2.9 (2.3,3.6)	2.5 (2.0,3.3)	3.2 (2.5,3.9)	3.5 (2.9,4.3)

(B) Prevalence per 10^5 persons (95% CI)

		Study period	2014	2015	2016	2017	2018
Belgium	Min	16.7 (15.0,20.4)	13.5 (12.0,16.7)	15.7 (14.0,19.2)	17.2 (15.4,21.0)	18.2 (16.3,22.1)	19.5 (17.5,23.5)
	Max	65.3 (59.3,71.3)	52.4 (47.2,57.6)	56.2 (51.0,61.5)	70.1 (63.7,76.5)	73.8 (67.2,80.5)	78.0 (71.2,84.8)

		Study period	2014	2015	2016	2017	2018
Denmark	Min	25.3 (NE)	25.2 (NE)	27.1 (NE)	24.5 (NE)	23.2 (NE)	26.5 (NE)
	Max	40.4 (38.6,42.3)	39.9 (38.1,41.8)	43.3 (41.4,45.2)	39.3 (37.4,41.1)	37.1 (35.4,38.9)	42.6 (40.7,44.5)
Finland	Min	18.4 (14.2,22.4)	19.5 (15.1,23.5)	17.8 (13.6,21.7)	17.4 (13.3,21.3)	17.9 (13.7,21.8)	19.5 (15.1,23.5)
	Max	37.6 (31.5,43.7)	39.7 (33.4,46.0)	36.3 (30.4,42.3)	35.6 (29.7,41.5)	36.5 (30.6,42.5)	39.8 (33.5,46.0)
Greece	Min	5.4 (4.0,15.2)	4.3 (3.1,11.7)	4.2 (3.0,14.1)	5.3 (4.0,15.7)	6.2 (4.8,16.7)	6.9 (5.4,17.7)
	Max	21.5 (17.5,25.4)	17.3 (13.7,20.8)	16.1 (12.7,19.6)	21.1 (17.2,25.0)	25.5 (21.2,29.9)	27.4 (22.9,31.9)
Norway	Min	13.1 (11.7,14.2)	11.0 (9.7,12.1)	11.7 (10.4,12.8)	13.8 (12.4,15.0)	15.3 (13.8,16.5)	13.4 (12.1,14.6)
	Max	33.3 (30.4,36.3)	27.5 (24.8,30.3)	29.9 (27.0,32.8)	35.7 (32.7,38.8)	40.3 (37.0,43.5)	32.7 (30.0,35.5)
Portugal	Min	6.7 (5.3,10.3)	NA	NA	NA	NA	9.1 (7.4,10.3)
	Max	11.3 (9.2,13.4)	7.0 (5.4,8.6)	9.4 (7.5,11.2)	10.5 (8.6,12.5)	12.1 (10.0,14.2)	19.7 (16.6,22.8)

The incidence/prevalence in each country was extrapolated from the weighted mean percentage of progressive-fibrosing behaviour. To calculate this weighted mean percentage for a given country, (1) the number of cases of each non-IPF F-ILD subtype in the country was divided by the total number of non-IPF F-ILD cases, and the result was multiplied by the overall (considering all countries) mean percentage of progressive-fibrosing behaviour of the corresponding non-IPF F-ILD subtype; and (2) the result of step 1 for all non-IFP F-ILDs was summed. This way, the incidence/prevalence estimates obtained accounted for the distribution of the different non-IPF F-ILD subtypes in the country, and for their individual potential for progression. Weighted country mean percentages used were 37.9% (Belgium), 23.1% (Denmark), 25.6% (Finland), 31.2% (Greece), 30.6% (Norway) and 38.5% (Portugal).

For convenience, the table shows the maximum range of estimates obtained in the analysis: minimum adjusted (by the corresponding PPV shown in Table 1) and maximum crude. For Finland, the table shows the single adjusted and the single crude estimate available. Minimum adjusted incidences in Portugal could not be obtained, so maximum adjusted values are reported instead.

Abbreviations: CI, confidence interval; NA, not available; NE, not estimable; IPF, idiopathic pulmonary fibrosis; F-ILD, fibrosing interstitial lung disease; PPV, positive predictive value.