



Burden of Disease and Productivity Loss in the European Economic Area in Patients Affected by Fibrosing Interstitial Lung Disease

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ABSTRACT

Introduction: Progression of fibrosis in interstitial lung diseases (ILD) has been associated with poor prognosis, lower quality of life for patients and caregivers, and higher healthcare costs. This study estimated the burden of disease and productivity loss of progressively fibrosing ILD, focusing on progressive pulmonary fibrosis other than idiopathic pulmonary fibrosis (non-IPF PPF) and systemic sclerosis-associated ILD (SSc-ILD) in the European Economic Area (EEA).

Methods: An economic model was built to estimate the clinical burden of SSc-ILD and

non-IPF PPF. The model was based on published data on disease prevalence and disease burden (in terms of comorbidities, exacerbations, and deaths) as well as on productivity loss (in terms of sick days, early retirement, permanent disability, and job loss). Aggregate income loss was obtained by multiplying productivity loss by the median daily income in each country/area of investigation. A sensitivity analysis was performed to test the impact of the variability of the model assumptions.

Results: In the whole EEA, a total of 86,794 and 13,221 individuals were estimated to be affected by non-IPF PPF and SSc-ILD, respectively. Estimated annual sick days associated with the diseases were 3,952,604 and 672,172, early retirements were 23,174 and 5341, permanently disabled patients were 41,748 and 4037, and job

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losses were 19,789 and 2617 for non-IPF PPF and SSc-ILD, respectively. Annual exacerbations were estimated to be 22,401–31,181 and 1259–1753, while deaths were 5791–6171 and 572–638 in non-IPF PPF and SSc-ILD, respectively. The estimated annual aggregate income loss in EEA, accounting for losses due to annual sick days, early retirements, and permanently disabled patients, was €1433 million and €220 million in non-IPF PPF and SSc-ILD, respectively. The productivity loss due to job losses was €194 million and €26 million in non-IPF PPF and SSc-ILD, respectively. The main driver of aggregate income loss variability was the prevalence.

Conclusion: The impact of non-IPF PPF and SSc-ILD on society is definitely non-negligible. Actions to reduce the burden on our societies are highly needed.

Keywords: Disease burden; Income loss; Indirect costs; Productivity loss; Progressive fibrosing interstitial lung disease; Systemic sclerosis

Key Summary Points

Why carry out this study?

The clinical burden of ILD is becoming increasingly recognized. The progressive forms of ILDs have particularly been associated with worse prognosis, decreased quality of life, and increased healthcare resource use.

Adopting the hypothesis that measuring the impact of ILD on society would help in allocating the proper resources, we aimed to estimate the burden of disease and productivity loss of progressive pulmonary fibrosis other than idiopathic pulmonary fibrosis (non-IPF PPF) and systemic sclerosis-associated ILD (SSc-ILD) in the European Economic Area (EEA).

What was learned from the study?

Non-IPF PPF and SSc-ILD heavily affect society, as indirect costs in the EEA were estimated at approximately €1432 million and €220 million, respectively. Job losses were responsible for costs of approximately €194 million and €26 million in non-IPF PPF and SSc-ILD, respectively.

In conclusion, ILD is a significant economic burden for society. Beyond providing health and palliative care to patients, it is crucial to find solutions that help minimize the impact of the disease on productivity.

INTRODUCTION

Interstitial lung diseases (ILDs) include more than 200 parenchymal pulmonary disorders, which are mostly rare [1]. They display varying degrees of inflammation, fibrosis, or both, and a wide range of clinical courses and prognoses [2]. The progressive fibrosis of lung parenchyma is responsible for the progressive deterioration in lung function and respiratory symptoms [1] and is associated with poor prognosis [1, 3], lower quality of life for patients and caregivers [4], and higher healthcare costs [4, 5]. The clinical objectives of managing progressive ILD are to prevent lung function deterioration, exacerbations, and quality of life deterioration and to increase survival [4]. In 2022, new practice guidelines defined progressive pulmonary fibrosis as an ILD of known or unknown etiology other than idiopathic pulmonary fibrosis (IPF) that has radiological evidence of pulmonary fibrosis, with at least two of the following three criteria occurring within the past year with no alternative explanation: (a) worsening respiratory symptoms; (b) physiological evidence of disease progression; and (c) radiological evidence of disease progression [6]. These guidelines also mention that nintedanib is the only drug recommended for treating progressive pulmonary fibrosis (PPF) as the

phase III clinical trial showed a statistically significant reduction in disease progression and the adverse events are reversible with discontinuation of the medication.

According to Cottin and colleagues [1], ILDs may be categorized as idiopathic interstitial pneumonias (IIPs), autoimmune ILDs, hypersensitivity pneumonitis, sarcoidosis, and other ILDs. As part of autoimmune ILDs, systemic sclerosis (SSc) associated with ILD (SSc-ILD) is of particular interest as it is an autoreactive immune connective tissue disease characterized by inflammation, immune dysregulation, microvascular damage, and progressive fibrosis of the skin and internal organs. SSc mostly affects women, and its peak onset is at 30–70 years of age. Thus, this represents a population whose productivity can be affected by the disease [1]. ILD in SSc presents early in the disease course [7] and impacts both survival and quality of life [8, 9].

Within the group of fibrosing ILDs (F-ILD), around 30% of them can become progressive. Results of a multinational study showed that some subtypes such as hypersensitivity pneumonitis are more prone to progression while others like sarcoidosis are unlikely to be progressive. In that study, the rate of progression of SSc-ILD was 37% [2].

While scientific knowledge of the clinical impact of ILD on patient outcomes has increased a lot in recent years, only some studies have calculated the direct costs borne by the national healthcare systems in Europe due to progressive pulmonary fibrosis other than idiopathic pulmonary fibrosis (non-IPF PPF) [10, 11] and SSc-ILD [12]. Indirect costs (i.e., the productivity loss) should also be taken into consideration to give a more complete picture of the disease burden.

Our study aimed to estimate the productivity loss and burden of two types of ILD, namely non-IPF PPF and SSc-ILD.

METHODS

A simple economic model was built to estimate the productivity loss of SSc-ILD and non-IPF PPF in the European Economic Area (EEA). The

model was based on published data on disease prevalence and impact, and on the region-specific economic value of labor.

Desktop Research

In July 2022, a medical literature search was conducted using PubMed for data about epidemiology and work productivity losses associated with non-IPF PPF (and SSc-ILD in particular). The keywords used for epidemiology data were “epidemiology”, “ILD”, “incidence”, “interstitial lung disease”, “prevalence”, and “pulmonary fibrosis”. The keywords used for productivity losses data were “burden of disease”, “disability”, “early retirement”, “economic impact”, “interstitial lung disease”, “job loss”, “productivity loss”, and “sick days”. Only articles reporting on European data were selected. Only articles in English with abstract available were considered. Data coming from institutional documents (gray literature) were used to determine the monetary value of working days in the EEA.

Ethical Considerations

This study is based on previously published data. No ethics committee approval was required for this study.

Input Data

Population

A prevalence of 27.9 per 10⁵ for non-IPF PPF and of 4.25 per 10⁵ for SSc-ILD was used as base case in the model. Furthermore, an incidence of 6.50 per 10⁵ and 0.75 per 10⁵ was used for non-IPF PPF and SSc-ILD, respectively. The data come from a retrospective study conducted in six European countries as the average of the minimum and maximum values for the overall countries' value (mean of the six countries included) [2].

Affected population was calculated by applying the aforementioned prevalence and incidence rates to the working-age population (assumed from 20 to 64 years) of each country/area from European and international statistics

institutions [13]. It was assumed that the population below 20 years old and above 64 years old do not work, thereby productivity loss due to the disease in these population groups has been considered negligible in this paper. For comorbidities, exacerbations, and deaths, the whole adult population (≥ 18 years) was considered.

Burden of Disease

Burden of disease measures the impact of living in a condition of illness. Here, we measure it by presenting data on comorbidities, exacerbations, and deaths due to both non-IPF PPF and SSc-ILD.

Comorbidities

Percentages of comorbidities were extracted from DELPHI studies conducted in a selection of European countries [4, 14] and are presented in Supplementary Materials (Table s1). They were multiplied by the relative affected adult population to calculate the estimated number of patients for each specific comorbidity.

Exacerbations

We assumed that only patients with a progressing form of ILD could experience exacerbations. We used the rate of disease progression from the PERSEIDS study for SSc-ILD to calculate the number of patients with progressive

SSc-ILD [2]. Given the rate of exacerbation depends on whether patients with non-IPF PPF are treated, and nintedanib is the only treatment that has been granted marketing authorization for non-IPF PPF, we considered placebo and nintedanib-treated data from the INBUILD phase 3 trial [15]. Table 1 shows the methodology to calculate the yearly exacerbation rate in the EEA, which was then multiplied by the affected adult population (ranging between the two extreme assumptions of all patients/no patient treated with nintedanib) to afford an estimated number of patients with exacerbations.

Deaths

The same as for exacerbations, death rate depends on whether patients are treated. Percentages were multiplied by the relative affected adult population (assuming that first all patients were treated with nintedanib and then all with placebo) to get an estimated number of deaths caused by non-IPF PPF and SSc-ILD in the INBUILD [15] and SENSICIS trials [16]. Annual death rate in untreated patients is 5.1% for patients with non-IPF PPF and 3.1% for patients with SSc-ILD, while it is 4.8% and 3.5% in treated patients for non-IPF PPF and SSc-ILD, respectively.

Income

Daily median income was calculated by dividing annual income [17] by the number of working days specific for EU27, UK, and EFTA (assumed to have the same working days as the EU [18]). Income was expressed in terms of euros (€).

Annual and daily median net incomes for each of the countries analyzed are reported in Table 2.

The daily median income was about €78 in the whole EEA, but with huge variations, ranging from €19 in Romania to €170 in Switzerland.

Productivity Loss

The economic impact in terms of sick days, early retirement, permanent disability, and job loss was estimated as described in Supplementary Materials (Table s2).

Table 1 Methodology to calculate the yearly exacerbation rate in the European Economic Area [15]

	Nintedanib	Placebo
(A) Total exacerbations	98	136
(B) Median follow-up time in months	19	19
(C) Median follow-up time in years (B/12)	1.58	1.58
(D) Patients at beginning of trial	332	331
(E) Total person-year (C × D)	526	524
Exacerbation rate (A/E)	0.19	0.26

Table 2 Annual and daily median net incomes in EEA

Country/area	Annual median income (€)	Daily median income (€)
EU27	18,296	72
Austria	27,428	109
Belgium	25,739	102
Bulgaria	5157	20
Croatia	8061	32
Cyprus	16,686	66
Czechia	10,625	42
Denmark	32,088	127
Estonia	12,623	50
Finland	25,456	101
France	22,680	90
Germany	25,015	99
Greece	8752	35
Hungary	6614	26
Ireland	28,130	111
Italy	17,532	69
Latvia	9437	37
Lithuania	9669	38
Luxembourg	37,844	150
Malta	16,240	64
Netherlands	28,441	113
Poland	8295	33
Portugal	10,800	43
Romania	4832	19
Slovakia	8703	34
Slovenia	15,415	61
Spain	15,892	63
Sweden	25,498	101
EFTA	41,070 ^a	163
Iceland	39,918	158
Liechtenstein	NA	NA

Table 2 continued

Country/area	Annual median income (€)	Daily median income (€)
Norway	40,241	159
Switzerland	43,051	170
UK	21,464	85
EU27 + EFTA	19,562 ^a	77
EEA (EU27 + EFTA + UK)	19,623 ^a	78

Data obtained from Eurostat 2021 (exceptions: Luxembourg, Malta, Portugal, Slovakia, Norway, Switzerland, and EU27 2020; Iceland and UK: 2018) [17] and National Central Banks, 2021 [18]

EEA European Economic Area, *EFTA* European Free Trade Association, *EU27* European Union including 27 countries (from 2020), *NA* not available, *Non-IPF PPF* non-idiopathic pulmonary fibrosis progressive pulmonary fibrosis, *SSc-ILD* systemic sclerosis-associated interstitial lung disease, *UK* United Kingdom

^aMean of median incomes

Main sources of data were from DELPHI studies conducted in a selection of European countries [4, 14]. Other retrieved publications provided information on some aspects of productivity loss, and were used in the sensitivity analyses.

Aggregate Income Loss

Aggregate income loss is an economic measure of the potential loss, in terms of economic productivity, that non-IPF PPF and SSc-ILD create in society, in particular the working class. The estimation is based on the appropriate combination of different variables affecting the working-age population on a yearly basis, considering the value loss due to sick days, early retirement, and permanent disability.

Total sick days were obtained by multiplying the affected population by mean sick days per patient, which in turn was the result of the number of sick leaves per year multiplied by duration of the sick leave in days. To obtain the economic value to society, total sick days were

then multiplied by the median daily income in each country/area of investigation, computed by dividing total annual income by working days [18] in a year.

Productivity loss due to early retirement was obtained by subtracting the affected incident population from the affected prevalent one and multiplying the result by the median annual income; the affected incident population is multiplied by half median annual income, thus assuming that the retirement happened on average during the middle of the year. Finally, productivity loss due to early retirement was computed as the sum of the two aforementioned figures.

Analogously, productivity loss due to permanent disability was obtained by first subtracting the affected incident population from the affected prevalent one and multiplying the result by the median annual income. To obtain total productivity loss due permanent disability, this figure was then added to the product of the affected incident population and half median annual income, again assuming that the event happened on average during the middle of the year.

Finally, aggregate annual income loss was computed by summing all the items obtained above. This cost is an estimation of the productivity loss that the disease inflicts on society in a year, in particular by lost added value for the aggregate economy.

Job Loss

Productivity loss due to job loss was left out of the aggregate result computation to prevent the likely risk of overlapping calculations which may lead to an overestimation of the total economic loss.

As above, productivity loss due to job loss was obtained by first subtracting the affected incident population from the affected prevalent one and multiplying the result by the median annual income. To obtain total productivity loss due to job loss, this figure was then added to the product of the affected incident population and half median annual income, again assuming that the event (i.e., being unemployed) happened on average during the middle of the year.

Sensitivity Analyses

A one-way sensitivity analysis was performed to evaluate the sensitivity of the aggregate income lost to each parameter. A specific variable was varied one at a time while maintaining all others fixed to test its impact on aggregate income lost. Parameters of prevalence and incidence were varied following their minimum and maximum value retrieved in the literature. All minimum and maximum values were taken from Hilberg et al. [2], except for the minimum value of non-IPF PPF prevalence, which was taken from Nasser et al. [19] (Supplementary Materials, Table s3). Cost for annual sick days, early retirement, and permanent disability varied by $\pm 20\%$.

While Cottin et al. [20] found that 20.7% of patients with SSc-ILD had sick leave daily allowances, it was not possible to input this information into our sensitivity analysis to calculate productivity loss.

RESULTS

Base Case

Affected Population

In the whole EEA, a total of 86,794 individuals were estimated to be affected by non-IPF PPF, and 13,221 by SSc-ILD. Germany, being the country with the greatest number of adult patients, accounts for the most elevated number of patients, i.e., an estimated 13,824 and 2106 for non-IPF PPF and SSc-ILD, respectively.

It was calculated that every year, non-IPF PPF determined an estimated 3,952,604 sick days in the whole EEA. Prevalent retired, permanently disabled, and unemployed patients add up to 23,174, 41,748, and 19,789 individuals, respectively. With regards to SSc-ILD, 672,172 sick days were estimated in the whole EEA and prevalent annual retired patients, permanent disabled patients, and unemployed patients added up to 5341, 4037, and 2617 individuals, respectively. Overall results are presented in Table 3 and details per country can be found in Supplementary Materials, Tables s4 and s5.

Table 3 Estimation of the total number of individuals affected by non-IPF PPF and SSc-ILD and number of annual events of sick days, affected prevalent individuals regarding early retirements, permanent disability, and job loss

Country/area	Affected population	Sick days (annual)	Patients retired early (annual)	Patients permanently disabled (annual)	Patients who lost their job (annual)
Non-IPF PPF					
EU27	73,535	3,348,800	19,634	35,371	16,766
EFTA	2441	111,167	652	1174	557
EEA (EU27 + EFTA + UK)	86,794	3,952,604	23,174	41,748	19,789
SSc-ILD					
EU27	11,202	569,490	4525	3420	2217
EFTA	372	18,905	150	114	74
EEA (EU27 + EFTA + UK)	13,221	672,172	5341	4037	2617

Working-age population figures, on which calculations were based, are from Eurostat, 2021 [21] (except for UK: last available data 2019)

EEA European Economic Area, EFTA European Free Trade Association, EU27 European Union including 27 countries (from 2020), Non-IPF PPF non-idiopathic pulmonary fibrosis progressive pulmonary fibrosis, SSc-ILD systemic sclerosis-associated interstitial lung disease, UK United Kingdom

Burden of Disease

Exacerbations and Deaths

The estimated annual number of patients who directly experienced an exacerbation or death due to non-IPF PPF is shown in Table 4. Between 22,401 and 31,181 patients with non-IPF PPF are estimated to have had an exacerbation and 5791–6171 patients with non-IPF PPF are estimated to have died across Europe. Between 1259 and 1753 patients with SSc-ILD are estimated to have had an exacerbation and 572–638 patients with SSc-ILD are estimated to have died across Europe. Details per country can be found in Supplementary Materials, Tables s6 and s7.

Comorbidities

Table 5 shows the estimated total number of patients affected by each specific comorbidity in the EEA both for SSc-ILD and non-IPF PPF. More than 30,000 patients with non-IPF PPF were estimated to suffer from fatigue, gastroesophageal reflux disease, pulmonary infection and depression and more than 4,000 patients

with SSc-ILD to suffer from gastroesophageal reflux disease, fatigue, pulmonary hypertension and depression across Europe.

Productivity Loss

Aggregate Income Loss

Table 6 presents productivity loss figures for non-IPF PPF and SSc-ILD. In the EEA, the annual aggregate income loss estimated for non-IPF PPF was €1,432,657,033, with the loss due to permanently disabled patients being the most burdensome among the factors considered (€723,809,823). Regarding SSc-ILD, the annual aggregate income loss was estimated to be €220,009,339, with the loss due to early retired patients being the most burdensome among the factors considered (€95,556,241). Tables s8 and s9 in Supplementary Materials provide data per country.

Job Loss

Table 7 shows an estimation of the productivity loss due to people losing their job as a

Table 4 Estimated annual number of patients who directly experienced an exacerbation or death due to non-IPF PPF and SSc-ILD

Country	Exacerbations all treated	Exacerbations all placebo	Deaths all treated	Deaths all placebo
Non-IPF PPF				
EU27	19,038	26,500	4921	5245
EFTA	609	848	157	168
EEA (EU27 + EFTA + UK)	22,401	31,181	5791	6171
SSc-ILD				
EU27	1070	1490	542	486
EFTA	34	48	17	16
EEA (EU27 + EFTA + UK)	1259	1753	638	572

EEA European Economic Area, *EFTA* European Free Trade Association, *EU27* European Union including 27 countries (from 2020), *Non-IPF PPF* non-idiopathic pulmonary fibrosis progressive pulmonary fibrosis, *UK* United Kingdom

consequence of both non-IPF PPF and SSc-ILD. These results are not part of the aggregate income loss above so that any possible double counting is ruled out. The estimated productivity loss due to job losses for both diseases is €219,841,167 (88.3% of which non-IPF PPF).

Sensitivity Analyses

Results of the deterministic sensitivity analyses are summarized as a tornado diagram to highlight the variables that had the most impact on aggregate income lost. The input providing the highest variability with respect to the base case for both non-IPF PPF (Fig. 1) and SSc-ILD (Fig. 2) was the prevalence.

DISCUSSION

Our results show that the burden of non-IPF PPF and SSc-ILD on society is significant in Europe. It was estimated that 86,794 patients with non-IPF PPF and 13,221 patients with SSc-ILD were living in Europe. While the prognosis of patients with non-IPF PPF and patients with SSc-ILD is poor, comorbidities, sick leaves, permanent disability, and early retirement contribute to the disease burden, not only for the

healthcare systems but also on society overall. We estimated the aggregated income loss to be €1433 million for non-IPF PPF and €220 million for SSc-ILD. Permanent disability and early retirement were the most important source of aggregate income loss, representing around half and 43% of costs for non-IPF PPF and SSc-ILD, respectively. Additionally, job losses resulting from the diseases were estimated to cost €194 million for non-IPF PPF and €26 million for SSc-ILD.

There are very few economic studies around the burden of PPF and SSc-ILD. A cost-effectiveness analysis about non-IPF PPF was conducted in the Netherlands by Westerink and colleagues [22], whose model was based on data coming from the INBUILD trial [23]. It showed that the societal costs per patient, including round trip to hospital, general practitioner, and specialist, healthcare worker/domestic support at home, and sick days, were in the range €1627–2403, with the lowest cost associated with patients treated with nintedanib. These figures are much lower than those calculated in our study, as we found that the estimated annual cost per patient was €16,506. However, it is difficult to compare such costs since the methodologies used are different, as were the

Table 5 Estimated total number of patients affected by each specific comorbidity in the EEA both for SSc-ILD and non-IPF PPF

	Non-IPF PPF	SSc- ILD
Respiratory function		
Pulmonary infection	35,206	3807
Chronic bronchitis	9372	897
Asthma	2764	366
Obstructive sleep apnea	17,062	494
Lung cancer	5647	458
Pulmonary embolism	4686	421
Pulmonary hypertension	23,791	4338
Chronic obstructive pulmonary disease	9132	604
Emphysema	11,775	604
Cardiovascular function		
Coronary artery disease (excluding MI)	14,900	1080
Heart failure	16,582	1354
Atrial fibrillation	14,179	1043
Myocardial infarction	4566	183
Deep vein thrombosis	3364	458
Cerebrovascular disease	3845	238
Metabolic disease		
Diabetes	19,586	1592
Obesity	17,303	1062
Gastroesophageal reflux disease	35,086	9848
Other diseases		
Depression	32,683	4137
Osteoporosis	24,392	3478
Cataracts	12,256	1354

Table 5 continued

	Non-IPF PPF	SSc- ILD
Fatigue	54,792	7377

EEA European Economic Area, *EFTA* European Free Trade Association, *EU27* European Union including 27 countries (from 2020), *MI* myocardial infarction, *Non-IPF PPF* non-idiopathic pulmonary fibrosis progressive pulmonary fibrosis, *SSc-ILD* systemic sclerosis-associated interstitial lung disease, *UK* United Kingdom

nature of costs. In the Westerink study, costs related to early retirements, permanent disability, and job losses were not included.

Another study conducted in France assessed the disease burden associated with progressive fibrosis. In this study, total median annual costs per patient were €18,362, including all hospitalizations, specific laboratory tests, imaging and treatment, and specific medical and paramedical costs but excluding sick leave, daily allowances, and transport costs [19]. While these costs are similar to those in Westerink et al.'s study, as our study focuses on productivity losses, comparison with the two aforementioned studies is irrelevant.

SSc is generally diagnosed during working age (mean 46 years) [24] and associated ILD arises within the first 5 years after diagnosis [25]. Therefore, in addition to increased direct costs, a huge economic burden is expected due to the loss of productivity. A small US claims data analysis performed by Zhou et al. [26] evaluated sick days and the relevant costs of 52 insured and employed patients with SSc-ILD compared with healthy controls. In the 6 months immediately following the diagnosis, they found that the sick days per patient were 23.2. Hypothesizing a comparison with our results by doubling the aforementioned figures to convert to 12-month values, we obtain that 46.4 annual sick days per patient. These data are very similar to the assumptions of our study (50.8 annual sick days). Nonetheless, comparing US to EEA productivity loss costs is irrelevant, as the median income in the USA

Table 6 Estimated productivity loss and aggregate income loss due to non-IPF PPF

Country	Annual sick days loss (€)	Annual early retired patients' loss (€)	Annual permanent disabled patients' loss (€)	Annual aggregate income loss (€)
Non-IPF PPF				
EU27	242,561,148	317,380,712	571,768,296	1,131,710,156
EFTA	18,074,923	23,656,320	42,589,590	84,320,833
EEA (EU27 + EFTA + UK)	307,067,510	401,779,700	723,809,823	1,432,657,033
SSc-ILD				
EU 27	41,249,447	75,480,148	57,046,928	173,776,523
EFTA	3,073,812	5,606,055	4,271,280	12,951,147
EEA (EU27 + EFTA + UK)	52,219,292	95,556,241	72,233,807	220,009,339

EEA European Economic Area, EFTA European Free Trade Association, EU27 European Union including 27 countries (from 2020), Non-IPF PPF non-idiopathic pulmonary fibrosis progressive pulmonary fibrosis, UK United Kingdom

[27] is 3-fold than that found in the EEA [17, 18].

The first follow-up European study to evaluate indirect costs associated with SSc-ILD was the study by Knarborg and colleagues [12] based on a Danish national patients registry. They evaluated the excess direct healthcare costs and indirect costs associated with SSc in patients with and without ILD 5 years before and 4 years after the diagnosis, finding reduced mean annual income per case of €9763 in SSc-ILD cohort compared with €6604 in the non-ILD SSc cohort. Foregone earnings were calculated not only for working cases but also for the entire Danish SSc population. Disability pension was the key driver of excess public transfer income in both cohorts after diagnosis. In our SSc-ILD study cohort, around one-third of annual income loss was due to permanent disabled patients' loss, which is a lower proportion than that found in our non-IPF PPF cohort, maybe as a result of the slow progression rate of fibrosis in SSc-ILD [1].

Antifibrotics were already used in IPF when the INBUILD trial [23], which reported its efficacy also in non-IPF PPF, was published, thus resulting in a paradigm shift toward an en bloc approach to antifibrotic therapy [6]. Pirfenidone is also an antifibrotic agent, with anti-

inflammatory, antioxidative, and antiproliferative properties. It was recommended for treatment of IPF in prior guidelines. However, the official ATS/ERS/JRS/ALAT Clinical Practice Guideline [6] found that data about the use of pirfenidone were insufficient to give a recommendation for its use in non-IPF PPF, as two randomized clinical trials with small sample sizes were analyzed [28, 29], one of which was terminated early as a result of futility triggered by slow recruitment [28].

Dyspnea, cough, and fatigue are the most common symptoms of non-IPF PPF and heavily affect health-related quality of life (HRQoL) [30]. Nintedanib proved to be able to significantly reduce the worsening of cough and dyspnea in patients with non-IPF PPF [31]. In fact, nintedanib had a statistically [32] and clinically [33] meaningful impact on HRQoL on the cough domain score of Living with Pulmonary Fibrosis (L-PF) questionnaire administered to patients with non-IPF PPF recruited in the INBUILD trial [15].

In addition to the disease-modifying drugs, a supportive care program should also be offered to patients in order to meet their needs and relieve the disease burden [34, 35]. The early diagnosis and management of the progressive behavior of the disease is particularly important

Table 7 Estimation of the productivity loss due to people losing their job as a consequence of both non-IPF PPF and SSc-ILD

Country	Job loss due to non-IPF PPF (€)	Job loss due to SSc-ILD (€)
EU27	153,375,368	20,281,116
Austria	4,799,900	630,844
Belgium	5,521,016	733,562
Bulgaria	672,989	87,669
Croatia	616,667	80,610
Cyprus	292,005	41,715
Czechia	2,140,938	281,563
Denmark	3,449,460	449,232
Estonia	309,264	44,181
Finland	2,520,144	330,928
France	27,057,240	3,572,100
Germany	39,423,640	5,215,628
Greece	1,728,520	227,552
Hungary	1,230,204	162,043
Ireland	2,630,155	351,625
Italy	19,407,924	2,568,438
Latvia	330,295	42,467
Lithuania	517,292	67,683
Luxembourg	491,972	56,766
Malta	170,520	24,360
Netherlands	9,300,207	1,222,963
Poland	6,100,973	804,615
Portugal	2,084,400	275,400
Romania	1,758,848	231,936
Slovakia	939,924	126,194
Slovenia	616,600	84,783
Spain	14,572,964	1,922,932
Sweden	4,768,126	624,701
EFTA	11,437,995	1,519,590
Iceland	279,426	39,918

Table 7 continued

Country	Job loss due to non-IPF PPF (€)	Job loss due to SSc-ILD (€)
Liechtenstein	NA	NA
Norway	4,084,462	543,254
Switzerland	7,275,619	968,648
UK	26,465,112	3,498,632
EU27 + EFTA	169,436,840	22,408,347
EEA (EU27 + EFTA + UK)	194,163,923	25,677,244

EEA European Economic Area, *EFTA* European Free Trade Association, *EU27* European Union including 27 countries (from 2020), *NA* not available, *Non-IPF PPF* non-idiopathic pulmonary fibrosis progressive pulmonary fibrosis, *SSc-ILD* systemic sclerosis-associated interstitial lung disease, *UK* United Kingdom

as it may be able to prevent the worsening of the quality of life, thus reducing the burden of the disease [34].

These measures are underused in Europe and generally accessed only at the final stages of the disease, despite carrying the potential to reduce symptom burden [36]. One of the reasons is that they are too often called “palliative care” and such terms often make patients perceive themselves as “doomed” [35]. Therefore, a comprehensive support strategy, generally indicated as “holistic care”, able not only to slow down the progression of the disease but also to offer supportive measures, symptom relief, and end-of-life care [34], has emerged in the last decade as an unmet need for patients affected by non-IPF PPF.

In particular, supportive measures include support groups, both nurse-led and among peers, pulmonary rehabilitation, and supplemental oxygen. Also education programs, where attended, have received the appreciation of patients [34]. In the BUILDup study [4], most panelists agreed that progressive fibrosing ILDs affect caregivers’ quality of life in terms of sleep and health, daily activities, emotional well-being, social life, and finances. As a result of

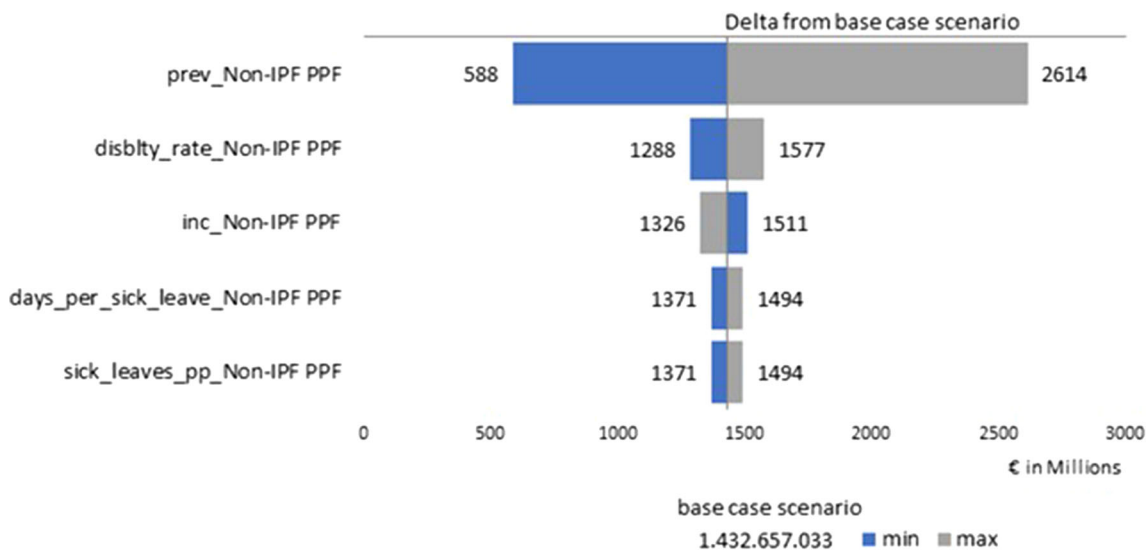


Fig. 1 Tornado diagram about the deterministic sensitivity analysis for non-IPF PPF. *Non-IPF PPF* non-idiopathic pulmonary fibrosis progressive pulmonary fibrosis

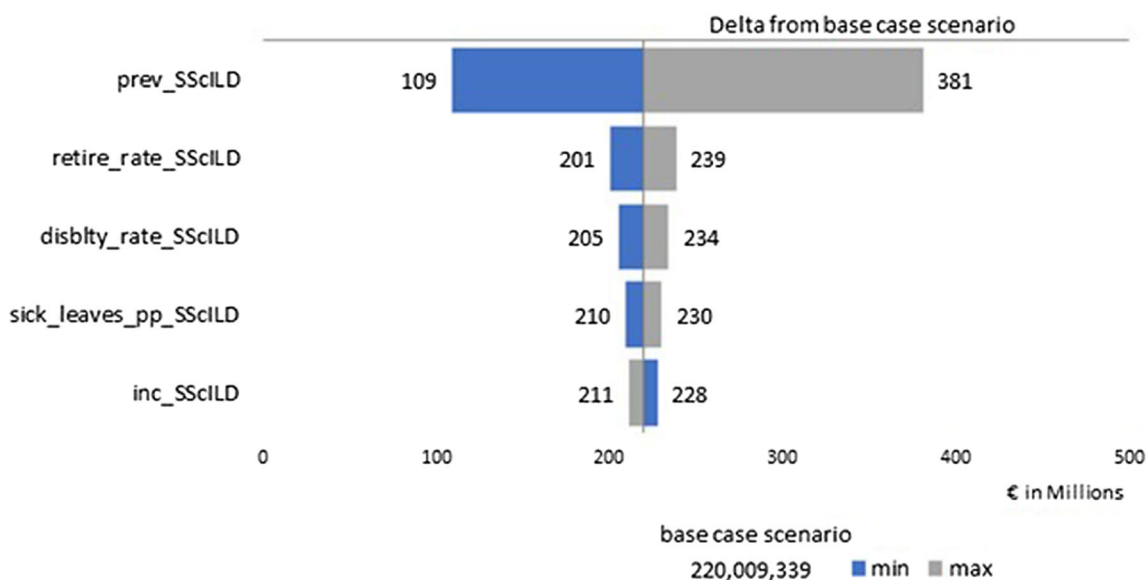


Fig. 2 Tornado diagram about the deterministic sensitivity analysis for SSc-ILD. *SSc-ILD* systemic sclerosis-associated interstitial lung disease

substantial psychological burden carried by caregivers, the need for emotional and educational support is apparent [35]. However, both for emotional and educational support groups, the impact in the long-term on well-being is still to be demonstrated. Pulmonary rehabilitation proved to be able to significantly increase exercise capacity, quality of life, and dyspnea in

the short term, but again data about the long term are lacking, even though the gains in quality of life seem to be preserved [34]. Supplemental oxygen is recommended by the official ATS/ERS/JRS/ALAT Clinical Practice Guideline [6] in patients with hypoxia, but few data support these recommendations [34].

Finally, end-of-life care means facing the conversation about end-of life decisions, in accordance with patient's preference and religious beliefs. As a result of the frequent avoidance of such a conversation, even though the majority of patients prefer to die at home, most of them actually die in the hospital [34].

In a review by van Manen and colleagues about IPF [37], a comprehensive program was summarized as the "ABCDE of IPF care", and then adapted by Kreuter et al. [35] to ILD care in general, i.e., "Assessing patients' needs; Backing patients by giving information and support; delivering Comfort care by focusing on treating symptoms and taking into account Comorbidities; striving to prolong life by Disease modification; helping and preparing patients and their caregivers for the eventual End-of-life events that are likely to occur". Besides, our study shows a significant proportion of patients with SSc-ILD and patients with non-IPF PPF were estimated to have fatigue or depression. A Greek study reported that depression was indirectly associated with disease severity, symptom burden, and quality of life in patients with IPF, reinforcing the need for mental support for patients with ILD [38].

In Europe, surveys conducted in European countries among healthcare professionals (HCPs) and patients with IPF and non-IPF PPF showed that less than 50% of patients had access to pulmonary rehabilitation, maybe as a result of incomplete reimbursements, unawareness, and physical distance issues [36]. In addition, as already reported in the literature, patients and their caregivers feel the need for better emotional and psychological support [36], but reimbursement and access to psychologists for this type of patients are still restricted. Therefore, the support groups mentioned above are the best alternative and have been shown to be appreciated by patients. In addition, the need for educational activities and active involvement of patients in the development of treatment plans emerged from these surveys [36].

Even though the course of non-IPF PPF is unpredictable, supportive care should be offered early, as it is able to partly relieve the disease burden [35]. Brereton and colleagues, who

analyzed several models of palliative care life-limiting illnesses, found that models of palliative care show several benefits for patients and caregivers and just few disadvantages, but the final conclusion about the cost-effectiveness of palliative care cannot be drawn because of the heterogeneity of diseases and strategies of palliative care considered [39]. We speculate that an improved state of health may reduce sick days and the relevant productivity loss.

In the future, novel approaches should be taken to diagnose ILDs early on or to prevent or limit their progression, ultimately limiting the burden on healthcare systems and societies. In the field of precision medicine, biomarkers at an acceptable cost could provide actionable information to clinicians for instance regarding disease activity or the need for treatment modification [40].

Our study has some limitations. First of all, as evidenced by Hilberg and colleagues [2], prevalence and incidence estimates about ILDs are highly variable, both according to the type of ILD considered and among European countries. Besides, in our study we used the mean of several countries and therefore did not reflect country variations or any potential fluctuation in prevalence with age. The uncertainty about the economic impact is the direct consequence of the uncertainty about epidemiological data. In our sensitivity analysis, disease prevalence is the factor that impacts aggregate income loss estimates the most. Given the large range of prevalence used in the sensitivity analysis based on a multicountry epidemiology study, it is likely that the actual aggregate income loss falls within that range.

Similarly, we applied data from BUILDup studies, which were based on opinions of European experts gathered and elaborated thanks to the DELPHI methods, by using averages [4, 14]. However, it is very likely that differences among countries exist, as reported about another respiratory disease, i.e., chronic obstructive pulmonary disease (COPD). In fact, in a systematic review conducted in some European countries [41], indirect costs varied greatly, as costs of work productivity loss ranged from €5735 (Germany) to €998 (Greece) and early retirement cost varied €19,031 (Germany)

to €3695 (Sweden). Besides, as BUILDup was based on expert opinions and not from patients themselves, productivity loss data should be taken with caution, and more research on this topic should be done.

We used the comorbidity data from BUILDup studies and not an average of different real-world evidence studies, which presents limitations. In the BUILDup study on PPF, the most prevalent comorbidities were fatigue (45.6%), pulmonary infection (29.3%), gastroesophageal reflux disease (29.2%), depression (27.2%), osteoporosis (20.3%), and pulmonary hypertension (19.8%) [4]. In Nasser et al.'s study in France, the most prevalent diseases were arterial hypertension (63.8%), gastroesophageal reflux disease (55.4%), cardiac arrhythmias (21.9%), depression (20.5%), and congestive heart failure (20.0%) [19]. While there is variability between studies, it seems our assumptions do not overestimate the high level of comorbidities in patients with ILD.

Our study excluded direct costs. Direct costs typically include hospitalizations such as for exacerbations, visits to health professionals, or medication. This type of information is not available in a several European countries and costs do not always follow the level of citizens income, making estimations difficult. Besides, some country healthcare systems can be composed of multiple financing systems and calculations of direct costs can differ across countries, some including value-added tax and others not.

We assumed in our model that patients with non-progressive SSc-ILD do not present exacerbations. As exacerbations are characterized by acute, clinically significant respiratory deteriorations, our assumption is valid for modeling disease burden and at worst underestimate the burden of disease. Besides, we assumed that 37% of patients with SSc-ILD are progressive, which was based on patient file review [2]. This is comparable to Wijsenbeek et al.'s study that shows that 31% of patients with SSc-ILD have progressive disease [3].

Other limitations include the fact that exacerbation rates and mortality with or without treatment are based on clinical trial data and not based on European real-world evidence over a longer follow-up period. While this

might affect our results overall, we assumed this approach to be appropriate enough for modelling purposes.

Finally, our study relies on few articles assessing the epidemiology and the societal burden of ILD. Although we conducted a sensitivity analysis to reflect potential variations in assumptions, more investigation is needed on productivity loss for patients with ILD.

CONCLUSION

Despite the limitations and possible biases about indirect costs of non-IPF PPF and SSc-ILD in the EEA, the results of our present study point towards a unique direction, i.e., that the impact of non-IPF PPF and SSc-ILD on society is definitely non-negligible, as in the EEA it is estimated at €1,432,657,033 and €220,009,339, respectively. Job losses are responsible for estimated costs of €194,163,923 and €25,677,244 in non-IPF PPF and SSc-ILD, respectively. It seems reasonable to undertake actions to reduce the burden on our societies.

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Declarations

Conflict of Interest. This manuscript is supported and funded by Boehringer Ingelheim. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors did not receive payment related to the development of the manuscript. Stephane Souillard and Pedro Pinheiro Martins are employees of Boehringer Ingelheim. Boehringer Ingelheim compensated AdRes HE&OR to do the analysis. Anders Lokke, Luca Castello, and Ole Hilberg have nothing to disclose.

Ethical Approval. This study is based on previously published data. No ethics committee approval was required for this study.

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