ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASE

Dynamics in diagnoses and pharmacotherapy before and after diagnosing idiopathic pulmonary fibrosis

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is a well-characterised interstitial lung disease. Typically, IPF diagnosis is delayed due to nonspecific symptoms, but can also be delayed due to treatment attempts on false indication or due to treatment targeting common comorbidities. This observational study aimed to assess the dynamics in the medication and diagnosis patterns in the period before and after an IPF diagnosis.

Methods: We identified all Danish patients with IPF between 2002 and 2017. We evaluated new and ongoing drug treatments and incident diagnoses 36 months before and 12 months after an IPF diagnosis by use of Danish nationwide registries. To aid interpretation, 10 random controls were recruited for each case.

Results: A total of 650 IPF patients were identified (median age 73 years (interquartile range 65–78), 70.3% males). Prior to the IPF diagnosis, the most prevalent diagnoses were dyspnoea and non-IPF interstitial lung diseases. For drug use, IPF patients had higher initiation rates for antibiotics, oral corticosteroids and mucolytics. In terms of drug volume, IPF patients used more respiratory drugs, antibiotics, immunosuppressants, corticosteroids, proton pump inhibitors, benzodiazepines and opium alkaloids within the 6 months preceding their IPF diagnosis, compared to the controls. Overall drug use decreased after an IPF diagnosis, mainly due to a reduced glucocorticoid and cardiovascular drug use.

Conclusion: Among IPF patients, an increased drug use was observed for diagnoses with symptoms overlapping those of IPF, particularly this was observed during the last 6 months before an IPF diagnosis. This emphasises the need for an increased IPF awareness.

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Introduction

Among the interstitial lung diseases (ILD), idiopathic pulmonary fibrosis (IPF) differs from all other ILD subtypes by its progressive pulmonary fibrosis and worse prognosis [1–3]. Except for two highly targeted antifibrotic drugs, pirfenidone and nintedanib, no pharmacological treatment has proven effective to IPF [2, 4, 5]. Usually the early symptoms of IPF progress over months to years with a diagnostic delay of up to 2–5 years [6–8], as IPF often is confused with more common diagnoses such as heart failure, gastroesophageal reflux or COPD [2, 9]. Treatment attempts for conditions similar to IPF are an independent risk factor for a delayed IPF diagnosis [10]. Incorrect initial diagnoses and additional diagnostic tests uncovering other diseases may lead to an increased drug use among IPF patients.

When the IPF diagnosis is established at a specialist centre, medication prescribed on a false indication should be discontinued [11]. On the other hand, IPF is associated with comorbidities such as arrhythmia, chronic heart failure, pulmonary hypertension, thromboembolic disease, lung cancer, obstructive sleep apnoea, osteoporosis, infections and reflux disease [12, 13]. Therefore, patients diagnosed with IPF might be continuously treated for their comorbidities [14]. No published study has systematically appraised the dynamics in medication and diagnostic profile in patients before and after an IPF diagnosis. In other types of diseases, a pharmacoepidemiological approach has successfully been used to assess such changes [15].

In this study, we aimed at assessing changes in the medication and diagnosis patterns in the period before and after an IPF diagnosis is established.

Methods and materials

Design

In this descriptive longitudinal study, we identified all incident cases of IPF in Denmark during the period 2002–2017. We used the Danish nationwide health and prescription registries to describe new drug treatments and diagnoses in the period leading up to and following the IPF diagnosis.

Data sources

The Danish National Health Service provides universal tax-supported healthcare for all Danish residents, thereby allowing truly population-based register studies [16]. We retrieved data from three Danish nationwide administrative registers that cover close to 100% of the Danish population: Danish Civil Registration System [16], The Danish National Patient Register (DNPR) [17], and the Danish Register of Medicinal Product Statistics (RMPS) [18].

The Danish Civil Person Register contains data on vital status (date of birth and death) and migrations to and from Denmark [16].

The DNPR holds information for all contacts to Danish hospitals since 1977 [17]. From 1995, outpatient clinic diagnoses and emergency department contacts are included in the DNPR. Diagnoses are recorded according to International Classification of Diseases (ICD), 8th revision from 1977 to 1993 and 10th revision, since 1994. The Danish National Health Board has modified the ICD10, using minor extensions of the codes where appropriate. Importantly, IPF has its own extended Danish ICD10 code J84.1A.

RMPS holds information on all prescribed drugs dispensed from public pharmacies since 1995 [18]. Prescription records data include the Central Person Registry number, date of dispensing, the substance, brand name and quantity. Drugs are categorised according to the Anatomical Therapeutic Chemical (ATC) code and the quantity is expressed by the use of the defined daily dose (DDD) [17, 18].

Study population

We identified all incident cases of IPF (ICD-10 (DK): J84.1A) in Denmark between January 1, 2002 and December 31, 2017. We excluded subjects who had <3 years of an available look-back period before their diagnosis. Ten control subjects were matched to each IPF case based on age and sex, as an aid when interpreting our findings for IPF. The controls were assigned an index date identical to the diagnosis date of their corresponding IPF case. The same exclusion criteria were applied to IPF cases and controls.

Description of drug use

Prescription drugs were categorised according to the fourth level of the ATC classification (*e.g.* A02BC, proton pump inhibitors) to achieve a suitable granularity of prescription data [19].

We analysed drug use in two ways: in the first analysis we defined incident use of drugs as the first prescription fill for a drug in the 6 months before an IPF diagnosis. Ongoing drug use was defined as any occurrence of a prescription for a drug in the same period with continuously prescription refilling. Discontinuation of a drug was defined as not refilling a prescription within 6 months after the IPF diagnosis. We tabulated the proportion of incident, ongoing and discontinuing users for the most used

drug classes among cases. For each drug, the median and interquartile range (IQR) of time between first prescription and IPF diagnosis was determined.

In the second analysis, we charted the number of different predefined drugs filled in 3-month intervals starting 36 months before the IPF diagnosis date and ending 12 months after. In this analysis, drugs were broadly categorised into six categories: 1) respiratory drugs (ATC: R03); 2) immunosuppressants (ATC: L04); 3) antibiotics (ATC: J01); 4) glucocorticoids (ATC: H02BA); 5) cardiovascular drugs (ATC: B01AA and C); or 6) others. In addition, we calculated the cumulative number of DDDs dispensed in each 3-month interval, while using the same broad categories. IPF cases were assumed to have a high mortality after their diagnosis were received [2, 20]. Therefore, in the calculations for a given 3-month interval, we included only the subjects who survived throughout the interval.

Description of discharge diagnoses

Inpatient and outpatient secondary care diagnoses were obtained from the DNPR. Only the first occurrence of a given diagnosis for a patient was considered, and to ensure a reasonable granularity, ICD10 diagnosis codes were grouped according to the third digit. The occurrence of new diagnoses in the 3 years prior to an IPF diagnosis was described, and the median time from the first non-IPF diagnosis to the IPF diagnosis and IQR were calculated. Among the cases, we described the prevalent diagnoses and the disease categories included in the Charlson comorbidity index and certain pre-selected disease categories relevant to the current study aim [21]. This categorisation is presented as table S1. To facilitate interpretation, comorbid diagnoses were described for both cases and controls.

In 2011, the clinical guideline for IPF was updated and issued [22], and the first antifibrotic drug pirfenidone was introduced. To reflect a possible change in IPF management, we carried out all analyses separately for the period 2002–2011 and 2012–2017, as well as for the entire study period. The interval for description of drug use was also extended to include 3 years prior to the IPF diagnosis.

Statistics and ethics

Data were analysed using the framework of the Danish Health Data Board, using Stata version 15.1. Anonymised individual-level data were available to researchers. For confidentiality reasons, reporting exact counts <5 is not permitted. Categorical data are presented as numbers and prevalence. Continuous variables are presented as median with IQR.

According to Danish law, approval from an ethics committee is not required for pure register-based studies [23].

Results

We identified 743 eligible IPF cases. Of these, 93 cases were diagnosed prior to 2002 or had less than 3 years of enrolment in the database, leaving a total of 650 IPF patients and 6500 population controls (figure 1). Among incident IPF patients, the median age was 73 years (IQR 65–78 years) and 70.3% (n=457) were males (table 1). Cardiovascular diseases occurred more prevalent among IPF patients compared to controls, but cancer (including lymphoma and leukaemia) occurred with almost similar prevalence among IPF patients and controls.

Within the study period, 464 IPF cases died (71.4%) compared to 1159 controls (17.8%). The median survival time among IPF cases was 29.1 months (IQR 8.1–65.1 months) within the entire study period 2002–2017 compared to 6.4 years (IQR 5.5–8.2 years) for controls. Sensitivity analyses stratified to period 2002–2010 and 2011–2017 are in the supplementary material.

Diagnoses prior to IPF

Among the pre-selected disease categories prior to IPF diagnosis, the most prevalent diagnoses were dyspnoea, non-IPF idiopathic interstitial pneumonias (IIPs) and pneumonia (14.0%, 13.2%, and 8.6%, respectively). All of these had a prevalence <1% in the control group. Among IPF patients, 4.3% (n=28) were given a COPD diagnosis during the period prior to the IPF diagnosis, compared to 0.5% (n=31) among the population controls (table 2).

From first occurrence for any of one the pre-selected disease categories, the median time was 2.3 months (IQR 1.9–2.4 months). Pulmonary hypertension appeared with the shortest median time up to the IPF diagnosis (median 1.7 months, IQR 1.0–4.2 months) (table 2).

The most prevalent ICD-10 diagnosis prior to the IPF diagnosis was "other interstitial lung disease than IPF" (J84 excluding J84.1A) (45.8%, n=298), followed by dyspnoea (14.3%, n=93), and respiratory failure (8.9%, n=58). Of the specific diagnoses, only atrial fibrillation and flutter and essential (primary) hypertension reached prevalence >1% among controls (table 3).

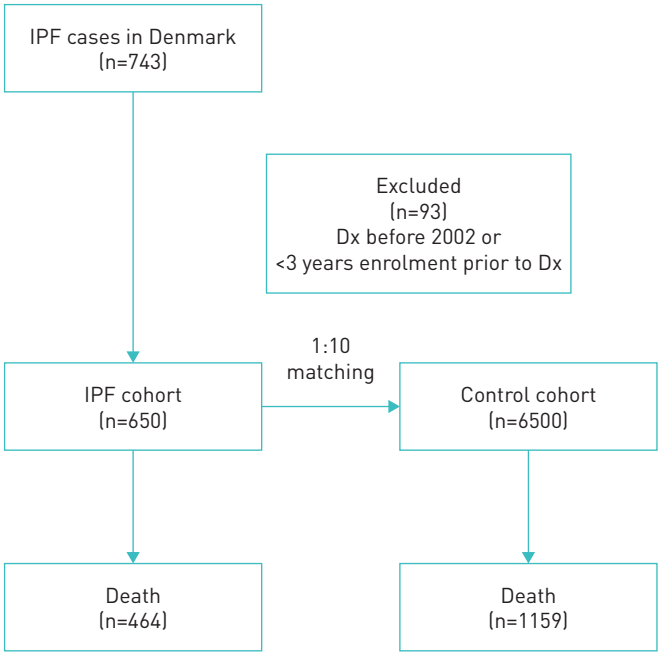

FIGURE 1 Study flow chart. IPF: idiopathic pulmonary fibrosis; Dx: diagnosis.

TABLE 1 Baseline characteristics including comorbid conditions among patients with a diagnosis of idiopathic pulmonary fibrosis (IPF) and sex- and age-matched controls

	IPF cases	Controls
Subjects	650	6500
Age years median (IQR)	73 (65–78)	73 (65–78)
Male	457 (70.3)	4570 (70.3)
Charlson comorbidity index#		
0	268 (41.2)	3428 (52.7)
1	129 (19.8)	1053 (16.2)
2	105 (16.2)	1015 (15.6)
⩾3	148 (22.8)	1004 (15.4)
Myocardial infarction	79 (12.2)	505 (7.9)
Heart failure	90 (13.8)	370 (5.8)
Peripheral vascular disease	69 (10.6)	444 (7.0)
Cerebrovascular disease	68 (10.5)	755 (11.9)
Dementia	11 (1.7)	136 (2.1)
Rheumatic disease	74 (11.4)	246 (3.9)
Ulcers	47 (7.2)	353 (5.6)
Liver disease, mild	16 (2.5)	76 (1.2)
Diabetes, uncomplicated	82 (12.6)	476 (7.5)
Hemiplegia	0 (0.0)	18 (0.3)
Kidney disease	30 (4.6)	211 (3.3)
Diabetes, complicated	39 (6.0)	236 (3.7)
Leukaemia	5 (0.8)	32 (0.5)
Lymphoma	9 (1.4)	62 (1.0)
Cancer, localised	106 (16.3)	1231 (19.4)
Liver disease, severe	6 (0.9)	15 (0.2)
Cancer, nonlocalised	8 (1.2)	75 (1.2)
HIV and AIDS	0 (0.0)	0 (0.0)

Data are presented as n (%) unless otherwise stated. IQR: interquartile range. #: categorised according to number of comorbidities.

TABLE 2 Frequency of 10 pre-specified disease categories among patients diagnosed with idiopathic pulmonary fibrosis (IPF) and sex- and age-matched population controls

Disease category	IPF cases		Controls	
	n (%)	First occurrence relative to IPF diagnosis months median (IQR)	n (%)	First occurrence relative to index date months median (IQR)
Dyspnoea	91 (14.0)	2.2 (0.9–3.7)	28 (0.4)	3.6 (2.7–4.4)
Non-IPF IIP	86 (13.2)	2.7 (1.0–4.3)	n<10	n<10
Pneumonia	56 (8.6)	2.0 (0.8–3.8)	42 (0.6)	2.9 (1.5–4.1)
COPD	28 (4.3)	1.9 (0.9–2.7)	31 (0.5)	2.8 (1.7–4.2)
Cough	19 (2.9)	2.8 (1.7–4.0)	n<10	n<10
Pulmonary hypertension	17 (2.6)	1.7 (1.0–4.2)	n<10	n<10
Osteoporosis	17 (2.6)	2.4 (1.6–4.1)	25 (0.4)	2.5 (1.4–4.5)
Heart failure	17 (2.6)	1.8 (0.5–3.9)	35 (0.5)	2.7 (1.0–3.8)
Cardiac valve disease	11 (1.7)	2.6 (2.2–3.2)	24 (0.4)	2.9 (1.6–4.1)
Diabetes	11 (1.7)	3.1 (1.9–4.3)	25 (0.4)	3.3 (2.2–4.6)

IQR: interquartile range; IIP: idiopathic interstitial pneumonia.

TABLE 3 The most prevalent diagnoses among patients with a diagnosis of idiopathic pulmonary fibrosis (IPF) established within 3 years prior to the IPF diagnosis and a randomly assigned index date among controls

Diagnosis	ICD-10	IPF cases		Controls	
		n (%)	First occurrence relative to IPF diagnosis months median (IQR)	n (%)	First occurrence relative to index date months median (IQR)
Interstitial pulmonary diseases other than J84.1A	J84	298 (45.8)	2.3 (1.0–3.9)	n<10	n<10
Abnormalities of breathing	R06	93 (14.3)	2.2 (0.9–3.7)	32 (0.5)	3.6 (2.2–4.4)
Respiratory failure, not elsewhere classified	J96	58 (8.9)	2.3 (0.9–4.5)	18 (0.3)	3.8 (1.9–5.0)
Pneumonia, organism unspecified	J18	51 (7.8)	2.2 (0.9–4.1)	32 (0.5)	3.2 (2.0–4.8)
Abnormal findings on diagnostic imaging of lung	R91	39 (6.0)	2.2 (1.1–4.0)	n<10	n<10
Atrial fibrillation and flutter	I48	37 (5.7)	1.9 (1.2–3.8)	69 (1.1)	3.1 (1.7–4.8)
Other COPD	J44	33 (5.1)	1.8 (0.5–3.0)	47 (0.7)	3.2 (1.7–4.3)
Bacterial pneumonia, not elsewhere classified	J15	24 (3.7)	2.6 (1.2–3.9)	22 (0.3)	2.8 (1.2–3.4)
Heart failure	I50	23 (3.5)	1.6 (0.5–4.7)	44 (0.7)	2.7 (1.4–4.4)
Cough	R05	20 (3.1)	2.8 (1.8–3.9)	n<10	n<10
Other pulmonary heart diseases	I27	19 (2.9)	1.9 (1.0–4.2)	n<10	n<10
Chronic ischaemic heart disease	I25	18 (2.8)	2.2 (0.5–3.4)	46 (0.7)	3.0 (1.8–4.2)
Osteoporosis without pathological fracture	M81	17 (2.6)	2.5 (1.6–4.1)	22 (0.3)	2.5 (1.4–3.8)
Non-insulin-dependent diabetes mellitus	E11	16 (2.5)	3.1 (1.8–4.4)	46 (0.7)	3.3 (1.9–4.6)
Nonrheumatic aortic valve disorders	I35	15 (2.3)	2.5 (2.1–3.2)	26 (0.4)	3.2 (1.6–4.2)
Essential (primary) hypertension	I10	15 (2.3)	2.7 (0.5–4.0)	73 (1.1)	3.1 (1.9–4.3)
Angina pectoris	I20	15 (2.3)	2.8 (2.3–4.7)	23 (0.4)	3.1 (2.0–4.7)
Senile cataract	H25	14 (2.2)	3.9 (1.5–4.2)	61 (0.9)	2.9 (1.3–4.4)
Other respiratory disorders	J98	13 (2.0)	1.7 (0.7–3.6)	n<10	n<10
Haemorrhage from respiratory passages	R04	13 (2.0)	2.6 (0.3–4.2)	11 (0.2)	3.2 (2.1–4.0)
Complications and ill-defined descriptions of heart disease	I51	12 (1.8)	2.0 (0.0–4.6)	n<10	n<10
Malaise and fatigue	R53	12 (1.8)	2.3 (0.6–3.4)	22 (0.3)	2.2 (1.1–3.2)
Malignant neoplasm of bronchus and lung	C34	10 (1.5)	2.9 (1.7–4.2)	18 (0.3)	2.3 (0.8–4.6)

ICD-10: International Classification of Diseases, 10th revision; IQR: interquartile range.

Pre- and post-diagnosis: use of prescription drugs

For several major drug classes, the IPF cases had a higher proportion of incident users within 6 months prior to IPF diagnosis compared to the controls. The largest absolute differences in new drug use proportions between IPF patients and controls was observed for combinations of penicillin and

TABLE 4 Dynamics of the most prevalent drug classes used by newly diagnosed patients with idiopathic pulmonary fibrosis (IPF) and their matched controls

Drug class, name	ATC	IPF cases			Controls		
		New users before IPF[#]	Ongoing users before IPF[¶]	Discontinued after IPF[+]	New users before index date[#]	Ongoing users before index date[¶]	Discontinued after index date[+]
Combinations of penicillin, including β-lactamase inhibitors	J01CR	63 (9.7)	127 (19.5)	32/86 (37.2)	76 (1.2)	158 (2.4)	94/163 (63.1)
Glucocorticoids, systemic	H02AB	56 (8.6)	223 (34.3)	33/153 (21.6)	50 (0.8)	277 (4.3)	85/262 (32.4)
Mucolytics	R05CB	42 (6.5)	105 (16.2)	15/80 (18.8)	17 (0.3)	36 (0.6)	n<10
Proton pump inhibitors	A02BC	38 (5.8)	242 (37.2)	18/193 (9.3)	102 (1.6)	1016 (15.6)	140/993 (14.1)
Selective β_2-adrenoreceptor agonists	R03AC	36 (5.5)	124 (19.1)	40/97 (41.2)	35 (0.5)	341 (5.2)	75/334 (22.5)
Loop diuretics	C03CA	31 (4.8)	152 (23.4)	24/108 (22.2)	58 (0.9)	543 (8.4)	48/522 (9.2)
Potassium	A12BA	28 (4.3)	123 (18.9)	18/85 (21.2)	71 (1.1)	506 (7.8)	53/483 (11.0)
Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics	R03AK	24 (3.7)	90 (13.8)	27/71 (38.0)	21 (0.3)	295 (4.5)	21/287 (7.3)
Macrolides	J01FA	23 (3.5)	122 (18.8)	56/92 (60.9)	39 (0.6)	216 (3.3)	147/208 (70.7)
Paracetamol	N02BE	23 (3.5)	193 (29.7)	21/144 (14.6)	155 (2.4)	1261 (19.4)	232/1219 (19.0)
Other immunosuppressants	L04AX	22 (3.4)	71 (10.9)	22/48 (45.8)	n<10	62 (1.0)	n<10
Fluoroquinolones	J01MA	21 (3.2)	45 (6.9)	16/27 (59.3)	48 (0.7)	98 (1.5)	n<10
Natural opium alkaloids	N02AA	20 (3.1)	49 (7.5)	n<10	64 (1.0)	196 (3.0)	57/187 (30.5)
Inhaled anticholinergics	R03BB	20 (3.1)	75 (11.5)	16/53 (30.2)	27 (0.4)	224 (3.4)	20/215 (9.3)
Penicillins with extended spectrum	J01CA	18 (2.8)	76 (11.7)	26/54 (48.1)	58 (0.9)	361 (5.6)	196/345 (56.8)
Osmotically acting laxatives	A06AD	17 (2.6)	23 (3.5)	n<10	43 (0.7)	143 (2.2)	40/123 (32.5)
Adrenergics in combination with anticholinergics	R03AL	16 (2.5)	34 (5.2)	n<10	22 (0.3)	68 (1.0)	14/59 (23.7)
Opium alkaloids and derivatives	R05DA	15 (2.3)	47 (7.2)	19/36 (52.8)	31 (0.5)	142 (2.2)	n<10
Bisphosphonates	M05BA	15 (2.3)	84 (12.9)	n<10	19 (0.3)	237 (3.6)	n<10
Other opioids	N02AX	14 (2.2)	71 (10.9)	18/54 (33.3)	75 (1.2)	422 (6.5)	153/409 (37.4)
Benzodiazepine-related drugs	N05CF	14 (2.2)	73 (11.2)	13/51 (25.5)	36 (0.6)	386 (5.9)	76/375 (20.3)
Selective serotonin reuptake inhibitors	N06AB	13 (2.0)	59 (9.1)	n<10	22 (0.3)	388 (6.0)	46/376 (12.2)
Aldosterone antagonists	C03DA	13 (2.0)	38 (5.8)	n<10	15 (0.2)	157 (2.4)	n<10
Platelet aggregation inhibitors	B01AC	12 (1.8)	224 (34.5)	15/168 (8.9)	62 (1.0)	1714 (26.4)	79/1675 (4.7)
Propulsives	A03FA	12 (1.8)	24 (3.7)	n<10	18 (0.3)	57 (0.9)	30/50 (60.0)
Statins	C10AA	12 (1.8)	235 (36.2)	13/182 (7.1)	68 (1.0)	2018 (31.0)	87/1991 (4.4)
Contact laxatives	A06AB	11 (1.7)	12 (1.8)	n<10	38 (0.6)	83 (1.3)	26/74 (35.1)
Thiazides and potassium in combination	C03AB	11 (1.7)	71 (10.9)	13/54 (24.1)	36 (0.6)	765 (11.8)	85/756 (11.2)
Corticosteroids and anti-infectives in combination	S01CA	10 (1.5)	13 (2.0)	n<10	66 (1.0)	131 (2.0)	101/131 (77.1)
Organic nitrates	C01DA	10 (1.5)	48 (7.4)	10/31 (32.3)	25 (0.4)	192 (3.0)	49/185 (26.5)
Opium cough suppressants and expectorants	R05FA	10 (1.5)	28 (4.3)	16/22 (72.7)	23 (0.4)	84 (1.3)	61/84 (72.6)
Systemic triazole antifungals	J02AC	10 (1.5)	23 (3.5)	n<10	20 (0.3)	51 (0.8)	n<10
Vitamin K antagonists	B01AA	10 (1.5)	46 (7.1)	n<10	27 (0.4)	378 (5.8)	19/370 (5.1)
Imidazole and triazole derivatives	D01AC	10 (1.5)	36 (5.5)	23/29 (79.3)	60 (0.9)	228 (3.5)	129/218 (59.2)
Glucocorticoids, inhaled	R03BA	10 (1.5)	31 (4.8)	13/26 (50.0)	16 (0.2)	158 (2.4)	30/158 (19.0)

Data are presented as n (%) or n/N (%). ATC: Anatomical Therapeutic Chemical classification. [#]: first ever occurrence of the drug class within 6 months before the index date/diagnosis date. [¶]: any occurrence of the drug class within the 6 months before the index date/diagnosis date. [+]: the absence of any prescriptions of the drug class after the index date/diagnosis date compared to ongoing use; the denominator represents ongoing users who also have a 6-month follow-up after the IPF diagnosis meaning that the denominator varies according to each drug.

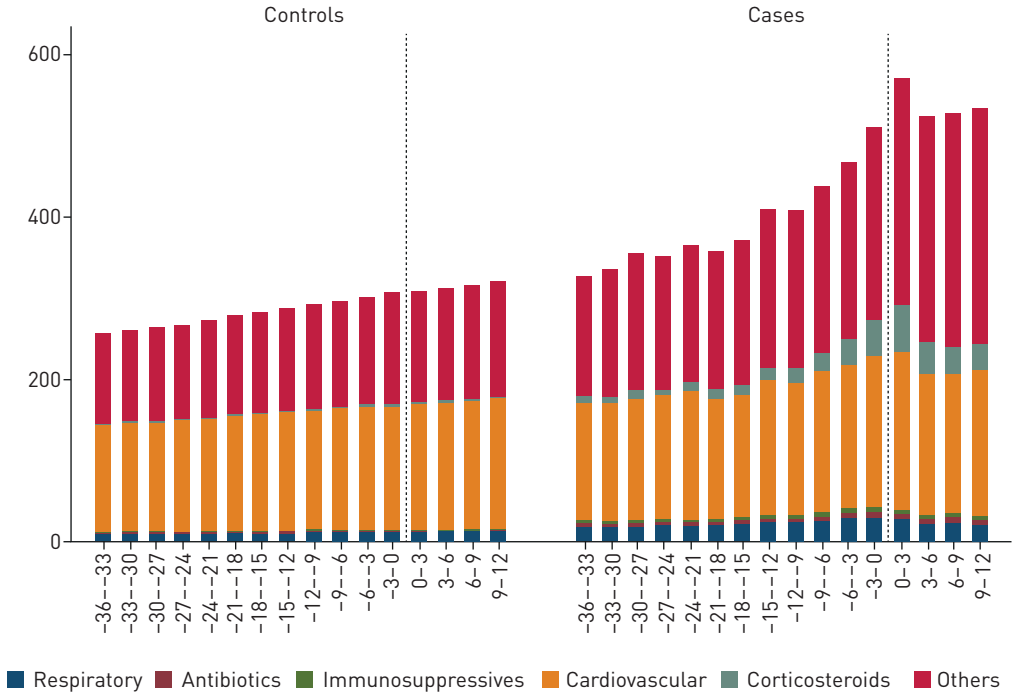

FIGURE 2 Average number of defined daily doses used within 3-month periods before and after the diagnosis date for cases with idiopathic pulmonary fibrosis and before and after the index date for their matched controls.

β-lactamase inhibitors, systemic glucocorticoids and mucolytics (9.7% *versus* 1.2%, 8.6% *versus* 0.8%, and 6.5% *versus* 0.3%, respectively) (table 4).

A detailed overview of discontinuation rates of drugs after an IPF diagnosis is also presented in table 4. Of note, only 21.6% of IPF patients discontinued systemic glucocorticoids compared to 32.4% of controls, and only 18.8% of IPF patients discontinued mucolytics compared to 45.7% of the controls. The opposite was observed for drugs for inhalation therapy (ATC-codes R03BB and R03BA), where 30.2 and 50.0% IPF patients discontinued inhalation therapy *versus* 9.3 and 19.0% among controls.

Among IPF patients, we observed a high volume consumed for respiratory drugs, antibiotics, immunosuppressants, in particular systemic glucocorticoids, and the category of other drugs (*e.g.* proton pump inhibitors, benzodiazepines and opium alkaloids) during the 12-month period before the IPF diagnosis (figure 2). These trends were not observed among controls.

Discussion

This 16-year nationwide longitudinal observational study aimed to investigate dynamics in diagnoses and use of pharmacotherapy up to and after an established IPF diagnosis. Surprisingly, we found that only to a limited extent IPF patients had been given diagnoses as COPD (4.3%) or heart failure (1.8%) before IPF. Given their low prevalence in the analyses, these diagnoses may not necessarily be incorrect, but actually represent true comorbid conditions to IPF due to common shared risk factors (*i.e.* tobacco use). Instead, nonspecific diagnoses were used in disease categories as dyspnoea (14.0%), broadly defined ILDs (13.2%) and pneumonia (8.6%). We interpret this as an indication of, that before the IPF diagnosis is established, there is a high level of suspicion among secondary care physicians that the patient may have an ILD, which prompt referrals to IPF specialist centres with access to multidisciplinary discussions. This may explain the low median time from first occurring respiratory diagnosis to IPF diagnosis of 2.3 months (table 3). Though other studies have found cough and malaise as early symptoms associated with IPF [24, 25] these appeared rarely in our register-based population with prevalence of 3.1% and 1.8%, respectively (table 3). These differences are very likely explained by methodological differences in the selection of IPF populations, but also that ICD-10 coding in Denmark primarily refers to diagnoses and more rarely symptoms. Thereby, more nonspecific respiratory symptoms are not systematically coded.

For prescription drug use, we found almost the same general level of drug use among cases and controls 36 months prior to IPF diagnosis. For IPF patients the drug use built up slowly 6months prior to the IPF

diagnosis and levelled thereafter. This may be explained by treatment attempts for differential diagnoses to IPF, especially the increased use of immunosuppressants and systemic glucocorticoids [10]. Inhaled bronchodilation therapy is not recommended as part of pharmacological IPF treatment. Furthermore, since the 2011 guideline on IPF there has been a strong recommendation against monotherapy with systemic glucocorticoids [22]. Surprisingly, a substantial proportion of the inhaled respiratory drugs, including inhaled corticosteroids, as well as systemic glucocorticoids continued after the IPF diagnosis. This may be due to pulmonary specialists not dedicating enough attention to deprescribing, due to deprescribing intention which is not properly communicated to primary care, due to slow tapering of systemic corticosteroid therapy, due to bronchodilators being used as soothing drugs, or due to a genuine continued need for these drugs (*e.g.* systemic glucocorticoids for IPF exacerbations) [2, 26]. From the register data available in this study, it is difficult to identify the exact causes.

There are only few previous studies describing dynamics in diagnoses and drug use before and after an IPF diagnosis. To some extent, our study findings concur with previous studies with regard to specific symptom presentation, and age and sex distribution [9, 11–13]. Guenther *et al.* [13] found dyspnoea to be the most dominant symptom (90.1%) in an IPF patient cohort, a result that supports our findings, based on ICD10 codes, which are some of the predominant pre-IPF diagnoses. On the other hand, some of our findings are atypical for this patient population in relation to previous IPF cohort observations. Comorbidity is frequent in IPF patients and has been reported to occur with a mean number of 2.68 comorbidities per patient [12], and the most prevalent comorbidity disease categories to be ischaemic heart disease and cardiovascular diseases [9, 12, 13]. However, these observations are not consistent with our findings, where selected cardiovascular diseases occurred only in less than 5% of the IPF patients, not including atrial flutter. This discrepancy may be attributable to the difference in use of data from nationwide administrative registers, and the use of registry data obtained from clinical IPF databases based on self-reported information [12, 13] and electronic medical records [10]. The same tendency also applies to IPF medication, exemplified by findings in a German study in which drugs related to heart failure/arrhythmia (30.6%) and cardiovascular disease (52.6%) dominated, and occurred with a higher proportion compared to our results [14]. This difference is likely due to analyses based on insurance claims data among ILD patients in which IPF patients were only a subset [13]. The observed overall median survival of 29 months from our cohort resembles findings from other studies [20, 27].

The first international consensus statement on IPF was published in 2000 [28], and followed up by evidence-based clinical guidelines on diagnosis and management in 2011 [22], 2015 [29] and 2018 [2]. During this 18-year period, the knowledge and understanding of IPF has increased and the pharmacological management of IPF has changed markedly. In the 2000 statement, systemic glucocorticoids were regarded as the cornerstone treatment in IPF, either as monotherapy or in combination with immunosuppressants. In the 2011 guideline, neither systemic glucocorticoid monotherapy, azathioprine nor N-acetylcysteine were recommended, and a minority of IPF patients were expected to benefit from a combination of all three drugs or pirfenidone [22]. However, this three-drug combination proved to confer an increased risk of death and hospitalisation [30] and was removed from the 2015 guideline [29] in which the antifibrotic drugs (*i.e.* pirfenidone and nintedanib), were recommended as first-choice IPF treatments [4, 5]. The only drugs, mentioned in both the 2000 and 2011 guidelines, were systemic glucocorticoids and to some extent N-acetylcysteine, a fact which partly may explain our observed findings regarding discontinuations for these drug groups. When splitting the observation periods into 2002–2010 and 2011–2017 we observed an ongoing systemic glucocorticoid use among 40% and 21.5% of the IPF cases, which is also previously observed (table S6 and S7) [13]. The decrease in post-diagnosis use of systemic glucocorticoids occurred when guidelines were changed to incorporate antifibrotic treatment with pirfenidone and nintedanib [22, 28]. Despite the apparent reduction in systemic glucocorticoid use between the two periods, a substantial use persisted in the 2011–2017 period, which is difficult to explain. Among the possible explanations are systemic glucocorticoid treatments of exacerbations or palliative use in patients with terminal IPF.

The median time from first occurrence of all pre-selected disease categories was around 2.3 months. This period may indirectly reflect the time span from when the tentative diagnosis was settled at referral hospitals to the decisive IPF diagnosis was made and coded at the tertiary ILD referral centres in concordance with other observations [6].

The main strength of this study is the population-based approach covering an entire nation during a 16-year observation period by linkage of data from three highly valid national registries. The linkage made it possible to perform an individual-based longitudinal study on diagnoses and drug use prior to and after an IPF diagnosis. As proxies for drug utilisation, we used prescription data from DNPR which possess high data completeness and thereby minimise the risk of information bias. Another strength is the inclusion of a nondiseased control group, which provide a reference for coprescribed medication, drug

persistence and the observed trends in diagnosing and prescribing on a given date. The main limitation of our study is that all IPF diagnoses (ICD10 code J84.1A) is retrieved from DNPR, as the validity of the IPF diagnosis code has not been formally evaluated as for other pulmonary diagnoses [31]. With updated IPF guidelines, it also became evident that referral to tertiary ILD centres with access to multidisciplinary discussions improved the diagnostic confidence concurrent with a reduced diagnostic latency and mortality [6, 32, 33]. By use of this guideline recommended multidisciplinary discussion approach from 2011 and onwards, we expect that the ICD10-codes registered during the observation period 2011–2017 actually represent true IPF diagnoses [34]. Finally, though the number of IPF cases are comparable to IPF cohorts in previous register-based IPF studies [9, 12–14], the small patient number, however, may limit the statistical precision.

The results from this study may indirectly support IPF to be underdiagnosed as a consequence of being mistaken for other respiratory diseases [6, 10]. We uncovered that an increasing drug use for especially systemic glucocorticoids, proton pump inhibitors, benzodiazepines and opium alkaloids and inhalation medication, could be an independent risk factor for IPF, but also for its diagnostic latency [6]. This latter issue could be revealed in future studies looking into which patients, general practitioners and physicians at referral hospitals, who were exposed to an increased knowledge on IPF risk factors.

In summary, the analyses from this nationwide study indicate that, among IPF patients, an increased drug use for diagnoses with symptoms like IPF exists, especially 6 months prior to IPF diagnosis. The increased drug use probably reflects the evident latency in IPF diagnostics, emphasises the need for an improved knowledge sharing and it prompts an increased focus on patients being referred to a specialist IPF centre.

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