Opportunities to diagnose fibrotic lung diseases in routine care: a primary care cohort study

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Summary at a glance: We analysed a primary care clinical cohort database to investigate respiratory symptoms and healthcare use in the 10 years prior to a diagnosis of pulmonary fibrosis. Utilisation progressively increased in the years prior to diagnosis, suggesting multiple opportunities for diagnosis at an earlier stage.

ABSTRACT

Background and objective: Temporal patterns of healthcare use in the period before a diagnosis of pulmonary fibrosis are poorly understood. We investigated trends in respiratory symptoms and lower respiratory healthcare resource utilisation (HRU) in the 10 years prior to diagnosis.

Methods: We analysed a primary care clinical cohort database (UK Optimum Patient Care Research Database) and assessed patients aged ≥40 years who had an electronically coded diagnosis of pulmonary fibrosis between 2005–2015 and a minimum 2 years' continuous medical records prior to diagnosis. Electronic codes for recognised causes of pulmonary fibrosis such as CTD, sarcoidosis or allergic alveolitis were exclusion criteria.

Results: Data for 2223 patients were assessed. Over the 10 years prior to diagnosis of pulmonary fibrosis there was a progressive increase in HRU across multiple lower respiratory (LR)-related domains. These further increased between months 24–13 and 12–0 prior to diagnosis. Five years before diagnosis, 18% of patients had multiple healthcare contacts for LR complaints; this increased to 79% in the year before diagnosis, with 38% of patients having five or more healthcare contacts.

Conclusions: There are opportunities to diagnose pulmonary fibrosis at an earlier stage; research into case-finding algorithms and strategies to educate primary care physicians is required.

Key Words: idiopathic pulmonary fibrosis (IPF), lower respiratory (LR), healthcare resource utilisation (HRU), diagnosis

Short title: Missed pulmonary fibrosis diagnostic opportunities

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a prototype of chronic, progressive fibrotic lung disease. It is estimated to affect between 14–43 people per 100,000; slightly more men than women, and has a mean age at presentation of 66 years [1–4]. The condition has a median post-diagnostic survival of 2–5 years and an associated 5-year survival of approximately 20% [3,5]. There is a lack of public awareness of IPF, yet it kills more people every year than leukaemia or ovarian cancer and the number of people affected is increasing [6].

Historically, treatment options for IPF were limited to symptom management and palliation, potentially providing little motivation for earlier diagnosis. However, even in the absence of any approved pharmacological treatment, delayed access to specialist interstitial lung disease (ILD) services has been associated with an increased risk of death [7]. The recent approval of two effective anti-fibrotic treatments (nintedanib and pirfenidone), which can slow disease progression, now heralds a new era for the management of patients with IPF [8,9]. Thus the importance of an early and accurate diagnosis is clear [10].

While early diagnosis and treatment of IPF is now widely advocated [11,12], exactly how it can be achieved remains less clear. Precision Medicine approaches and genomic techniques to phenotype patients with fibrotic lung disease are being widely researched with the goal of identifying blood- or lung-specific molecular markers to enhance diagnostic accuracy [13].

However, such methodologies require expertise available only in specialist centres, access to which first requires a suspicion, or a diagnosis, of lung fibrosis. A fundamental challenge to the diagnostic and specialist referral pathway is the limited understanding of the natural history of pulmonary fibrosis; it is thought that some patients may be symptomatic for more than 5 years before a formal diagnosis [14].

As all patients with pulmonary fibrosis (including IPF) in the United Kingdom (UK) will first present in primary care, primary care medical records provide an important resource for understanding temporal patterns of healthcare system utilisation (HRU) prior to diagnosis. In this study we assessed patterns of HRU up to 10 years prior to a diagnosis of pulmonary fibrosis to inform potential strategies for earlier identification.

METHODS

Data source and study approvals

The Optimum Patient Care Research Database (OPCRD) contains anonymised, longitudinal medical records for patients registered at primary care practices across the UK [17]. It includes demographic, lifestyle, diagnostic and HRU data recorded in primary and secondary care. At the time of the study it comprised records for approximately 2.5 million patients registered across approximately 525 primary care practices.

The OPCRD is approved by the Health Research Authority of the UK NHS for clinical research use (REC reference: 15/EM/0150). Access to the database for the purposes of this study was approved by the OPCRD's Anonymised Data Ethics and Protocol Transparency Committee (approval code, ADEPT0616). The study protocol was developed by an independent steering committee of the Respiratory Effectiveness group (REG) and registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; registration number EUPAS12086) [18].

Study design and population

This was a historical cohort study including an observation period of 2–10 years (as available) immediately prior to an index date at which patients received a first diagnostic code for pulmonary fibrosis. The data extraction cut-off date was December 31st 2015. Cases were identified from diagnostic (Read) code lists developed by members of the REG ILD Working Group and aligned with published IPF-related observational research conducted in the

UK (see Supplementary Table S1 and S2) [6,14]. Acknowledging the potential for variations in coding practice between healthcare professionals, cases were labelled as “pulmonary fibrosis-clinical syndrome” (PFCS) in the presence of a code considered diagnostic of pulmonary fibrosis and the absence of codes associated with recognised causes of ILD, such as a connective tissue disease (CTD). A subpopulation of patients with only IPF-specific diagnostic codes—here termed “IPF clinical syndrome” (IPFCS)—was identified (Supplementary Table S1).

Eligible patients were aged ≥40 years at diagnosis and diagnosed with PFCS between 2005–2015. Patients diagnosed before 1990, with less than two years of continuous medical records immediately prior to diagnosis, or with a diagnosis of CTD, sarcoidosis or allergic alveolitis at any point were excluded.

Outcome measures

Characteristics at diagnosis

Key characteristics of the study population described included: demographic (age, sex, anthropomorphic measures); lifestyle (smoking history); clinical features (lung function [FVC, FEV_1/FVC] recorded closest to diagnosis); common comorbidities, and use of obstructive lung disease (OLD) pharmacotherapy in the year preceding PFCS diagnosis.

Healthcare resource utilisation

Temporal patterns in respiratory symptoms were evaluated by assessment of population-level functional impairment and per-patient annualised cough coded primary care consultations (cough event rate) over the two and 10 years prior to PFCS diagnosis. Functional impairment was evaluated using the mini-Medical Research Council (mMRC) score. Scores were captured as a feature of the research database's systematic data capture protocol. Availability of mMRC scores, therefore, reflects patients' willingness to participate in routine data collection rather than their clinical situation.

Two- and 10-year trends in lower respiratory (LR) HRU were evaluated by assessment of annualised per-patient rates of: primary care consultations, chest radiography (CXR), hospitalisations, emergency room attendances, and antibiotics and oral steroid (acute and maintenance) prescriptions coded for an LR complaint. LR complaint codes included those for LR tract infections (e.g. bronchitis, tracheitis, pneumonia), non-infective LR conditions (e.g. chronic respiratory failure), and respiratory symptoms (e.g. breathlessness, cough, wheezing).

Opportunities for possible earlier PFCS diagnosis were explored and quantified by evaluating the number and percentage of unique patients with 0, 1, 2, 3, 4, ≥5 LR-related primary care contacts within each 1-year period in the decade preceding PFCS diagnosis. Prevalence of potential differential pulmonary diagnoses (chronic obstructive pulmonary disease [COPD], asthma and lung cancer) at time of PFCS diagnosis, and their proximity to

PFCS diagnosis, were also explored.

Statistical analysis

Summary statistics (n [%]) were used to describe patient characteristics at time of PFCS diagnosis. Temporal changes in LR symptoms and HRU patterns were assessed annually over the ten years prior to PFCS diagnosis. A comparison in survival among IPF patient with (versus without) concomitant lung cancer was made using a log-rank (Mantel-Cox) test. All analyses were conducted using STATA (version 14).

RESULTS

There were a total of 2,223 eligible PFCS patients (Fig. 1) including 743 patients eligible for the IPFCS subgroup (Supplementary Fig. S1).

Cohort characteristics

The PFCS study cohort comprised more men (62.9%) than women with an overall mean (standard deviation [SD]) age of 72.6 (9.7) years. Two-thirds of patients (67.2%) were current or former smokers. Cardiac or pulmonary conditions were the most common comorbidities at the time of PFCS diagnosis: ischaemic heart disease (32.4%), COPD (22.6%), lung cancer (18.0%), and asthma (13.9%). Mean (SD) FVC was 2.9 (5.7) L and FEV_1/FVC 0.78 (0.1). Almost one-quarter of patients (23.2%) had received a prescription for a short-acting $beta_2$-agonist (SABA) in the year prior to PFCS diagnosis (Table 1). PFCS and IPFCS patient characteristics were broadly similar (Tables 1 and S3, respectively). In patients with OLD, the diagnosis of COPD

occurred a mean (SD) 5.1 (6.7) years, and asthma a mean (SD) 12.1 (14.1) years, prior to PFCS diagnosis. 40% of patients received their asthma diagnosis within 5 years of being diagnosed with PFCS (60% within 10 years).

Functional impairment (assessed by mMRC) scores prior to PFCS diagnosis were available for 52% of the cohort. When stratified by time between mMRC assessment and PFCS diagnosis, there were no pronounced temporal trends, although a slight reduction in the proportion of patients without signs of functional impairment was apparent over the 10-year study period (Fig. S2).

Mortality data following PFCS diagnosis were available in the primary care records of 32% of the cohort at the data extraction cut-off date, with survival significantly shorter among patients with (versus without) a concomitant lung cancer diagnosis (p=0.046).

Healthcare resource utilistation

There was a marked increase in incidence of cough events in the lead up to PFCS diagnosis (Fig. 2). Mean (SD) annual per-patient cough event rate increased 10-fold over the 10-year observation period (from 0.06 [0.3] per patient per year (pppy) 10-years prior to diagnosis to 0.58 [0.6] in the year immediately prior to diagnosis), doubling in the penultimate two years. A similar, trend was seen in the IPFCS cohort, with mean cough event rates increasing from 0.05 to 0.13 pppy over the same 10-year period.

Increasing trends in LR HRU were evident over the 10-year observation period (Fig. 3 and Table 2). Mean (SD) annualised rates of primary care

consultations associated with LR complaints increased from 0.4 (1.3) pppy in the year 10 years prior to diagnosis, to 4.5 (1.6) pppy in the year immediately prior to diagnosis. Similarly, antibiotic and acute oral steroid prescriptions coded for LR events also increased over the same 10-year period (0.08 [0.3] to 0.81 [0.7] pppy and 0.02 [0.2] to 1.07 [0.7] pppy, respectively). The pattern of increasing LR HRU was consistent in the IPFCS cohort (Table S4 and Fig. S3).

A 10-fold increase in chest X-rays (CXR) was seen when comparing the 10 years prior to diagnosis with the year immediately prior to diagnosis (mean [SD] annual rate of 0.03 [0.2] to 0.40 [0.5] pppy, respectively; Fig. 3 and Table 2). There was no clear 10-year trends in secondary care contacts associated with LR complaints (hospital admissions or ER attendances) or incidence of pneumonia, although there was a 3-fold increase in pneumonia incidence in the two years immediately prior to PFCS diagnosis (data not shown).

All-cause primary care consultations were also examined to explore whether increases in LR consultations reflected a general escalation in all-cause HRU as the cohort aged over the 10-year period. All-cause consultations did increase over the 10-year period, but LR complaints became a more dominant driver of HRU accounting for 10% and 37% of all primary care consultations in the year ten years and in the year immediately prior to diagnosis, respectively (Supplementary Fig. S4). The increasing contribution of LR to all-cause primary care consultations (particularly in the year immediately prior to diagnosis) was also evident in the IPFCS cohort.

Ten years prior to PFCS diagnosis, 18% of patients visited primary care for a LR reason over a 1-year period. Of these patients, only 6.3% consulted multiple times and 1.5% five times or more. Five years later, approximately 30% of patients had consulted at least once in the year for an LR complaint, 14.4% multiple times and 3.8% at least five times. In the year immediately prior to PFCS diagnosis, almost all patients (99.9%) had visited primary care at least once for a LR complaint, 78.8% multiple times and 38.0% at least five times (Fig. 4 and Supplementary Table S5).

DISCUSSION

Our findings show that in the years preceding a diagnosis of PFCS there is a progressive increase in HRU across a number of domains: cough, LR consultations, antibiotic and oral steroid prescriptions, and CXR. Eighteen percent of patients made multiple primary care visits with some form of LR complaint five years before PFCS diagnosis; this had increased to almost 80% in the year before diagnosis, 38% having five or more primary health care contacts. The data shows that opportunities exist for earlier referral for investigation of suspected pulmonary fibrosis in primary care health setting.

Whilst the natural history of OLD is growing [19], that of fibrotic lung diseases remains limited. Research into fibrotic lung disease has traditionally been restricted to evaluations conducted within specialist centres; large-scale primary care databases offer an opportunity to study more widely representative and generalisable populations.

We analysed a historical dataset that has been widely used in primary care studies and is regarded as high quality [17,19] Key anthropomorphic measures (age, body mass index) and lung function measures are consistent with previous IPF cohort studies [6,8,9,20]. The diagnosis of PFCS was based on the presence of codes considered diagnostic of pulmonary fibrosis and the absence of codes associated with recognised causes of ILD (e.g. CTD). While potentially including patients with a form of pulmonary fibrosis other than IPF, analysis of the subgroup of patients with diagnostic codes considered more specific for IPF demonstrated comparability between these groups. All such

patients need specialist referral for investigation irrespective of final diagnosis; additional studies would be required to validate specific diagnostic groups, including investigation of the correlation of primary care diagnostic codes with diagnosis received in specialist care.

Certain data were only available for a subset of patients, potentially limiting their interpretation. Spirometry is not routinely performed in primary care and utilisation varies according to diagnosis, with patients suspected to have COPD or asthma more likely to have spirometry performed. Additionally, secondary care data requires manual reporting between secondary and primary care colleagues, and subsequent manual entry into the primary care records, resulting in inevitable under-reporting and potential under-estimation of HRU in secondary care.

Our findings extend those of Hewson *et al* who identified increasing breathlessness and cough in the five years prior to a diagnosis of IPFCS [14]. We identified a progressive increase in HRU across a number of LR-related domains over the 10-years (and in particular the penultimate two years) preceding a diagnosis of PFCS. This may reflect the progression of symptoms from minor to moderate/severe, whereby symptoms begin to affect quality of life so healthcare is increasingly sought. The parallel increase in LR-related consultations and prescriptions for acute oral steroid and antibiotics suggests that infective episodes could act as a trigger, unmasking or increasing symptoms, and so precipitating HRU and subsequent diagnosis. Alternatively, the increase in acute prescriptions may represent empirical trials

by primary care physicians following repeated patient attendances for persistent symptoms of uncertain aetiology.

The finding that 38% of patients had five or more LR consultations in the year preceding IPF diagnosis is suggestive that repeated primary care attendances are required to initiate further investigations or specialist referral. Given the potential for misdiagnosis we investigated the relationship of respiratory comorbidities to PFCS diagnosis. No clear association was identified, with COPD and asthma diagnoses occurring an average of five and 12 years before PFCS diagnosis, respectively. While these timelines may suggest the true presence of alternative respiratory diagnoses, the findings could reflect possible misdiagnosis of initial dyspnoea and functional impairment associated with early-onset PFCS.

Patients consistently report dissatisfaction with the time taken to diagnosis [15,16]. Our study identifies that there are repeated opportunities for earlier specialist referral and investigation. Studies investigating how to effectively increase awareness of pulmonary fibrosis among primary care physicians are required. This may include re-emphasis of the importance of routine lung auscultation in primary care to check for the presence of crackles, particularly in older patients who present with repeated LR complaints over a short time period. In older populations, there may be value in promoting a joint spirometric assessment / lung auscultation approach to obstructive and fibrotic lung disease diagnosis. Future research should seek to link primary

and secondary care data and to focus on the development of a pulmonary fibrosis risk algorithm for integration within clinical decision management systems.

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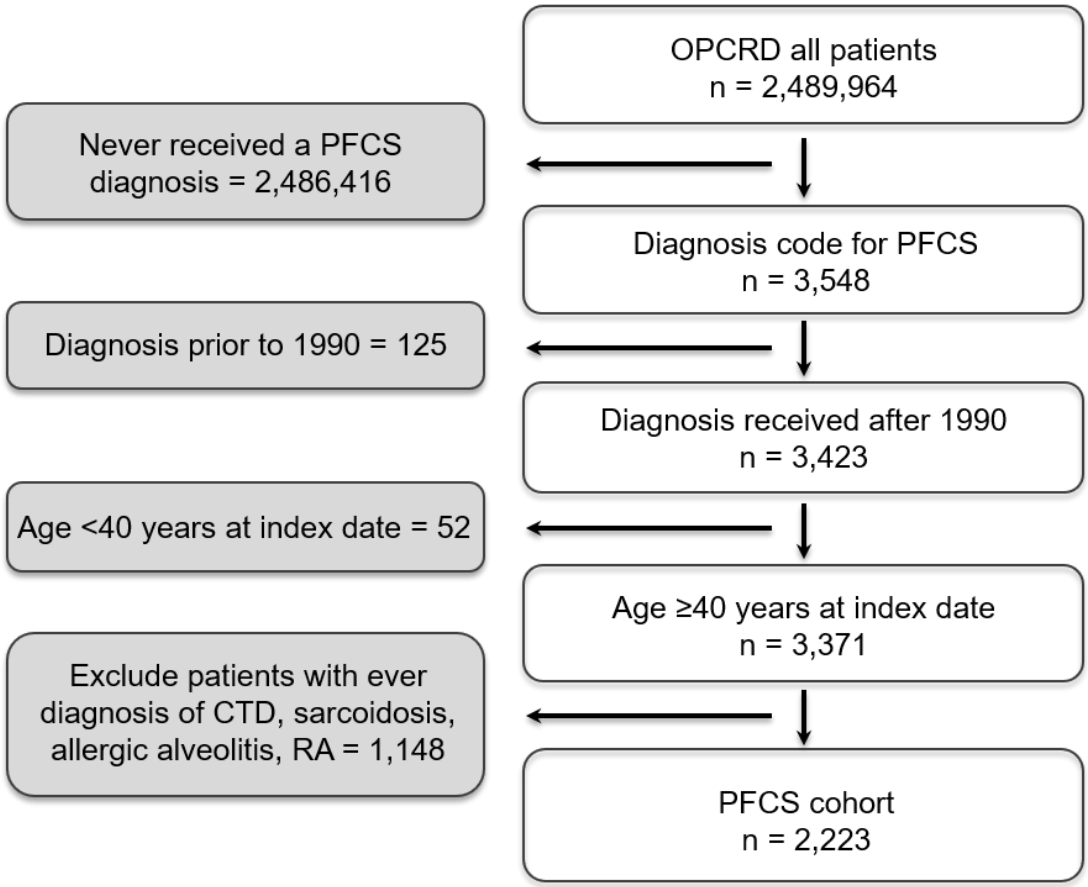
Figure 1. Pulmonary fibrosis clinical syndrome (PFCS) eligibility flow diagram

Figure 2. Increase in cough-related events in the ten years prior to PFCS diagnosis

Figure 3. Temporal HRU trends in the 10 years prior to PFCS diagnosis

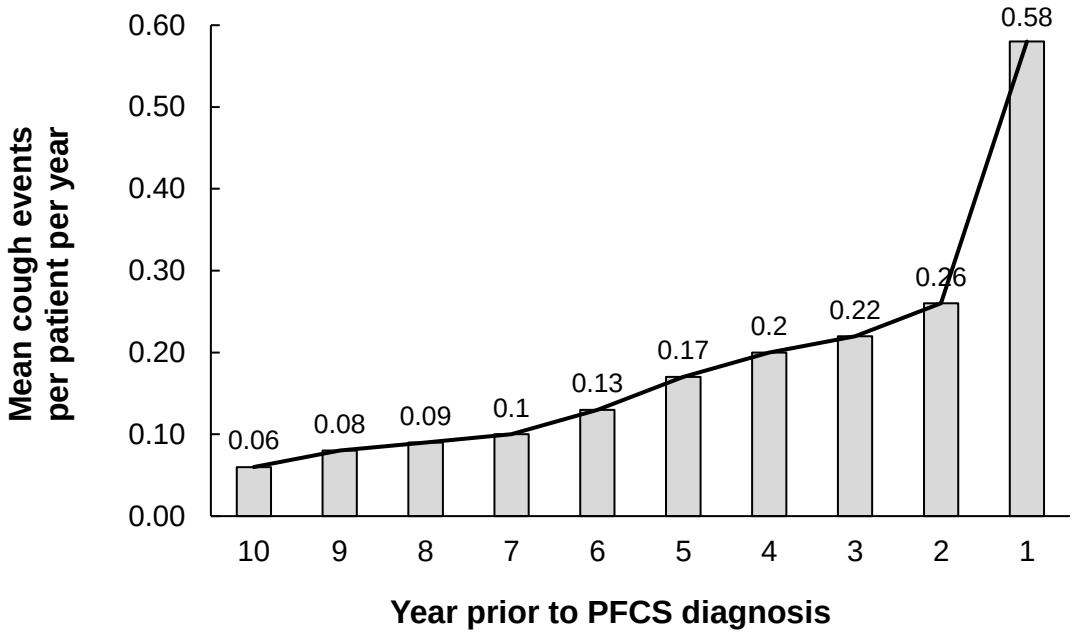
Figure 4. Distribution of LR healthcare contacts over the 10 years prior to PFCS diagnosis

Fig. 1. Pulmonary fibrosis clinical syndrome (PFCS) eligibility flow diagram



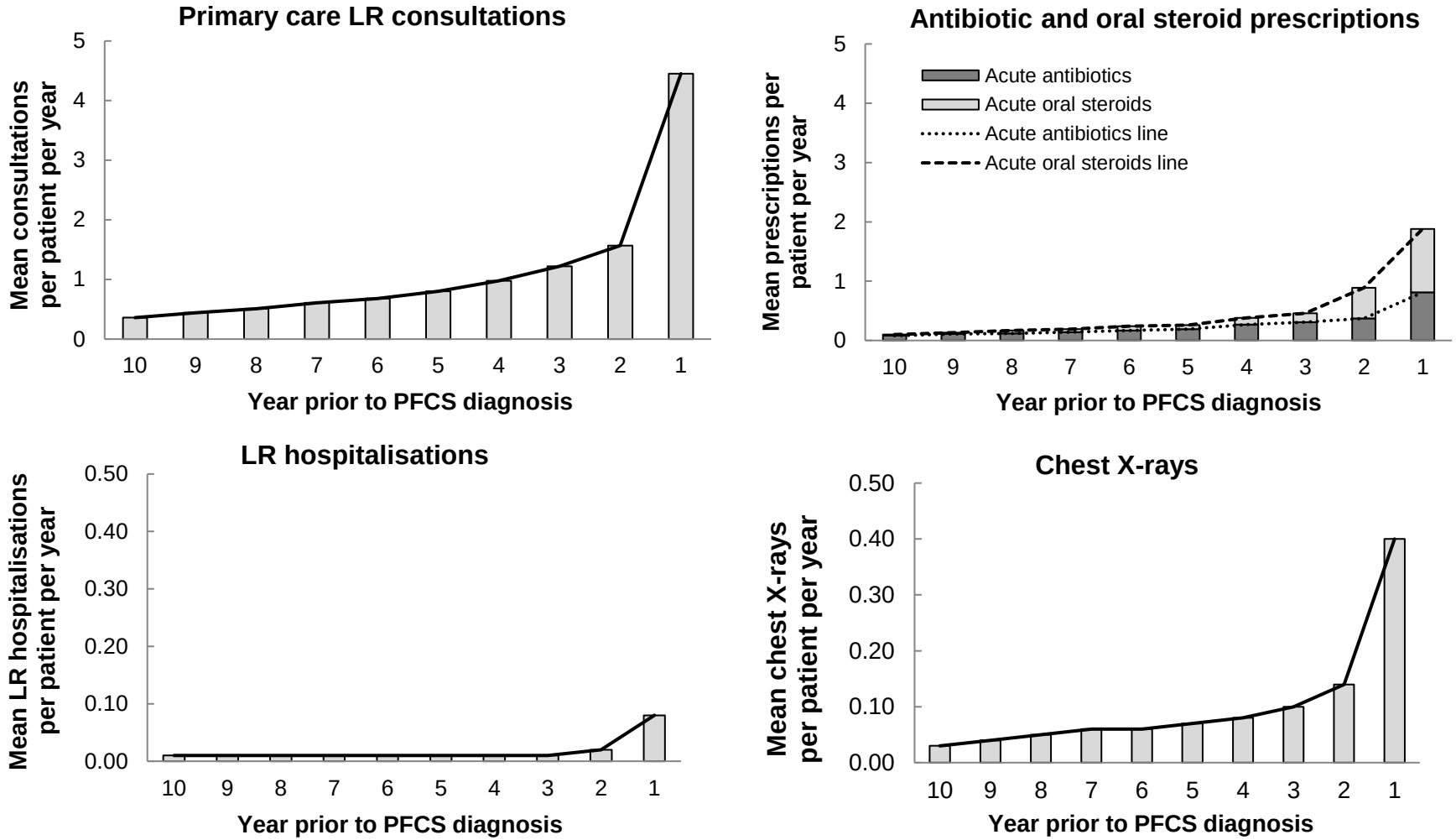
CTD: connective tissue disease; OPCRD: Optimum Patient Care Research Database (OPCRD); RA: rheumatoid arthritis;

Fig. 2. Increase in cough-related events in the ten years prior to PFCS diagnosis



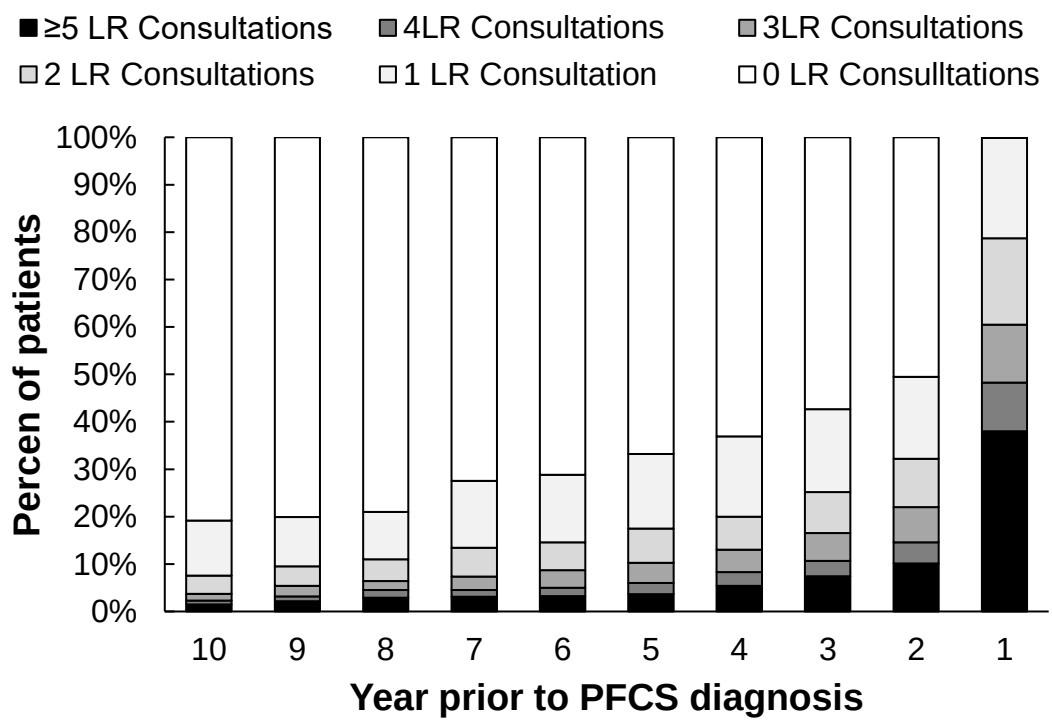
Number of patients with non-missing data in year 10 to year 1 prior to PFCS diagnosis: 1474, 1533, 1598, 1686, 1772, 1861, 1944, 2019, 2087, 2223

Fig. 3. Temporal HRU trends in the 10 years prior to PFCS diagnosis



Number of patients with non-missing data in year 10 to year 1 prior to IPFCS diagnosis: 1474, 1533, 1598, 1686, 1772, 1861, 1944, 2019, 2087, 2223

Fig. 4. Distribution of LR healthcare contacts over the 10 years prior to PFCS diagnosis



Number of patients with non-missing data in year 10 to year 1 prior to PFCS diagnosis: 1474, 1533, 1598, 1686, 1772, 1861, 1944, 2019, 2087, 2223

Table 1. Baseline characteristics at time of PFCS diagnosis

Characteristic	n = 2,223
Male sex, n (%)	1,399 (62.9)
Age at index date (y), mean (SD)	72.6 (9.7)
BMI (kg/m2), mean (SD)	27.3 (7.0)
Smoking status	
Never	688 (32.8)
Current	280 (13.4)
Former	1,127 (53.8)
Comorbidities, n (%)	
COPD	503 (22.6)
Asthma	309 (13.9)
Ischaemic heart disease	720 (32.4)
Heart failure	249 (11.2)
Hypertension	118 (5.3)
Myocardial infarction	258 (11.6)
Lung Cancer	401 (18.0)
Sleep Apnoea	18 (0.8)
GERD*	170 (7.7)
Anxiety and depression	55 (2.5)
Any prescriptions in year prior to PFCS diagnosis, n (%)	
SABA	514 (23.2)
SAMA	133 (6.0)
ICS	196 (8.8)
ICS/LABA	210 (9.4)
Lung Function	
Without comorbid COPD	**n = 245**
FVC (L), mean (SD)	2.9 (5.7)
FEV1/FVC ratio, mean (SD)	0.78 (0.1)
With comorbid COPD	**n = 74**
FVC (L), mean (SD)	2.5 (0.9)
FEV1/FVC ratio, mean (SD)	0.72 (0.2)

*Active comorbidities defined as recorded within two years prior to diagnosis; SABA: short-acting beta-agonist; SAMA: short-acting anti-muscarinic; ICS: inhaled corticosteroid; GERD: gastroeosophogeal reflux disease

Table 2. Temporal trends in healthcare resource utilisation in the 10 years prior to PFCS diagnosis

	Year prior to PFCS diagnosis									
	10	**9**	**8**	**7**	**6**	**5**	**4**	**3**	**2**	**1**
n (non-missing)	1474	1533	1598	1686	1772	1861	1944	2019	2087	2223
Primary care, mean (SD) pppy										
LR consultations	0.36 (1.3)	0.44 (1.3)	0.51 (1.4)	0.61 (1.5)	0.68 (1.7)	0.80 (1.9)	0.98 (2.0)	1.23 (2.3)	1.57 (0.9)	4.45 (1.6)
Prescriptions issued for LR complaints, mean (SD) pppy										
Antibiotics	0.08 (0.3)	0.11 (0.5)	0.12 (0.5)	0.14 (0.5)	0.17 (0.6)	0.19 (0.6)	0.27 (0.7)	0.31 (0.8)	0.37 (0.5)	0.81(0.7)
Acute oral steroid	0.02 (0.2)	0.02 (0.2)	0.05 (0.3)	0.05 (0.3)	0.07 (0.4)	0.07 (0.4)	0.12 (0.5)	0.15 (0.7)	0.52 (0.4)	1.07 (0.6)
Secondary care, mean (SD) pppy										
LR hospital admissions*	0.01 (0.1)	0.01 (0.1)	0.01 (0.1)	0.01 (0.1)	0.01 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.3(0.1)	0.08 (0.2)
LR hospital admissions (sen')†	0.01 (0.1)	0.01 (0.1)	0.01 (0.1)	0 (0.1)	0.01 (0.1)	0.01 (0.1)	0.01 (0.1)	0.01 (0.1)	0.01 (0.1)	0.05 (0.1)
Diagnostics, mean (SD) pppy										
Chest X-Rays	0.03 (0.2)	0.04 (0.2)	0.05 (0.3)	0.06 (0.3)	0.06 (0.3)	0.07 (0.3)	0.08 (0.3)	0.10 (0.4)	0.14 (0.2)	0.40 (0.5)

*LR code recorded on same day as inpatient admission; †LR code recorded within 14 days of an inpatient admission.
sen: sensitivity