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Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review

John Hutchinson, Andrew Fogarty, Richard Hubbard, Tricia McKeever

Epidemiology and Public Health, University of Nottingham, Nottingham, UK

Correspondence and requests for reprints should be addressed to John Hutchinson, University of Nottingham, C100 Clinical Sciences Building, City Hospital Campus, Hucknall Road, Nottingham, NG5 1PB, United Kingdom. Telephone: +44(0)1158 231359. Fax: +44(0)1158 231337. Email: john.hutchinson@nottingham.ac.uk

120 character summary: Incidence of idiopathic pulmonary fibrosis varies worldwide but seems to be increasing – rates around 3-9 per 100000/yr.

Word count: 3424

Abstract

Introduction: As idiopathic pulmonary fibrosis emerges as an important public health problem, there is a need to coordinate data on incidence and mortality globally. This study aims to systematically assess all available studies to investigate the global burden of disease.

Methods: Medline and Embase databases were searched systematically for all population-based studies of incidence or mortality of idiopathic pulmonary fibrosis. Clinical case series and prevalence studies were excluded. The search was supplemented using Google search engine, hand-searching of references and conference abstracts. Data were extracted independently by two authors using a pre-specified proforma, with assessment of methodological quality.

Results: 34 studies were identified providing data from 21 countries from 1968-2012. 28 studies reported incidence data, and eight reported mortality data. In studies from year 2000 onwards, we estimated a conservative incidence range of 3-9 cases per 100,000 per year for Europe and North America. Incidence was lower in East Asia and South America. The majority of studies showed an increase in incidence over time.

Conclusions: The incidence of idiopathic pulmonary fibrosis is increasing worldwide, and rates are coming together across countries. Current data suggest incidence is similar to that of conditions such as stomach, liver, testicular and cervical cancers.

Abstract word count: 199

Introduction

The incidence of idiopathic pulmonary fibrosis (IPF) has been reported in several studies worldwide and appears to be increasing (1-3), but different methodologies of case ascertainment and classification systems have prevented valid comparison between studies. A small number of published reviews have examined incidence and prevalence data from certain countries (4-8), but to date there has been no comprehensive systematic review of international incidence and mortality data in IPF.

This study aims to review all population-based studies of incidence and mortality of IPF worldwide, in an attempt to define the global burden of disease.

Methods

Data Sources and Searches

The review was registered on the PROSPERO international database of systematic reviews on 6 February 2014 (registration number CRD42014007452), with a pre-specified protocol. We aimed to include all original studies and abstracts assessing incidence or mortality of IPF, with no restrictions on language that might exclude certain areas of the world. We excluded prevalence studies and clinical case series, and focussed only on population-based studies with a specified denominator population. We excluded studies that examined interstitial

lung disease (ILD) other than IPF (for example, in association with connective tissue disease) but included studies that looked broadly at ILD with possible sub-classification.

We searched Medline (1946 – Present) and Embase (1974 – Latest) using OvidSP, with the latest search in June 2014. We used the terms 'idiopathic pulmonary fibrosis', 'interstitial lung disease', 'pulmonary fibrosis', 'cryptogenic fibrosing alveolitis', 'usual interstitial pneumonia' and 'idiopathic fibrosing alveolitis', combined with 'incidence', 'mortality', 'death' and 'epidemiology'. The full search strategy is detailed in the appendix. We supplemented this search using Google search engine with combinations of the search terms. We hand-searched abstract lists from the American Thoracic Society, British Thoracic Society and European Respiratory Society annual conferences, and screened reference lists of selected articles, as well as review articles identified. We also planned to review the websites of national statistics agencies for routine mortality data: this process was completed separately prior to the main review and has been published separately (9).

Study Selection

All stages of paper selection/elimination were performed independently by two authors – screening of titles (JH, RH), review of abstracts (JH, TM), and screening of papers and additional sources (JH, AF) – with disagreements resolved in each case by discussion. Non-English texts were translated using Google Translate with a plan for more comprehensive translation in case of any uncertainty as to the message or relevance.

Data Extraction and Quality Assessment

Data extraction took place using a pre-designed form that was piloted on four different studies independently by two reviewers (JH, TM) before use by the same two reviewers for the remaining studies, with review of scoring and final agreement reached by consensus discussion. Data extracted included region and time period of study, source of data, condition studied, case definition, age of cases, exclusion criteria, and incidence and mortality figures as provided. An assessment of methodological quality was made using a scoring system developed by consensus based on previous tools (10-12) (Appendix Table 1).

Meta-analysis of results was contemplated if data were suitably homogenous, but with an expectation that variable methodologies might make descriptive analysis more appropriate.

Results

1934 titles were screened, with selection of 109 abstracts, and the full texts of 35 of these were obtained for review (Figure 1). These were supplemented by 13 records identified via additional sources (5 from conference proceedings, 7 from direct internet searching or reference lists of citations and review articles, 1 published by our group prior to this review). From this total of 48 studies, 32 were selected for inclusion in the analysis. 2 further studies were added after a repeat search. One study in abstract form (13) was replaced with the full version (14) after this was published during the review process of the current work.

The included papers covered 21 countries, with data from 1968 to 2013. Eight studies examined mortality from IPF (1, 9, 15-20) and 28 reported incidence (1-3, 14, 19, 21-43). Most studies were from Europe and North America (25 studies), with a minority from Asia (five studies) and South America (two studies). Two multi-national studies included data from Oceania. Quality scores varied but eight studies scored full marks, with 29 out of the 34 studies (85%) scoring on at least half of the available criteria.

For clarity, incidence and mortality data are grouped by type of study: large pre-existing databases, local record systems, questionnaire surveys of physicians, and routine mortality statistics.

Large databases

The most frequent data sources used were pre-existing large databases (13 studies) (Table 1). There were four studies from Europe: three from the United Kingdom and one from Denmark. All sampled nationwide health databases. The UK studies showed an incidence of 4.6 per 100,000/year (95% confidence intervals (CI) 4.3-4.9) between 1991 and 2003 (21), 7.44 per 100,000/year (95% CI 7.12-7.77) between 2000 and 2008 (1), and 8.65 per 100,000/year (95% CI 8.40-8.90) from 2000-2012 (22). The Danish study in contrast reported a decreasing incidence of IPF, with a crude incidence of 7.27 per 100,000/year (95% CI 6.97-7.57) for 1995-2000, and 5.28 per 100,000/year (95% CI 5.01-5.56) for 2001-2005 (23).

Four studies from North America all used insurance claims databases. Raghu *et al* introduced broad and narrow diagnostic criteria (see Table 1), and reported an age-adjusted incidence of IPF, extrapolated to the overall US population, of 16.3 per 100,000/year (broad criteria) and 6.8 per 100,000/year (narrow criteria) (2). A later study from Raghu *et al* examined Medicare data from 2001-2011 and reported an incidence of IPF of 93.7 per 100,000/year in people aged 65 years and older (43), limiting comparison to other studies. This incidence estimate also used a slightly broader case definition. The incidence remained stable over the time period under study. The authors defined broad and narrow subgroups similarly to their previous study (2), and reported lower incidence rates of 31.1-43.0 per 100,000/year and 15.9-31.1 per 100,000/year respectively.

Two other insurance datasets provided less precise incidence estimates from North America. Ehrlich *et al* reported the age-adjusted incidence of 'pulmonary fibrosis' in diabetics and non-diabetics in California as 14 per 100,000/year and 9 per 100,000/year respectively (27). Saad *et al* reported the incidence of interstitial lung disease (but not IPF

specifically) in a Canadian cohort (28), and the authors were able to provide an incidence of IPF specifically for 2006 of 36.6 per 100,000/year (probable cases) (P Ernst, personal communication, May 2014).

Four studies from East Asia also used insurance and claims databases, and all reported lower incidence rates, ranging from 1.2-4.16 per 100,000/year (3, 24-26). Lai *et al* (3) noted the severity of IPF was higher and survival lower in Taiwan than in other studies, suggesting milder cases were not being captured. Data from the other three studies were more limited or needed extrapolation, but the incidence estimates calculated were all in a similar range. One additional study using large databases was from Brazil, where the incidence of IPF was calculated 0.26 per 100,000/year in 1996, rising to 0.48 per 100,000/year in 2010 (19).

Local records

Nine studies were classified as using local records to arrive at incidence statistics (Table 1). Coultas *et al* (29) investigated the incidence of ILD in New Mexico from 1988-1990 with thorough attempts to locate all cases. The crude incidence of IPF was calculated as 10.7 per 100,000/year in males, and 7.4 per 100,000/year in females. In a later study, Fernandez-Perez *et al* (30) investigated the incidence of IPF in Minnesota from 1997 to 2005, again with efforts to identify and verify all cases using international criteria (44, 45). Overall age- and sex-adjusted incidence in residents aged 50 years and older was 17.4 per 100,000/year (95% CI 12.4-22.4) (broad criteria), and 8.8 per 100,000/year (95% CI 5.3-12.4) (narrow criteria). In contrast to UK data, incidence appeared to decrease in later years (2003-2005) but case numbers were low.

Four studies from after the year 2000 examined incidence of IPF in regions of Europe (14, 31, 32, 42). The incidence ranged from 1.3 per 100,000/year in Denmark (42), to 7.5 per 100,000/year (coding criteria) or 9.3 per 100,000/yr (after additional case review) in Italy (14). Three older European studies examined incidence of IPF using earlier case terminology (33-35), with incidence of cryptogenic fibrosing alveolitis (CFA) ranging from 0.74-1.28 per 100,000/year in the Czech Republic from 1984-1998 (34), to 4.3 per 100,000/year in Norway over 1984-1998 (33).

Questionnaire surveys

Six studies estimated the incidence of IPF across a country by surveying pulmonary physicians (Table 1) (36-41). The highest incidence of IPF was reported in the most recent study, by Musellim *et al* from Turkey, where an estimated incidence of 4.69 per 100,000/year could be calculated (37) and the lowest incidence of IPF was from Flanders, Belgium, from 1992-1996, where Thomeer et al reported an incidence of IPF of only 0.22 per 100,000/year (41).

Routine mortality statistics

Routine mortality statistics were used in eight studies (Table 2). Two studies compared mortality data across countries (9, 15), three explored data from the USA (16-18), one looked specifically at the UK (1), and two reported data from Brazil (19, 20). All studies commented on change over time.

Hubbard *et al* (15) examined mortality from pulmonary fibrosis in seven countries, predominantly from the 1980s. Crude incidence rates were reported graphically for each country over time. Mortality was highest in the UK (>1 per 100,000) and lowest in Germany and the USA (<0.2 per 100,000). There was an increase in rate ratios over time in most countries, but no change in Germany or New Zealand, and a fall in the USA.

We recently reported more contemporaneous data from ten countries (9). Using broad codes, age-standardised rates ranged from 4.68 per 100,000 (Sweden) to 13.36 per 100,000 (Northern Ireland), with an increase in all countries over time. For more specific codes (available for selected countries), mortality varied from 4.64 per 100,000 (Spain) to 8.28 per 100,000 (England and Wales). Multiple cause mortality data (IPF listed anywhere on the death certificate, rather than only underlying cause of death) were available for three countries, and found to be higher, at 12.98 per 100,000 in England and Wales (2010) and 9.37 per 100,000 in the USA. There was less variation between countries in this analysis than previously, and while mortality increased year on year in the UK, multiple cause mortality data for the USA plateaued from 2003 onwards.

Three studies looked at multiple cause mortality in the USA using death certificate reports. Age-adjusted mortality increased from 3.2 per 100,000 in 1979, to 3.65 per 100,000 in 1991

(16), with an overall rate of 5.08 per 100,000 for 1992-2003 (17), and 7.57 per 100,000 for 1999-2003 (18).

Navaratnam *et al* (1) explored mortality of IPF in the UK from 1968-2008 and found that overall age-standardised mortality was 2.54 per 100,000 (95% CI 2.52-2.56) with a change from 0.92 per 100,000 in 1968-1972 to 5.10 per 100,000 in 2005-2008. The year on year increase in mortality was calculated at 5%.

Two Brazilian studies reported lower levels of mortality from IPF. Rufino *et al* noted an increase in mortality from 0.65 per 100,000 in 1996 to 1.21 per 100,000 in 2010 (19) and Fortuna *et al* noted an increase in mortality in the southern Brazilian state of Rio Grande do Sul, from 0.22 per 100,000 (1970s), to 0.48 per 100,000 (1990s) (20).

Overall incidence and mortality by geographic region

Most studies came from Europe and North America. In Europe, the highest rates were reported in the UK (1, 22), with a strong increase over time. Lower rates were noted in Scandinavia (23, 33) and southern Europe (36, 38-40), although some of these studies were likely subject to underreporting, and a more recent study from Italy had a higher incidence (14). In the USA, mortality statistics were lower and estimates using narrow criteria suggested an incidence of between 5-8 per 100,000 (2, 17, 18, 30). Both incidence and mortality studies from South America suggested a low incidence (0.4-1.2 per 100,000) (19, 20). Insurance claims-based incidence studies from East Asia also showed a low incidence (1.2-3.8 per 100,000) (3, 24, 25), although routine mortality statistics from Japan suggested a higher incidence (adjusted mortality rate of 10.26 per 100,000 for broad coding). Adjusted mortality statistics from Oceania ranged from 5.08-6.49 per 100,000 (9).

Overall incidence over time

The majority of studies reporting temporal trends in incidence of IPF showed an increase over time. Studies from the 1980s tended to have lower rates (15, 16, 34, 35), while later studies using similar data showed far higher rates (1, 17). Increasing incidence rates were particularly evident in UK datasets (1, 21), but also noted in South America (19, 20), East Asia (3) and Europe (34). However, mortality data from the USA appeared to plateau in some studies, and a decline was noted in studies from the USA (15, 30) and Denmark (23).

Summary statistics

Due to variation in study methodology, lack of confidence intervals for most studies, and differing time periods, formal meta-analysis to derive summary statistics was not possible. Attempts using those studies with confidence intervals produced a very high I^2 statistic of >98%, suggesting extremely high heterogeneity (values >75% considered 'high') (46), and this was also the case when we created roughly-estimated confidence intervals from available raw data from other incidence studies.

The overall range of incidence statistics varied from 0.22-93.7 per 100,000/year. In an attempt to deal with potential outliers and describe an estimate applicable to Europe and North America, we excluded studies from Asia and South America (different populations), and also questionnaire surveys with likely underreporting. We excluded older studies (with data prior to year 2000) and used narrow (rather than broad) criteria to limit over-diagnosis. This yielded a range of 2.8 to 9.3 per 100,000/year, as an estimate of IPF incidence.

Discussion

This review summarises 34 studies of IPF incidence and mortality, and draws together different types of work from across the world. Varying study methodologies, time periods and case definitions makes summary statistics difficult, but incidence ranges from 0.2 per 100,000/year to 93.7 per 100,000/year, with a tighter range of 3 to 9 per 100,000/year based on conservative estimates from Europe and North America. Incidence rates increased over time in most countries, and appear to be coalescing worldwide, but seem to be lower in Asia and South America. Current data suggest the incidence of idiopathic pulmonary

fibrosis worldwide is comparable to that of several malignancies, including stomach, liver, testicular and cervical cancers (47, 48).

Different study designs have different strengths and weaknesses. Large dataset studies and routine mortality statistics benefitted from large numbers of patients, but at the expense of clinical verification of diagnoses, with potential for misclassification. Some databases were also not representative of the underlying population. Mortality studies rated highly on quality scoring and allowed comparison across countries, but a major limitation was that IPF might not be the underlying cause of death, or may have been misdiagnosed in life. Many countries only report the most common respiratory causes of death, such as pneumonia or chronic obstructive pulmonary disease (COPD), and full ICD-10 codes are used infrequently - hence the broad codes used to identify cases in some of our countries will almost certainly classify other diseases as IPF. Whether this is counterbalanced by underreporting on death certificates is unclear.

Local records studies covered smaller geographical regions, but where possible diagnoses were verified by review of clinical records, in some cases with external review using international diagnostic criteria. While potentially more accurate, this approach limits the size of the population under review. The most detailed assessment was probably by Fernandez-Perez *et al* (30), but this identified only 24 cases of narrowly-defined IPF over eight years. Incidence statistics from these studies may also be difficult to apply to the wider population. Quality assessment varied considerably due to limited information regarding methodology and case verification in some studies.

The lower incidence found in questionnaire surveys undoubtedly reflects inadequate reporting of cases from participating centres. The highest level was reported most recently,

in Turkey in 2013 (37) - this may reflect increased effectiveness of questionnaire surveys in the internet age, where electronic registration and widespread awareness of international guidelines may enhance uptake and participation. Despite criticism of these studies, later questionnaires have provided greater detail on subdivisions of idiopathic interstitial pneumonia (such as non-specific interstitial pneumonia (NSIP) and cryptogenic organising pneumonia (13)) than has been possible using ICD-10 coding, and therefore give some idea of the proportion of cases of IPF that might be over-diagnosed using routine coding studies.

The ideal incidence study would sample a large dataset, but with an attempt at validating clinical diagnoses by review of records. Agabiti *et al*'s study from Lazio, Italy, followed this approach in a region of 4.7 million people with sampling from six hospitals (14), and also highlighted additional cases with review of less specific codes. Alternatively, with greater acceptance of international guidelines, more widespread use of imaging technology and greater education of clinicians, there may be less uncertainty regarding diagnosis of interstitial lung disease. Part of the difficulty assessing epidemiological studies in IPF results from the varying classification methods used, which have altered over time, making ILD less robust a diagnosis than conditions such as breast cancer or myocardial infarction. Consolidating international diagnostic criteria, as has happened with COPD, should help to address this.

In most studies, the incidence of IPF appears to be increasing over time, although two good quality studies in Denmark (23) and the USA (30) showed a decrease. Low patient numbers may limit the reliability of the observed decline demonstrated in the US study, and in the Danish study there was a possibility that prevalent cases may have been included in the earlier time period, with more cases of 'other' interstitial lung disease in the later time

period suggesting diagnostic transfer. The increasing incidence seen in UK studies seems unlikely to be purely due to coding issues, and more needs to be done to assess the reasons behind international variation in incidence.

There are several explanations why incidence and mortality of IPF may vary across countries. The lower incidence in South America may be due to under-diagnosis or under-reporting on death certificates. Both studies here used routine data, and the level of industrialisation in Brazil means that other diseases may have more of a focus in healthcare terms. In East Asia, the higher severity of disease in study subjects from insurance datasets likely reflects exclusion of milder cases, and may explain the lower incidence than in western countries. The higher mortality data from Japan in our study of death certification data may give weight to this (9). However, the coding used here was broad, and sub-classification suggested the majority of cases were recorded as 'unspecified ILD' rather than 'IPF', which might imply a different spectrum of ILD in East Asia.

In this review, we have attempted to include all incidence and mortality studies, including those presented purely as conference abstracts. We placed no language restrictions on our search strategy, however it is likely that some studies in other languages will have been missed by using English search terms. By focussing solely on population-based studies, we will have excluded a number of clinical case series from tertiary centres in more diverse areas of the world that may have provided indications of incidence, but it was considered that using these reports would require too many assumptions to be reliable. The fact that we included studies with differing methodologies and time periods did limit our ability to pool incidence statistics, but we felt our scope was appropriate.

Overall, available data is relatively consistent with regards the incidence and mortality of IPF worldwide. Most variation is likely a result of heterogeneity in study design, although there are trends that warrant further investigation, such as the apparent reduced incidence in East Asia and the contrast between incidence increasing in the UK and plateauing in the USA. Further studies should ideally be designed to allow appropriate comparisons across countries and we have proposed recommendations for future work (accepting the limitations researchers may face achieving these) (Appendix Table 2).

In summary, we have comprehensively searched for available data on incidence and mortality from idiopathic pulmonary fibrosis worldwide. Although different study methodologies limit comparisons, incidence does appear to be increasing in most regions worldwide, and rates are coming together. The variation between countries across different studies may reflect a transition in IPF incidence across the World from high to low incidence, and understanding why this is so may provide useful insights into the cause or causes of the disease.

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Tables

Table 1: Incidence of IPF in studies using large databases, local records, and questionnaire surveys

Author	Year	Country / region	Years studied	Type of data source	Condition studied	Case definition	Incidence per 100,000/yr †	Type of rate	Quality score	Comments
Large database studies										
Europe										
Maher*(22)	2013	UK	2000-2012	Nationwide primary care database ('CPRD')	IPF	n/a	8.65	Crude	5	Limited data available on methodology. Large numbers but reliant on accuracy of coding. May include other IIP.
Navaratnam(1)	2011	UK	2000-2008	Nationwide primary care database ('THIN')	IPF	Read codes for IFA/CFA/ PF	7.44	Crude	8	Large numbers, but reliant on accuracy of coding. May include other IIP.
Kornum(23)	2008	Denmark	1995-2000	Nationwide health database	IPF *(and ILD)*	ICD-10 J84.1	7.27 4.17	Crude Age-adjusted	9	Possible prevalent cases in earlier years. Reliant on accuracy of coding.
			2001-2005	Nationwide health database	IPF *(and ILD)*	ICD-10 J84.1	5.28 2.91	Crude Age-adjusted		
Gribbin(21)	2006	UK	1991-2003	Nationwide primary care database ('THIN')	IPF	Read codes for CFA, IFA	4.6	Crude	8	Large numbers, but reliant on accuracy of coding. May include other IIP.
North America										
Raghu(43)	2014	USA	2001-2011	Medicare database – 5% random sample	IPF	ICD-9 CM 516.3 and 515	93.7 (overall)	Crude, patients >65	6	Only patients >65 years. Medicare dataset may not be representative.
						ICD-9 CM 516.3	31.1-43.0 (broad) 15.9-31.1 (narrow)	Crude, patients >65		
Saad(28)	2013	Quebec, Canada	1990-2005	Health insurance plan database	ILD	ICD-9, ICD-10 codes	81 (probable) 35 (definite)	Crude, ILD overall	5	Not specific for IPF, sample may not be representative.
					IPF	ICD-10 J84.1	36.6 (probable)	Crude		Only data from one year.

Ehrlich(27)	2010	California, USA	1996-2005	Health insurance plan database	PF	ICD-9 516.3/ 515	9 (non-diabetics) 14 (diabetics)	Age-adjusted, by diabetic status	5	Only hospitalised patients, not specific for IPF, sample may not be representative.
Raghu(2)	2006	USA	1996-2000	Healthcare claims database	IPF	ICD-9 516.3	16.3 (broad) 6.8 (narrow)	Age-adjusted	8	Database may not be representative of wider population.
South America										
Rufino*(19)	2013	Brazil	1996-2010	Ministry of Health data	IPF	ICD-10 J84.1	0.48	Crude	6	Limited data available on methodology.
Asia										
Han*(24)	2013	South Korea	1992-2010	Healthcare claims from insurance medical cohort	IPF	n/a	4.16 (broad) 1.84 (narrow)	Crude, patients >30	6	Denominator over 30yrs. Estimated rates based on stable person-years over time, so potential underestimate. Sample may not be representative.
Lai(3)	2012	Taiwan	1997-2007	Health insurance database / Government records	IPF	ICD-9 516.3	1.4 (broad) 1.2 (narrow)	Crude	7	Only more severe cases included.
Ohno(26)	2008	Japan	2005	Medical benefits database	IPF (and IIP)	2002 ATS guidelines (44)	1.22	Crude	4	Extrapolated from sample of cases. Sample may not be representative.
Munakata*(25)	1994	Japan	1979-1992	Medical benefits database	IIP	n/a	1.23	Crude	0	Very limited data available on methodology. Sample may not be representative.
Local records studies										
Europe										
Hyldgaard(42)	2014	Aarhus, Denmark	2003-2009	Hospital registry and lists of HRCT scans from University Hospital	IPF (and ILD)	ICD-10 codes, ATS/ERS 2011 criteria (49)	1.3	Crude	6	Single centre study. Cases reviewed by international criteria.

Duchemann*(31)	2013	Seine Saint Denis, France	2011	Hospitals and GPs in region	ILD	n/a	11.68	Crude	3	Unclear how cases identified. Verification by expert panel review. Publication of full paper likely to yield more data.
Agabiti(14)	2014	Lazio, Italy	2005-2009	Regional hospital and mortality systems	IPF	ICD-9 CM 516.3, ATS/ERS 2011 criteria	7.5 (coding) 9.3 (after case review)	Crude	7	Hospitalised patients only. Case review of random sample of records.
Szafranski*(32)	2012	Radom, Poland	2000-2009	Hospital admissions database – single hospital	IPF (and ILD)	ICD-10 J84.1	2.8	Crude, in patients >14	7	Single centre, only age>14 in denominator
Von Plessen(33)	2003	Bergen, Norway	1984-1998	Hospital registers for two local hospitals	CFA	ICD-8 517, ICD-9 516.3, 515	4.3	Crude, in hospitalised patients >16	6	Hospitalised patients only. Only age>16 in denominator.
Kolek(34)	1994	Czech Republic	1981-1990	Multiple hospitals medical records review	CFA	n/a	1.28 (in 1990)	Crude	5	Unclear case definition.
Liebetrau(35)	1992	Thuringia, Germany	1986-1990	Patient population of tertiary hospital	PF	n/a	2.42 (in 1988)	Crude	3	Unclear case definition.
North America										
Fernandez-Perez(30)	2010	Minnesota, USA	1997-2005	Population-based medical records linkage system	IPF	ATS/ERS 2002 criteria	17.4 (broad) 8.8 (narrow)	Age-adjusted, in patients>50	9	Low numbers, only patients >50
Coultas(29)	1994	New Mexico, USA	1988-1990	Population-based, multiple sources (e.g. medical records, autopsies)	IPF (and ILD)	ICD-9 516.3, 515	10.7 (male) 7.4 (female)	Crude	8	Small region
Questionnaire Surveys										

Musellim(37)	2013	Turkey	2007-2009	Questionnaire registration system	IPF (as %ILD)	ATS/ERS 2002 criteria	4.69	Crude	5	Lack of response from certain centres
Karakatsani(36)	2009	Greece	2004	Departments of pulmonology with an interest in ILD	IPF (and ILD)	ATS/ERS 2002 criteria	0.93	Crude	5	60% response rate, lower proportion IPF than other registries
Tinelli(40)	2005	Italy	1998-2000	Respiratory medicine centres	IPF (as %ILD)	Clinical expertise	0.8	Crude	3	Unclear denominator population. No clear diagnostic criteria.
Lopez-Campos(38)	2004	Southern Spain	1998-2000	Questionnaire registration system from 29 hospitals	IPF (and ILD)	ICD-9 516.3	1.4	Crude	7	Other IIP classed under IPF code
Xaubet(39)	2004	Spain	2000-2001	Respiratory centres with an interest in ILD	IPF (as %ILD)	ATS/ERS 2002 criteria	2.9	Crude	5	62% response rate
Thomeer(41)	2001	Flanders, Belgium	1992-1996	Respiratory medicine centres	IPF (and ILD)	Local guidelines	0.22	Crude	5	Some IPF cases likely other types of IIP. No clear diagnostic criteria.

* Abstract only. † Average incidence for time period available; latest incidence stated where no average given (plus Kolek and Liebetrau studies), incidence extrapolated from ILD data where % of IPF cases given.

IPF: idiopathic pulmonary fibrosis; CFA: cryptogenic fibrosing alveolitis; ILD: interstitial lung disease; IIP: idiopathic interstitial pneumonia; PF: pulmonary fibrosis; IFA: idiopathic fibrosing alveolitis. ATS: American Thoracic Society. ERS: European Respiratory Society. ICD-*n [CM]*: International Classification of Diseases, n^{th} Revision, *[Clinical Modification]*. CPRD: Clinical Practice Research Datalink; THIN: The Health Improvement Network. n/a: not available.

Broad criteria: one of more claims with a diagnostic code for IPF, but no claims for another diagnostic code for ILD. Narrow criteria: as for broad criteria, with a relevant diagnostic test on or before their first diagnosis date. Broad and narrow criteria based on 2002 ATS/ERS guidelines for Fernandez-Perez study (44).
Probable cases from Saad study: received diagnosis of ILD from rheumatologist or pulmonary physician, or ILD was primary discharge diagnosis. Definite cases in addition had confirmatory diagnosis within 90 days.
ICD-10 code J84.1 is currently the most specific code for IPF, but may include other IIP. ICD-9 code 516.3 is roughly equivalent; code 515 is 'post-inflammatory fibrosis'

Table 2: Mortality from IPF in studies using routine mortality statistics

Author	Year	Country / region	Years studied	Type of data source	Condition studied	Case definition	Incidence per 100,000†	Type of rate	Quality score	Comments
Multicentre										
Hutchinson(9)	2014	England & Wales Australia Canada Japan New Zealand Northern Ireland Scotland Spain Sweden USA	2001-2012 2000-2011 2000-2011 2009-2011 2006-2010 2009-2011 2001-2012 2000-2011 2000-2012 1999-2010	National statistics agencies	IPF	ICD-10 J84 (less specific)	9.84 (2012) 6.49 (2011) 7.52 (2011) 10.26 (2011) 5.55 (2010) 13.36 (2011) 10.71 (2012) 5.38 (2011) 4.68 (2012) 7.80 (2010)	Age-adjusted	9	Possible coding misclassification, IPF may not be cause of death.
		England & Wales Australia Canada Spain USA	2001-2012 2000-2011 2000-2011 2000-2011 1999-2010	National statistics agencies	IPF	ICD-10 J84.1 (more specific)	8.28 (2012) 5.08 (2011) 6.38 (2011) 4.64 (2011) 6.16 (2010)	Age-adjusted		
Hubbard(15)	1996	England & Wales Scotland Australia Canada USA New Zealand Germany	1979-1992 1979-1991 1979-1991 1979-1991 1979-1988 1980-1987 1987-1992	National statistics agencies	IPF and PF	ICD-9 516.3, 515	Specific data not available	Crude	8	Possible coding misclassification, IPF may not be cause of death
Europe										
Navaratnam(1)	2011	UK	1968-2008	UK Office of	IPF	ICD-8 517	5.10 (2008)	Age-adjusted	9	Possible coding

				National Statistics		ICD-9 516.3, 515 ICD-10 J84.1				misclassification, IPF may not be cause of death
North America										
Pinheiro(18)	2008	USA	1999-2003	US NCHS	IPF ‡	ICD-10 J84.1	7.57	Age-adjusted	9	Possible coding misclassification. Multiple cause of death not comparable to other data.
Olson(17)	2007	USA	1992-2003	US NCHS	IPF ‡	ICD-9 516.3, 515 ICD-10 J84.1	5.08	Age-adjusted	9	
Mannino(16)	1996	USA	1979-1991	US NCHS	IPF and PF ‡	ICD-9 516.3, 515	3.65 (1991)	Age-adjusted	9	
South America										
Rufino*(19)	2013	Brazil	1996-2010	Ministry of Health	IPF	ICD-10 J84.1	1.21 (2010)	Crude	7	Possible underreporting. Limited information on reliability of data.
Fortuna(20)	2003	Rio Grande do Sul, Brazil	1979-2000	Regional Center for Health Information	IPF	ICD-8 517 ICD-9 516.3, 515 ICD-10 J84.1	0.68 ('96-'98)	Age-adjusted	9	

* Abstract only. †average incidence, or latest incidence (with year(s) specified) for large time periods.
‡ Multiple cause of death data used (rather than underlying cause of death).

IPF: idiopathic pulmonary fibrosis; PF: pulmonary fibrosis. NCHS: National Center for Health Statistics. ICD-n: International Classification of Diseases, nth Revision.

ICD-10 code J84.1 is currently the most specific code for IPF, but may include other IIP. J84 is a broader category that represents 'other interstitial pulmonary diseases', and will include some conditions that are not IPF. ICD-9 code 516.3 is roughly equivalent to J84.1; code 515 is 'post-inflammatory fibrosis'.

Figure legends

Figure 1: Flow diagram of search process

Figure 2: Incidence of IPF over time according to various studies (countries). Included studies used variable case definitions (see Table 1). Where broad and narrow criteria for IPF were reported, narrow criteria have been plotted. Where incidences were reported only as a range over several years, the latest years have been plotted. 95% confidence intervals plotted where provided. For Raghu (2014) study, lowest incidence estimate plotted. For Agabiti (2014) study, most definitive estimate plotted.

Figures

Figure 1

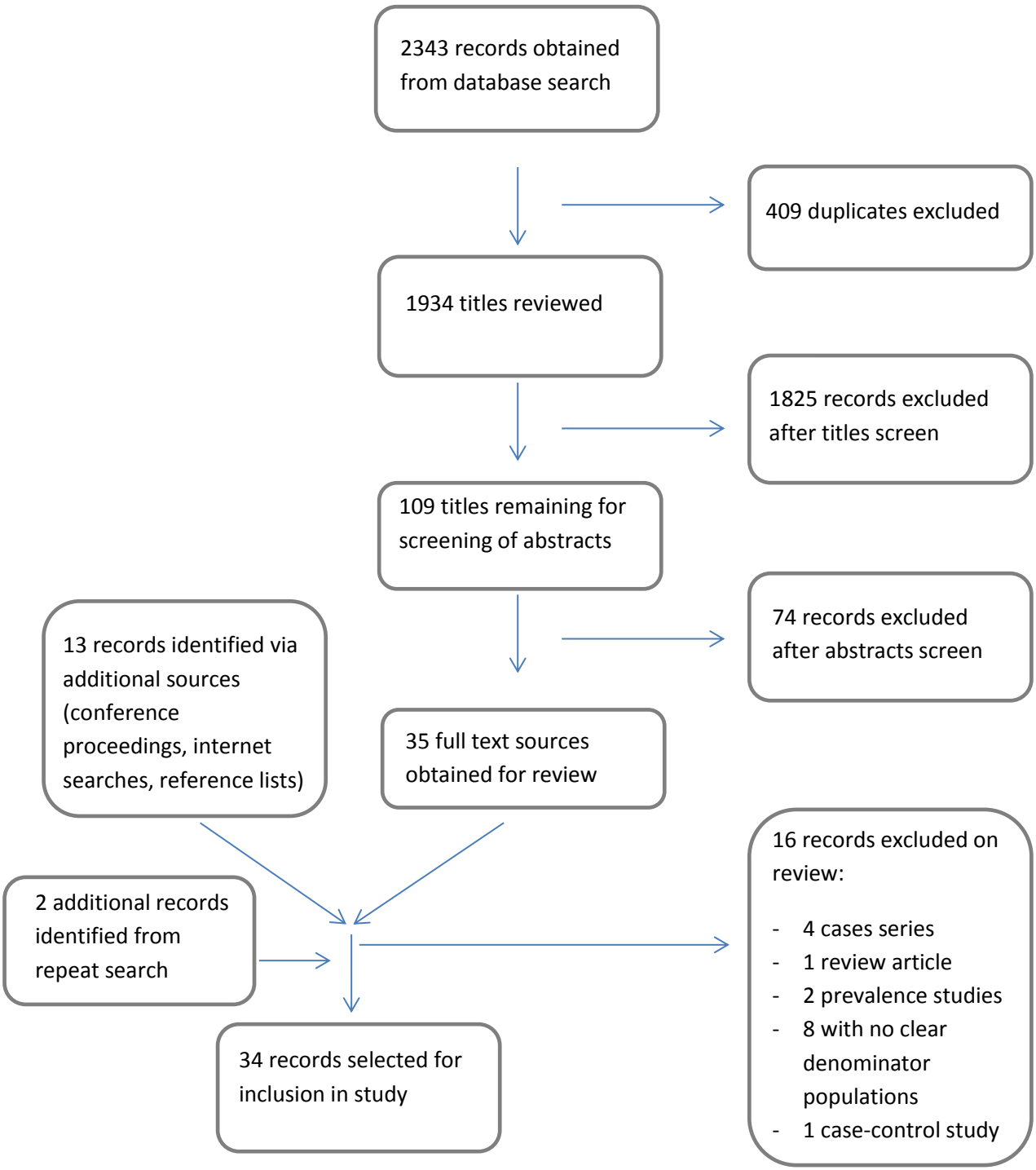
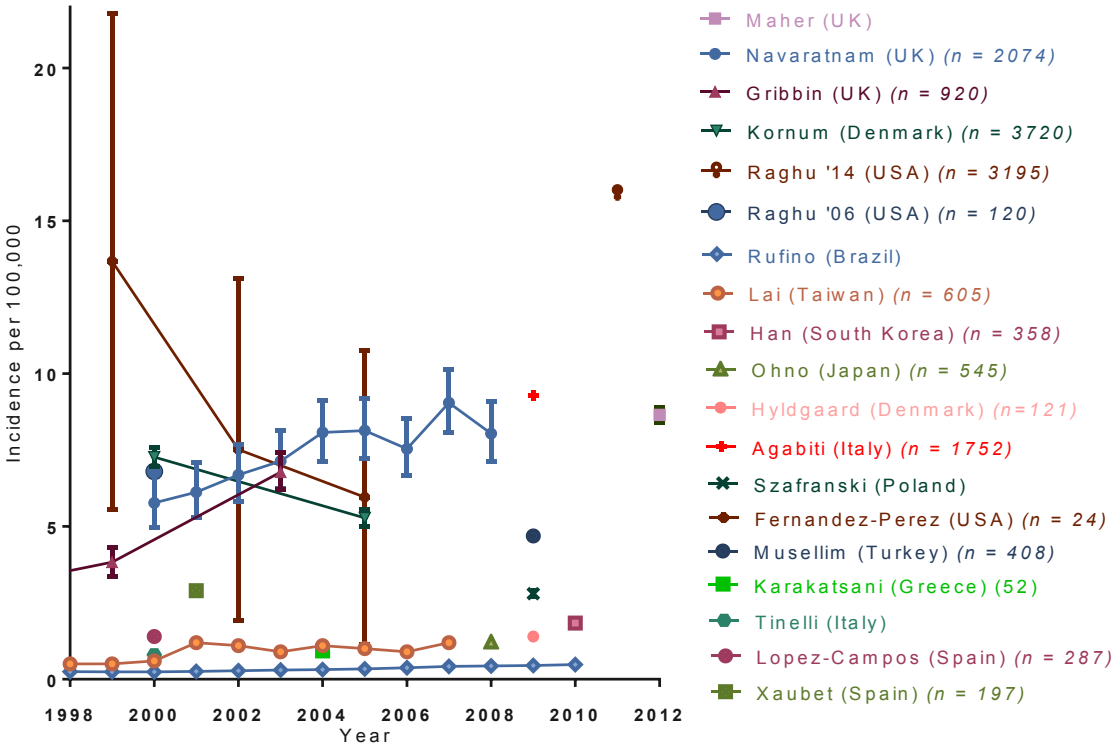


Figure 2


Incidence per 100,000
0
5
10
15
20
1998
2000
2002
2004
2006
2008
2010
2012
Year
Maher (UK)
Navaratnam (UK) (n = 2074)
Gribbin (UK) (n = 920)
Kornum (Denmark) (n = 3720)
Raghu '14 (USA) (n = 3195)
Raghu '06 (USA) (n = 120)
Rufino (Brazil)
Lai (Taiwan) (n = 605)
Han (South Korea) (n = 358)
Ohno (Japan) (n = 545)
Hyldgaard (Denmark) (n=121)
Agabiti (Italy) (n = 1752)
Szafranski (Poland)
Fernandez-Perez (USA) (n = 24)
Musellim (Turkey) (n = 408)
Karakatsani (Greece) (52)
Tinelli (Italy)
Lopez-Campos (Spain) (n = 287)
Xaubet (Spain) (n = 197)

Appendix

Full search strategy using OvidSP:

Search strategy developed by the authors (clinical and non-clinical academics with interests in IPF, epidemiology and medical statistics) with a trained medical librarian.

Search History (15 searches) *(close)*

# ▲	Searches
1	Idiopathic Pulmonary Fibrosis/
2	Lung Diseases, Interstitial/
3	Pulmonary Fibrosis/
4	(idiopathic pulmonary fibrosis or cryptogenic fibrosing alveolitis or interstitial lung disease or usual interstitial pneumonia or idiopathic fibrosing alveolitis).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, tn, dm, mf, dv, kw]
5	(IPF or CFA or ILD or UIP).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, tn, dm, mf, dv, kw]
6	1 or 2 or 3 or 4 or 5
7	incidence/
8	exp mortality/
9	death/
10	Epidemiology/
11	7 or 8 or 9 or 10
12	6 and 11
13	limit 12 to "all adult (19 plus years)" [Limit not valid in Embase; records were retained]
14	limit 13 to humans
15	limit 13 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained]

Appendix Table 1: Study methodological quality scoring

Population definition		Case definition	
Is the sampled population characteristic/ representative of the total population?	☐	Is IPF clearly defined and appropriate?	☐
Is there a precise denominator population?	☐	Are rates specific for IPF documented? (not just ILD?)	☐
Are inclusions / exclusions / age ranges clearly stated?	☐	Are rates age-standardised?	☐
Is the study period well defined?	☐	Do rates clearly measure incidence or mortality? (not prevalence)	☐
Is the response rate >70% of total? *or* Has the dataset been fully sampled? *or* Has case registration been near complete?	☐	Total score:	☐

Appendix Table 2: Recommendations for incidence and mortality studies of IPF

1	Codes used to identify cases should ideally be up-to-date and internationally agreed. ICD-10 code J84.1 is currently the most specific code for searching for IPF in databases, but may include other types of idiopathic interstitial pneumonia. ICD-10 CM (clinical modification) codes proposed for use in the USA from 2014 may be adopted elsewhere: J84.112 will then be the most specific code for IPF and will ensure differentiation from other forms of IIP. ICD-11 is due in 2017.
2	Clinical verification of a sample of cases should be undertaken, if possible, to ensure validity. 2011 ATS/ERS/JRS/ALAT guidelines have wide support and should be used to confirm diagnoses (49).
3	In countries where insurance datasets are used, broad and narrow criteria proposed by Raghu (2) have been used in a number of studies internationally and seem reasonable to assess cases, although efforts should be made to ensure milder cases are not missed, and to ensure that datasets are representative of the wider population.
4	In countries where pre-existing datasets do not exist, questionnaire surveys may be a useful alternative, if efforts are made to enhance ease of reporting, measure response rates, and standardise diagnostic processes.
5	Incidence rates should be reported per 100,000/year using a clear overall denominator population. Age-specific denominator populations should be avoided if possible to ensure reliable comparisons. Age-adjusted rates should be reported if available, with use of an appropriate reference population that is clearly specified.
6	National statistics agencies should aim to report causes of death by at least 4-digit ICD-10 codes, and ideally report both underlying cause of death and multiple cause of death data.