Increasing global mortality from Idiopathic Pulmonary Fibrosis in the 21st century

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JPH, TMM, AWF and RBH conceived and designed the study. JPH collated and analysed the data, with support from TMM, AWF, VN and RBH. VN provided the UK cohort data. All authors were involved in data interpretation. JPH wrote the first draft, and all other authors were involved in revisions and final approval prior to submission.

Running head: Global pulmonary fibrosis mortality

Subject code: 9.23 – Interstitial lung disease Word count: 3529

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

There is limited recent data on temporal trends in global mortality from pulmonary fibrosis.

What This Study Adds to the Field

Mortality from pulmonary fibrosis continues to increase around the world, despite the fact that death certification records are likely to underestimate true mortality.

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Abstract

Rationale: Recent evidence from the United Kingdom suggests that the number of deaths from idiopathic pulmonary fibrosis is increasing, although comparable international data are limited.

Objectives: We aimed to collate death certification data from multiple countries to determine global trends in mortality from idiopathic pulmonary fibrosis.

Methods: Data were obtained from the national statistics agencies of countries with relevant mortality records. Age-standardised mortality rates were calculated, and Poisson regression modelling was used to calculate rate ratios. Meta-analysis was used to calculate an overall estimate of mortality change over time.

Measurements and Main Results: Ten countries provided mortality data on pulmonary fibrosis over a period from 1999 to 2012. Age-standardised mortality ranged between 4 and 10 per 100,000 population for the most recent years of data, being lowest in Sweden (4.68 per 100,000), Spain (5.38 per 100,000) and New Zealand (5.55 per 100,000), and highest in the UK (9.84 per 100,000 in England and Wales, 10.71 per 100,000 in Scotland) and Japan (10.26 per 100,000). Positive associations with male sex and increasing age were consistently observed across all countries. There was an overall 2-3% annual increase in mortality depending on codes used for classification – for broad codes, overall rate ratio

1.03 (95% confidence intervals 1.02-1.04, p<0.001), for narrow codes, overall rate ratio 1.02 (95% confidence intervals 1.01-1.03, p<0.001). Validation in a local cohort showed that idiopathic pulmonary fibrosis was recorded as the underlying cause of death in two-thirds of known cases and anywhere on the death certificate in 80% of cases.

Conclusions: Mortality from idiopathic pulmonary fibrosis is increasing steadily worldwide, despite that fact that death certification will almost certainly underestimate true mortality. We estimate that there will be between 28000-65000 deaths in Europe and 13000-17000 deaths in the USA from idiopathic pulmonary fibrosis clinical syndrome in 2014. Variation between countries remains but is less than previously reported.

Abstract word count: 307

Keywords: idiopathic pulmonary fibrosis, epidemiology, mortality rates

Introduction

There is recent evidence of increasing incidence and mortality from idiopathic pulmonary fibrosis (IPF) in the United Kingdom (1), but less evidence from elsewhere in the World, with varying estimates from a limited number of historical studies with different methodologies (2). Mortality registration statistics, compiled from death certification, are the most frequent means of assessing mortality, despite some limitations (1, 3-5), particularly ascertainment completeness.

Mortality statistics are based on the International Classification of Diseases, Tenth revision (ICD-10) (6). IPF is classified under the overall code of J84 ('other interstitial pulmonary diseases'), with a specific code of J84.1 ('other interstitial pulmonary diseases with fibrosis'). We have previously selected cases of IPF using both J84.1 and the less specific code J84.9 ('interstitial pulmonary disease, unspecified'), with the rationale that many of these cases coded as J84.9 would have IPF (7). The two other codes under overall code J84 (J84.0 and J84.8) refer to 'alveolar and parietoalveolar conditions' and 'other specified interstitial lung disease' respectively, and are rarely used. Other idiopathic interstitial pneumonias such as non-specific interstitial pneumonia (NSIP) and cryptogenic organising pneumonia (COP) may also be classified under J84.1 according to some online databases (8, 9) but this is not clear in official guidance (6). Conditions such as sarcoidosis (D86), occupational or inhalational interstitial lung disease (J60-70) and connective tissue disease associated interstitial lung disease (J99.0, J99.1) are classified elsewhere (6). Mortality statistics are collated primarily based on one underlying cause of death (10), but additional multiple causes of death, when reported, have been useful in conditions such as IPF when the underlying cause of death may be unrelated (11).

This study aims to examine mortality from IPF across a number of countries using death certification data, in an attempt to assess current mortality rates, changes over time, and any regional differences.

Methods

Cause of death data were obtained from national statistics agencies worldwide. Websites were searched for all countries in Europe, North America, Australia, New Zealand, and countries in the G20 group of major economies. Underlying cause of death data were obtained for J84, and where available, more specific sub-codes (J84.1 and J84.9) were also obtained. J84.0 and J84.8 were only rarely used and therefore J84 was assumed to roughly approximate J84.1 and J84.9 for countries where sub-classification was unavailable. The term IPF-clinical syndrome (IPF-CS) was used to describe identified cases (1, 7), acknowledging that a minority may not be 'true' IPF. Multiple cause of death data (featuring all diseases mentioned on death certification) were obtained in addition to underlying cause of death where available: these records would be expected to include all cases where IPF was listed as either the underlying cause of death or as a secondary cause.

For each country, deaths were grouped in the following age categories: 0-44 years, 45-54 years, 55-64 years, 65-74 years, 75-84 years, 85 years and over. Crude mortality rates were calculated per 100,000 population, for ICD-10 codes J84, J84.1 alone, and J84.1 combined with J84.9. Age-standardised mortality rates were calculated by standardising to the 2013 European Standard Population (12). Poisson regression modelling was used to calculate mortality rate ratios by sex, age and year, and to calculate trend data for individual

countries. Meta-analysis using the random effects model was used to determine an overall estimate of change in mortality over time across countries. Data analysis was completed using Stata, version 11 (StataCorp, TX, USA).

To assess the validity of death certification in the UK as a measure of IPF mortality, the cause of death data for a recent cohort of patients with confirmed IPF were sought for all deaths. This cohort comprised 211 incident cases of IPF from England and Wales, recruited from 2010 to 2012 for another study (13), whose imaging had been reviewed by two experienced thoracic radiologists and confirmed as definite or probable usual interstitial pneumonia (UIP), the histological correlate of IPF, according to 2011 ATS/ERS criteria (14).

Results

Deaths from ICD-10 code J84 were available for England & Wales (2001-2012), Australia (2000-2011), Canada (2000-2011), Japan (2009-2011), Northern Ireland (2009-2011), New Zealand (2006-2010), Scotland (2001-2012), Spain (2000-2011), Sweden (2000-2012) and the United States (1999-2010). Data for specific codes J84.1 and J84.9 were available for England & Wales, Australia, Canada, Spain and USA. Multiple cause of death data were available in addition for England & Wales, Australia and the USA. Individual state-level data were available for the USA, but where values were less than ten deaths, data were suppressed for reasons of confidentiality, restricting the ability to calculate age-specific rates in smaller states. Data were therefore analysed for the largest five states, where suppressed data were minimal. Three years of data were outliers: Spain in 2005 (very

few deaths recorded) and USA multiple cause of death data in 2006 and 2007 for J84 (apparent excess of deaths from J84.8 in all states) (Table 1).

Comparison between ICD-10 codes

For the five countries with all codes available, J84.1 comprised 78-95% of all J84 codes for underlying cause of death over the years available, with J84.9 comprising 4-20% of codes. There was a lower proportion coded as J84.1 in the 0-44 age category. J84.1 and J84.9 combined therefore comprised the vast majority of total J84 cases: greater than 98% for almost all years of data. While most data from Japan was only available by three-digit ICD-10 code (J84), there were overall totals available, by sex, for each of the sub-codes. While over 99% were J84.1 and J84.9 combined, 70-75% of cases were sub-classified as J84.9, in contrast to elsewhere where the majority were classified as J84.1.

For reasons of clarity, J84.1 and J84 overall data are presented in the main text, with J84.1+J84.9 combined data reported in the data supplement.

Mortality across countries by underlying cause of death

Using the broad J84 classification, crude mortality varied from 2.54 per 100,000 population (Sweden, 2000) to 11.08 per 100,000 (Japan, 2011) (Table 2). Age-standardised mortality rates were highest in Northern Ireland, Scotland and Japan, and lowest in Sweden, Spain and New Zealand (Figure 1, Table 2), varying from 4.68 to 13.36 per 100,000 for the latest years available.

Males had consistently higher mortality than females, with mortality rate ratios for male sex from 1.59 in the USA (95% confidence interval (CI) 1.57-1.60, p<0.001) to 2.68 in Japan (95% CI 2.63-2.74). Meta-analysis of rate ratios for male vs female sex showed an overall estimate of 2.06 (95% CI 1.77-2.40, p<0.001, see Figure E1, data supplement). Mortality was significantly higher with increasing age. Mortality rates broadly increased over time for all countries. Adjusted annual increases in mortality ranged from 1-4%, with the exception of Northern Ireland where there was limited data and a large rise. The rate of increase was highest for England & Wales, Scotland and Japan (4%), and lowest for the USA (1%). Meta-analysis of mortality rate ratios over time showed an annual 3% increase over time (1.03, 95% CI 1.02-1.04, p<0.001) (Figure 1).

Using the more precise J84.1 coding, crude and age-standardised mortality rates were slightly lower but in similar proportions across the countries (Table 3 / Figure 2). The highest age-standardised rate was in England & Wales (8.28 per 100,000, in 2012), and the lowest in Spain (4.64 per 100,000, in 2011). Rate ratios for increasing age vs younger age were higher than using the broader J84 code. Rate ratios again increased over time for all countries, with the highest annual increase in England & Wales (annual increase 1.03, 95% CI 1.027-1.034, p for trend <0.001) and the lowest in the USA (annual increase 1.01, 95% CI 1.011-1.014, p for trend <0.001). Meta-analysis of rate ratios over time showed a 2% increase over time (rate ratio 1.02, 95% CI 1.01-1.03, p<0.001) (Figure 2).

We repeated the analysis excluding deaths under age 65 years, to enhance specificity of cases for IPF. Summary rate ratios by meta-analysis remained the same for all ICD-10 codes. We also performed a sensitivity analysis for J84 data excluding Japan and

Northern Ireland (countries with only three years of data), but there was no change in the meta-analysis.

Mortality using multiple cause of death data

Multiple cause of death data from the USA, Australia and England & Wales yielded considerably more deaths in each country (see Table 1). Age-standardised mortality rates were consequently higher than when examining underlying cause of death, and highest in England & Wales – for J84.1, mortality was 12.98 per 100,000 in 2010, compared to 9.85 per 100,000 in Australia, and 9.37 per 100,000 in the USA (Figure 3). Data for the broad code J84 were not analysed due to concerns over accuracy in the USA data (erroneous raw data for 2006/2007).

For England & Wales, mortality rate ratios over time were similar to underlying cause of death data. However, the rate of increase was less for Australia, and there was no increase over time in the USA. Using Poisson regression for combined USA, Australia and England & Wales data (years with data available for all three countries) there was less chance of having a diagnostic code of J84.1 in the USA compared to England & Wales (rate ratio 0.87, 95% CI 0.86-0.88, p <0.001), and also less chance in Australia (rate ratio 0.83, 95% CI 0.81-0.85, p<0.001) (Table 4). The mutually adjusted (for age and sex) mortality rate ratio for annual change was 1.00 (95% CI 1.001-1.003, p for trend=0.004). Meta-analysis using the random effects method (including all years with data available) showed individual rates of 1.03 for England & Wales (95% 1.027-1.032, p<0.001), 1.01 for Australia (95% CI 1.00-1.01, p=0.016), and 1.00 for USA (95% CI 0.999-1.001, p=0.701) (Table 4), with an overall rate of 1.01 (0.99-1.03, p=0.280).

Subnational data from the USA was limited due to suppressed data where there were small numbers of deaths. Using multiple cause of death data, *crude* mortality rates were available for all states, and ranged from 3.18 per 100,000 (Nevada) to 9.75 per 100,000 (Vermont) in 2010 for code J84.1. For the top 5 most populous states (California, Texas, New York, Florida, Illinois) with full age-specific data, the highest rates were in Texas (crude rate 5.44 per 100,000, age-standardised rate 10.69 per 100,000) and lowest in New York (crude rate 4.29 per 100,000, age standardised rate 6.42 per 100,000) (Table 5). While crude mortality rates increased over time, age-standardised rates remained relatively stable. Rate ratios for annual increase over time showed a marginal increase for Florida, Illinois and New York, but a marginal decrease for California and Texas, with an overall rate ratio by meta-analysis of 1.00 (95% CI 0.99-1.01, p=0.687).

Repeating the analysis for each country using multiple cause of death data excluding those aged under 65 made no change to summary rate ratio estimates for either code.

Validity of death certification

In the UK cohort study to date, there were 124 deaths out of 211 patients with IPF (median follow-up 2 years). Of these, 83 (67%) had IPF-CS coded as an underlying cause of death, and 102 (82%) had it elsewhere on the death certificate. For 8 of these patients, the code used was J84.9, whereas the remaining 116 used J84.1. There was considerably variability in text used on certificates, including idiopathic pulmonary fibrosis, pulmonary fibrosis, idiopathic fibrosing alveolitis, usual interstitial pneumonia, and interstitial lung disease. The latter two were coded as J84.9, even though both would be reasonable clinical calls as IPF. One case was classed as non-specific interstitial pneumonia (NSIP) and coded as J84.9. Of the 41 patients with alternative underlying causes of deaths, the majority were

due to ischaemic heart disease or cardiac failure (16 patients) and lung cancer (8 patients). Three patients had COPD chosen as the underlying cause of death when in text form it appeared to be given equal status to IPF.

Discussion

This study has shown worldwide variation in mortality from IPF-CS. Crude mortality rates varied from 3 per 100,000 to 9 per 100,000, being lowest in New Zealand, Sweden and Spain, and highest in the UK and Japan. There was an increase in age-standardised mortality rates over time in most countries studied that was more pronounced in some, such as the UK. The rate of increase was least in the USA, where rates were lower than in the UK, and using multiple cause mortality data there was no apparent increase over the time period studied. The clear association with male sex and increasing age described previously was confirmed across all countries in this study. Multiple cause of death data revealed considerably more deaths where IPF-CS was listed anywhere on the death certificate, strongly suggesting that it is often not listed as the underlying cause of death. Analysis of cause of death in a UK cohort of IPF patients revealed that IPF-CS was listed as the underlying cause of death in 2/3 of cases, and anywhere on the death certificate in 80%, suggesting mortality data may underestimate incidence by 20-30%.

The strengths of our study are the inclusion of international data from many countries, including some not previously studied, and that we have focussed on data from the first decade of the 21st century, which has only previously been assessed in England & Wales (1). This has allowed consistent use of more contemporary ICD-10 codes. We have

also been able to compare alternative coding methods, and both underlying and multiple cause mortality data for three countries. Our validation cohort is also the most recent attempt to assess the reported cause of death of patients with IPF, following previous work in the 1990s from the UK (15) and USA (5), and continues to show that death certification underestimates disease burden. The use of meta-analysis to combine national disease incidences gives a global composite estimate that can be considered a synthesis of the best available data into global summary statistics, with the high heterogeneity statistics an inevitable consequence of comparisons between different populations and cultures.

The key limitations of our study relate to the variability in cause of death data and its reliability. Although our validation cohort analysis shows that more patients with IPF have the disease listed on their death certificate than in earlier studies (5, 15), a significant proportion of patients with IPF will die from another cause, particularly cardiovascular disease or lung cancer, and even if IPF is listed as a contributing factor, multiple cause of death data are not as widely published. When IPF is the underlying cause of death, it may be misclassified or misdiagnosed, depending on the extent of diagnostic work-up prior to death, and also due to coding irregularities, and our validation cohort analysis provides evidence that cases of confirmed IPF are sometimes coded as 'unspecified' (ICD-10 code J84.9). ICD-10 code J84.1 is the most specific code for IPF, and this is supported by it being less common in younger patients, with higher rate ratios for increasing age, consistent with IPF being a disease of older people (16, 17). However, using J84.1 may miss these unspecified cases and so may underestimate mortality. Using broader codes is less accurate but likely closer approximates to true numbers. It is therefore likely that the combination of data used in our study for IPF-CS gives a reasonable estimation of true IPF mortality. Our

validation cohort was only from one country (England) and so may not be representative of other countries.

The only prior comparison of international mortality rates was by Hubbard *et al* in 1996, where data from seven countries (mainly from the 1980s) were used to compare cause of death from cryptogenic fibrosing alveolitis (CFA) and post-inflammatory fibrosis (PIF) (3). The authors found an increase in mortality from CFA over time for England & Wales, Scotland, Canada and Australia, but no increase for Germany or New Zealand, and a fall for the USA. There was considerable variation in mortality rates across countries. Mannino *et al* looked at US multiple cause mortality data for a similar period, and noted a slight increase in mortality from IPF over time, although with much lower rates than in the UK (11). The authors speculated that part of this might be due to coding practice in the USA, noting that PIF (ICD-9 code 515) featured more prominently than IPF (ICD -9 code 516.3) under the subheadings for 'fibrosis', in contrast to the UK where CFA featured more prominently under the subheading for 'alveolitis'. Olson *et al* updated this work by looking at US mortality rates from 1992-2003 (4), and noted a continued rise in mortality rates. Reasons postulated for the increase in mortality over this time period included changing smoking patterns in previous decades, greater use of high-resolution computed tomography, and a stricter classification system that saw IPF more explicitly linked with the usual interstitial pneumonia pattern of disease, which has a poorer prognosis (18). Our data suggest that while deaths from IPF-CS continue to increase in the USA, age-standardised rates have gone up less since 2003, and for J84.1 coding specifically appear to have plateaued. This is in contrast to England & Wales where rates are much higher and increasing.

The trend for increasing mortality from IPF-CS worldwide could reflect a true increase in disease incidence, but alternative explanations require consideration. These include greater physician awareness of the diagnosis, increasing use of diagnostic imaging, a desire amongst specialists to 'categorise' previously-labelled non-specific disease, reduced coding of pneumonia as an underlying cause of death due to ICD-10 guidance favouring chronic conditions such as respiratory and neurological disorders, and improved management of other chronic conditions such as cardiovascular disease, reducing deaths from competing causes. It is unclear how much the variation between countries reflects true differences in disease or the above factors. For example, the contrast between the proportion of deaths due to 'unspecified' interstitial lung disease in Japan (70-75%) and elsewhere (10-20%) warrants further exploration. Previous literature has suggested a lower incidence of IPF in East Asia (19, 20) although this likely relates to sampling of insurance databases featuring mainly severe disease. Assessment of data from other countries in East Asia would be very useful to explore these patterns further.

There are three reasons why mortality from IPF-CS in the USA may not be increasing as much as elsewhere in the world. It may be that the true incidence of IPF is less in the USA, that it is underdiagnosed, or that it is being coded incorrectly. The suggestion of poor coding noted by Mannino *et al* (11) is supported by Coultas and Hughes' death certificate study (5) that showed interstitial lung disease listed as an underlying cause of death in only 23% of known patients (and anywhere on the death certificate in 46%) – less than Johnston *et al*'s similar work in the UK (15) where the rates were 38% and 56% respectively. It seems likely that coding of IPF has improved in the USA over time but it may still be suboptimal. Fell *et al* showed that the combination of increasing age and suggestive radiology could

reasonably predict IPF in unclear cases without the need for surgical lung biopsy (16), but it may be that there is reluctance to code the diagnosis without biopsy evidence. On the other hand, Fernandez-Perez *et al* (21) investigated the incidence of IPF in Minnesota from 1997 to 2005 with thorough case ascertainment and review, and also noted a decline in incidence. A further validation study of death certification in the USA would be useful to explore the reliability of coding further.

If mortality rates from IPF-CS continue to increase as expected, the current year could potentially see anywhere from 28000-65000 deaths from IPF across Europe (using our lowest and highest mortality rates for underlying cause of death data (table 3), summary estimates for yearly increase, and a European population of approximately 740 million), which could equate to 42000-95000 clinical cases, loosely assuming the 2/3 percentage of cases dying from IPF found in our cohort to be representative of the wider population. For the USA the numbers would be approximately 13000-17000 deaths and 19000-25000 cases. Using the strictest code (J84.1), assuming rates continued to increase, there would be a doubling of deaths from IPF-CS in 36 years.

In summary, we have assessed mortality from IPF-CS across several countries, and demonstrated that it continues to increase with time in most countries studied, with some geographical variations. However, rates are reasonably consistent, with less variation than was evident in previous work (3), suggesting we may be approaching the true level. With new drugs for IPF on the market, it is important that there are reliable estimates of global disease burden. Increasing mortality rates may be due to true increases in incidence, but it is likely that some of the trends relate to changes in diagnostic or coding practices. Increasing openness, detail and accuracy with death certification is likely to improve the

utility of registration systems in future, and prospective IPF registries being set up in various countries may provide a linked resource to help validate routine mortality data. Recent international guidance from the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association published in 2011 (14) should help standardise and encourage specific diagnosis and a follow-up to the current study in several years would be useful to assess the impact.

Acknowledgements / data sources

England & Wales: Office for National Statistics, www.ons.gov.uk, accessed Nov 2013, additional multiple cause mortality data courtesy of Vanessa Fearn, Life Events and Population Sources Division, ONS, Jan 2014. Australia: Australian Bureau of Statistics, www.abs.gov.au, age-specific data supplied by Dimity Stephen, Health and Vital Statistics Unit, ABS, Jan 2014. Canada: Statistics Canada, Canadian Vital Statistics Database. www5.statcan.gc.ca/cansim, accessed Jan 2014. Japan: e-stat - Portal Site of Official Statistics of Japan, accessed Dec 2013, http://www.e-stat.go.jp/SG1/estat/NewListE.do?tid=000001028897. Northern Ireland: Northern Ireland Statistics & Research Agency, www.nisra.gov.uk, accessed Nov 2013. New Zealand: Statistics New Zealand, http://www.health.govt.nz/nz-health-statistics/health-statistics-and-data-sets/mortality-data-and-stats, accessed Nov 2013. Scotland: General Register Office for Scotland, www.gro-scotland.gov.uk/statistics, accessed Nov 2013. Spain: Instituto Nacional de Estadistica, www.ine.es/jaxi/menu.do?type=pcaxis&path=%2Ft15%2Fp417&file=inebase&L=1, www.ine.es/en/inebmenu/mnu_cifraspob_en.htm, accessed Nov 2013. Sweden: National Board of Health and Welfare, http://www.socialstyrelsen.se/statistics, accessed Nov 2013. USA: Centers for Disease Control and Prevention, National Center for Health Statistics, CDC Wonder Online Database, www.wonder.cdc.gov, accessed Nov 2013 and Jan 2014. Additional population data from US Census Bureau International Database: http://www.census.gov/population/international/data/idb/informationGateway.php.

ICD-10 coding data from World Health Organisation (WHO), International Statistical Classification of Disease and Related Health Problems, Tenth Revision (ICD-10) – www.who.int/classifications/icd10.

The 2013 European Standard Population, created by Eurostat, divides 100,000 people into 5-year age brackets, with greater weight on older age groups than previous standard populations, to account for demographic changes in Western countries. Using our age categories the distribution was 0-44yrs – 54000, 45-54yrs – 14000, 55-64yrs – 12500, 65-74yrs – 10500, 75-84yrs – 6500, 85+ yrs – 2500.

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Figure legends

Figure 1: A - Age-standardised mortality rates from J84 ('other interstitial pulmonary diseases') for selected countries by year, using underlying cause of death data. Age-standardised to 2013 European Standard Population. B - Meta-analysis of mortality rate ratios for annual increase in mortality from J84 over time, for underlying cause of death data, using random effects model.

Figure 2: A - Age-standardised mortality rates from J84.1 ('other interstitial pulmonary diseases with fibrosis') for selected countries by year, using underlying cause of death data. Age-standardised to 2013 European Standard Population. B - Meta-analysis of mortality rate ratios for annual increase in mortality from J84.1 over time, for underlying cause of death data, using random effects model.

Figure 3: Age-standardised mortality rates from J84.1 ('other interstitial pulmonary diseases with fibrosis') for England & Wales, Australia and USA over time, using multiple cause of death data. Age-standardised to 2013 European Standard Population.

Tables

Table 1: Countries included in analysis, with years of data and number of deaths per available ICD-10 code (J84: other interstitial pulmonary diseases; J84.1: other interstitial pulmonary diseases with fibrosis; J84.9: interstitial pulmonary disease, unspecified)

Country	Years of data analysed	Deaths from J84	Deaths from J84.1	Deaths from J84.1 and J84.9 (combined)
Underlying cause of death data				
England & Wales	2001-2012	38861	34473	38426
Australia	2000-2011	9325	7754	9182
Canada	2000-2011	17792	15350	17588
Japan	2009-2011	40928	n/a	n/a
Northern Ireland	2009-2011	398	n/a	n/a
New Zealand	2006-2010	699	n/a	n/a
Scotland	2001-2012	4341	n/a	n/a
Spain	2000-2004, 2006-2011	18563	16840	18344
Sweden	2000-2012	4153	n/a	n/a
USA	1999-2010	168637	135460	166222
Multiple cause of death data				
England & Wales	2001-2012	65770	59734	65643
Australia	2000-2011	17588	14829	17501
USA	1999-2010	220075 (excluding 2006/07 - outlier data)	214794	262595

Table 2: Crude and age-standardised mortality rates per 100,000 population from J84 ('other interstitial pulmonary diseases'), using underlying cause of death data

Country	Crude mortality rates per 100,000 population over time												
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
England & Wales		4.55	4.75	4.93	5.26	5.26	5.47	5.92	6.28	6.25	6.81	7.64	8.22
Australia	3.09	3.42	3.66	3.37	3.49	3.08	3.77	3.78	4.26	4.12	4.68	4.44	
Canada	3.55	3.80	3.75	3.66	4.58	4.96	4.66	4.85	4.89	5.14	5.30	5.42	
Japan										9.69	10.38	11.08	
Northern Ireland										5.91	6.76	9.37	
New Zealand							2.75	3.36	3.40	3.31	3.52		
Scotland		4.66	5.64	5.83	5.81	6.63	6.76	7.27	7.72	7.72	7.79	9.30	8.88
Spain	2.96	3.22	3.48	3.61	3.62		3.77	4.30	4.05	4.15	4.56	4.74	
Sweden	2.54	2.69	3.09	3.25	3.54	3.55	3.51	3.42	3.66	3.69	4.11	3.88	4.25
USA	4.40	4.59	4.18	4.38	5.11	4.86	4.97	5.01	5.15	5.19	5.27		

Country	Age-standardised mortality rates per 100,000 population over time												
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
England & Wales		6.39	6.19	6.42	6.82	6.72	6.97	7.57	7.93	7.85	8.47	9.41	9.84
Australia	5.11	5.63	5.89	5.33	5.41	4.78	5.72	5.69	6.46	6.11	6.87	6.49	
Canada	5.93	6.30	6.05	5.81	7.31	7.74	7.11	7.21	7.14	7.36	7.57	7.52	
Japan										9.42	9.93	10.26	
Northern Ireland										8.22	9.80	13.36	
New Zealand							4.79	5.74	5.52	5.35	5.55		
Scotland		6.43	7.47	7.84	7.67	8.82	8.82	9.26	9.55	9.72	9.70	11.34	10.71
Spain	3.73	4.07	4.37	4.47	4.51		4.63	5.23	4.87	4.91	5.33	5.38	
Sweden	2.84	3.10	3.59	3.72	4.01	4.07	4.04	3.90	4.13	4.14	4.60	4.37	4.68
USA	7.01	7.22	6.57	6.86	7.95	7.50	7.63	7.62	7.76	7.71	7.80		

Age-standardised to 2013 European Standard Population

Table 3: Crude and age-standardised mortality rates per 100,000 population from J84.1 ('other interstitial pulmonary diseases with fibrosis') over time, using underlying cause of death data

Country	Crude mortality rates per 100,000 population over time												
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
England & Wales		4.33	4.48	4.61	4.87	4.81	4.88	5.28	5.50	5.32	5.77	6.59	6.90
Australia	2.56	2.89	3.14	2.90	2.97	2.64	3.13	3.23	3.57	3.31	3.80	3.47	
Canada	3.06	3.21	3.30	3.18	4.05	4.34	4.11	4.18	4.21	4.42	4.43	4.60	
Spain	2.78	3.01	3.28	3.37	3.39		3.43	3.92	3.65	3.71	3.94	4.09	
USA	3.48	3.63	3.40	3.61	4.23	3.99	4.00	4.04	4.11	4.09	4.12		

Country	Age-standardised mortality rates per 100,000 population over time												
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
England & Wales		6.09	5.84	6.03	6.33	6.15	6.23	6.75	6.96	6.71	7.19	8.13	8.28
Australia	4.23	4.80	5.04	4.60	4.65	4.13	4.74	4.84	5.44	4.97	5.59	5.08	
Canada	5.09	5.40	5.36	5.09	6.47	6.82	6.29	6.25	6.16	6.33	6.33	6.38	
Spain	3.51	3.80	4.11	4.17	4.21		4.22	4.78	4.40	4.40	4.63	4.64	
USA	5.62	5.78	5.40	5.70	6.62	6.21	6.18	6.21	6.24	6.14	6.16		

Age-standardised to 2013 European Standard Population

Table 4: Deaths, crude and age-standardised mortality rates, Poisson regression modelling and rate ratios for annual increase in mortality for J84.1 ('other interstitial pulmonary diseases with fibrosis') for England & Wales (E&W), Australia and USA, using multiple cause of death data, from 2001-2010

	Deaths	Person years (millions)	Crude mortality rate (per 100,000 population)	Age-standardised mortality rate (per 100,000 population)	Mutually adjusted (for age and sex) mortality rate ratio (95% confidence intervals)	
Overall data						
Sex						
Female	109664	1887.95	5.81	6.73	1.00	
Male	133081	1825.06	7.29	13.53	1.78	(1.77-1.79)*
Age group (years)						
0-44	3304	2308.71	0.14	0.11	0.01	(0.01-0.01)
45-54	7311	524.15	1.39	1.13	0.07	(0.06-0.07))
55-64	20991	394.75	5.32	5.10	0.25	(0.25-0.25)
65-74	53786	254.38	21.14	22.00	1.00	
75-84	95554	168.54	56.69	63.08	2.76	(2.73-2.79)
85+	61799	62.47	98.92	114.40	5.13	(5.08-5.19)†
Country						
E&W	47285	537.91	8.79	11.37	1.00	
Australia	12440	204.85	6.07	9.47	0.83	(0.81-0.85)*
USA	183020	2970.25	6.16	9.55	0.87	(0.86-0.88)*
By male sex						
Age group (years)						
0-44	1545	1168.63	0.13	0.11	0.00	(0.00-0.01)
45-54	3913	258.06	1.52	1.29	0.05	(0.05-0.06)
55-64	12539	191.35	6.55	6.52	0.24	(0.23-0.24)
65-74	33146	118.12	28.06	29.59	1.00	
75-84	54582	69.57	78.45	85.00	2.80	(2.76-2.84)
85+	27356	19.33	141.56	153.53	5.06	(4.98-5.14)†
Country						
E&W	29651	263.89	11.24	15.98	1.00	
Australia	7384	101.79	7.25	12.70	0.76	(0.74-0.78)*
USA	96046	1459.37	6.58	11.90	0.74	(0.73-0.75)*
By female sex						
Age group (years)						
0-44	1759	1140.09	0.15	0.12	0.01	0.01-0.01
45-54	3398	266.09	1.28	0.98	0.84	0.08-0.09
55-64	8452	203.40	4.16	3.68	0.27	0.27-0.28
65-74	20640	136.26	15.15	14.42	1.00	
75-84	40972	98.97	41.40	41.16	2.73	2.69-2.78
85+	34443	43.15	79.83	75.27	5.27	5.18-5.36†
Country						
E&W	17634	274.02	6.44	6.75	1.00	
Australia	5056	103.06	4.91	6.25	0.94	(0.91-0.97)*
USA	86974	1510.88	5.76	7.20	1.09	(1.07-1.10)*

Country	Rate ratio	95% Confidence Intervals	p value
England & Wales	1.03	1.027-1.032	<0.001
Australia	1.01	1.00-1.01	0.016
USA	1.00	0.999-1.001	0.701

Age-standardised to 2013 European Standard Population. *p<0.001, †p for trend<0.001

Table 5: Deaths, crude and age-standardised mortality rates, Poisson regression modelling and rate ratios for annual increase in mortality for J84.1 ('other interstitial pulmonary diseases with fibrosis') for five most populous states in USA, using multiple cause of death data, from 2001-2010

	Deaths	Person years (millions)	Crude mortality rate (per 100,000 population)	Age-standardised mortality rate (per 100,000 population)	Mutually adjusted (for age and sex) mortality rate ratio (95% confidence intervals)	
Overall data						
Sex						
Female	30845	603.45	5.11	6.71	1.00	
Male	34024	585.56	5.81	10.82	1.61	(1.58-1.63)*
Age group (years)						
0-44	327	762.01	0.04	0.03	0.01	(0.01-0.01)
45-54	2332	164.39	1.42	1.43	0.07	(0.07-0.08)
55-64	6013	117.28	5.13	5.25	0.27	(0.26-0.28)
65-74	14277	75.89	18.81	19.37	1.00	
75-84	25018	50.79	49.26	52.05	2.69	(2.63-2.75)
85+	16902	18.66	90.59	98.87	5.21	(5.09-5.32) †
State						
California	19928	392.97	5.07	9.00	1.00	
Florida	14156	193.81	7.30	8.53	0.96	(0.94-0.98)*
Illinois	8005	138.90	5.76	9.18	1.03	(1.01-1.06) ‡
New York	9043	210.81	4.29	6.42	0.71	(0.70-0.73)*
Texas	13737	252.51	5.44	10.69	1.21	(1.18-1.23)*
By male sex						
Age group (years)						
0-44	133	387.06	0.03	0.03	0.01	(0.00-0.01)
45-54	1211	80.73	1.50	1.53	0.06	(0.06-0.67)
55-64	3446	56.07	6.15	6.26	0.26	(0.25-0.27)
65-74	8333	34.73	24.00	24.20	1.00	
75-84	13647	20.95	65.14	65.56	2.73	(2.65-2.80)
85+	7254	6.02	120.44	120.30	5.07	(4.91-5.23) †
State						
California	10460	195.57	5.35	11.05	1.00	
Florida	7799	94.72	8.23	10.65	0.98	(0.95-1.01) §
Illinois	4096	68.10	6.01	11.43	1.05	(1.01-1.09) ||
New York	4726	101.84	4.64	8.17	0.75	(0.72-0.77) *
Texas	6943	125.32	5.54	12.79	1.17	(1.14-1.21) *
By female sex						
Age group (years)						
0-44	194	374.96	0.05	0.04	0.01	(0.007-0.009)
45-54	1121	83.65	1.34	1.33	0.94	(0.09-0.10)
55-64	2567	61.21	4.19	4.24	0.29	(0.28-0.30)
65-74	5944	41.16	14.44	14.56	1.00	
75-84	11371	29.83	38.11	38.55	2.65	(2.57-2.74)
85+	9648	12.63	76.36	77.43	5.36	(5.19-5.53) †
State						
California	9468	197.40	4.80	6.94	1.00	
Florida	6357	99.09	6.42	6.40	0.93	(0.90-0.96))*
Illinois	3909	70.80	5.52	6.93	1.01	(0.98-1.05) ¶
New York	4317	108.97	3.96	4.67	0.68	(0.66-0.71))*
Texas	6794	127.19	5.34	8.59	1.24	(1.20-1.28))*

State	Rate ratio	95% Confidence Intervals	p value
California	0.99	0.98-0.99	<0.001
Florida	1.01	1.00-1.01	0.016
Illinois	1.01	1.00-1.01	0.056
New York	1.00	1.00-1.01	0.161
Texas	0.99	0.98-0.99	<0.001

Age-standardised to 2013 European Standard Population.*p<0.001, †p for trend<0.001, ‡ p=0.015, § p=0.158, || p=0.006, ¶ p=0.517

Figures

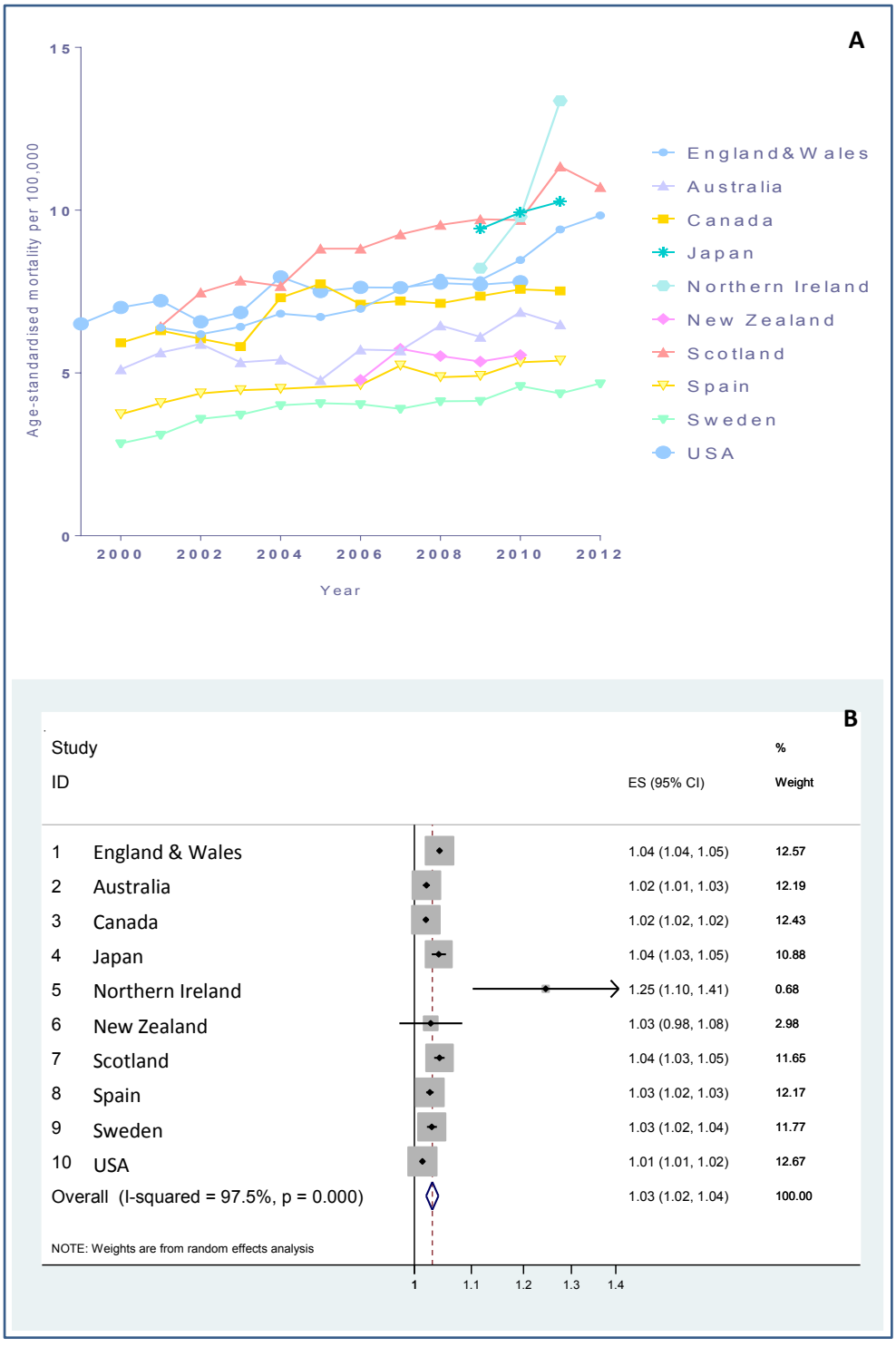

Figure 1

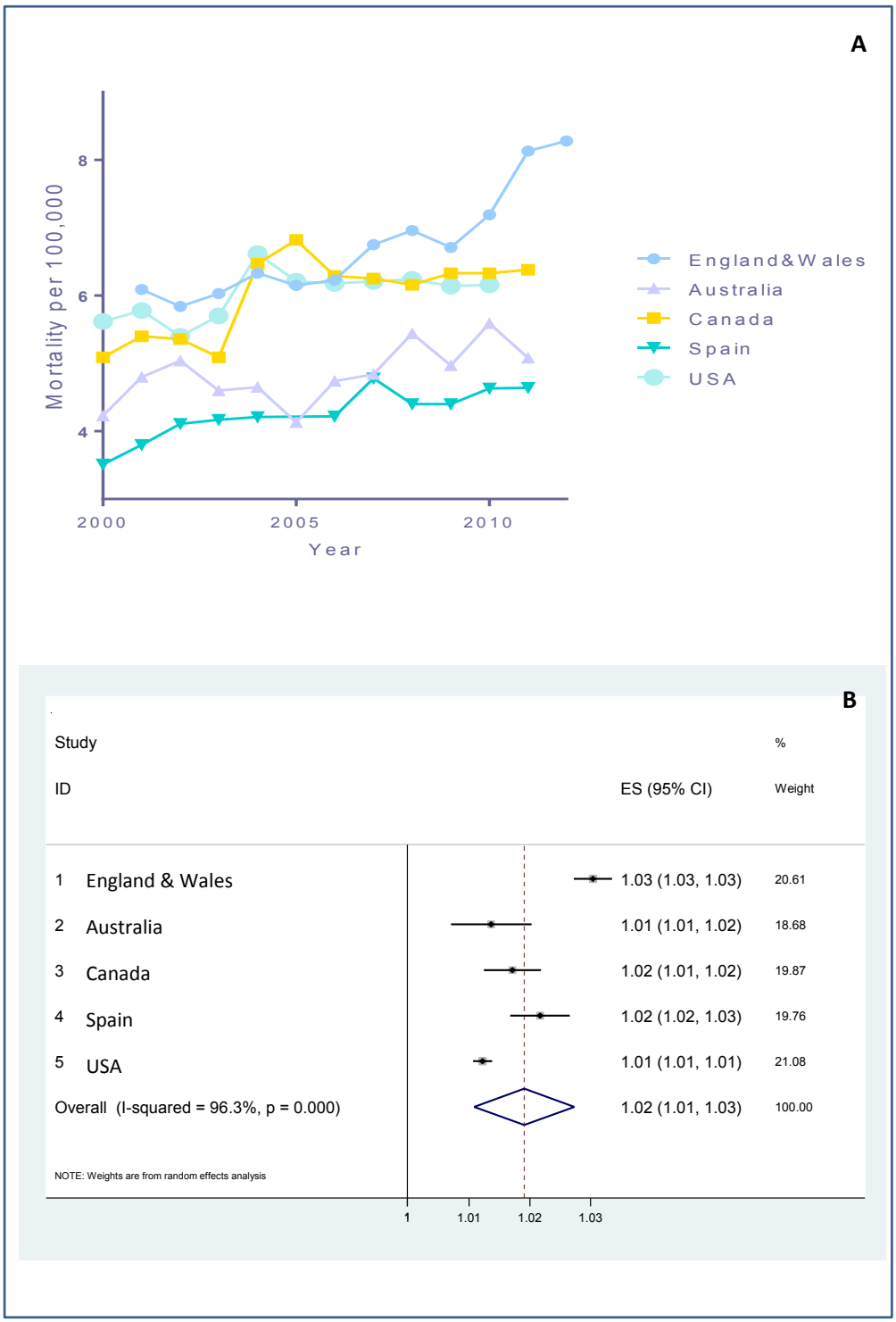
A
Mortality per 100,000
8
6
4
2000
2005
2010
Year
England&Wales
Australia
Canada
Spain
USA
B
Study
ID
ES (95% CI)
%
Weight
1 England & Wales
1.03 (1.03, 1.03)
20.61
2 Australia
1.01 (1.01, 1.02)
18.68
3 Canada
1.02 (1.01, 1.02)
19.87
4 Spain
1.02 (1.02, 1.03)
19.76
5 USA
1.01 (1.01, 1.01)
21.08
Overall (I-squared = 96.3%, p = 0.000)
1.02 (1.01, 1.03)
100.00
NOTE: Weights are from random effects analysis
1
1.01
1.02
1.03

Figure 2

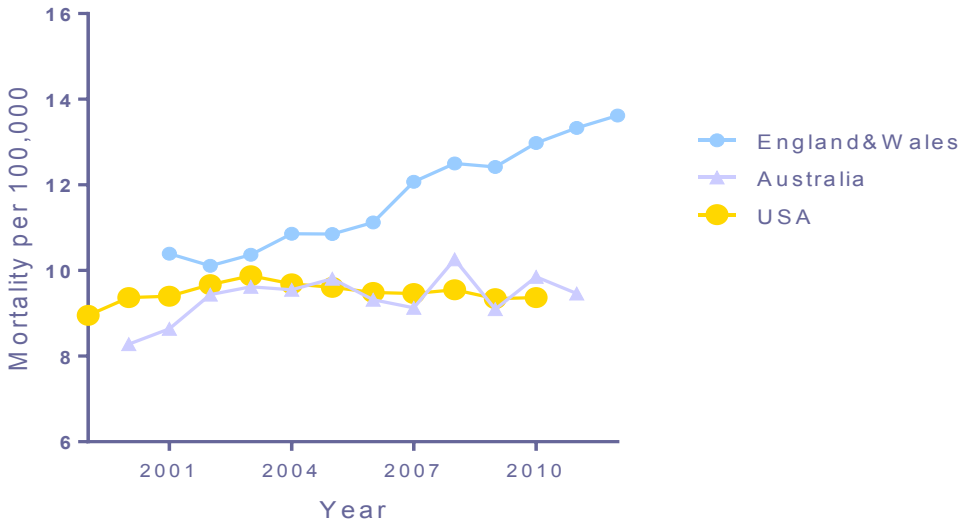
16
14
12
10
8
6
Mortality per 100,000
2001
2004
2007
2010
Year
England&Wales
Australia
USA

Figure 3

Increasing global mortality from Idiopathic Pulmonary Fibrosis in the 21st century

John Hutchinson, Tricia McKeever, Andrew Fogarty, Vidya Navaratnam, Richard Hubbard

Data Supplement

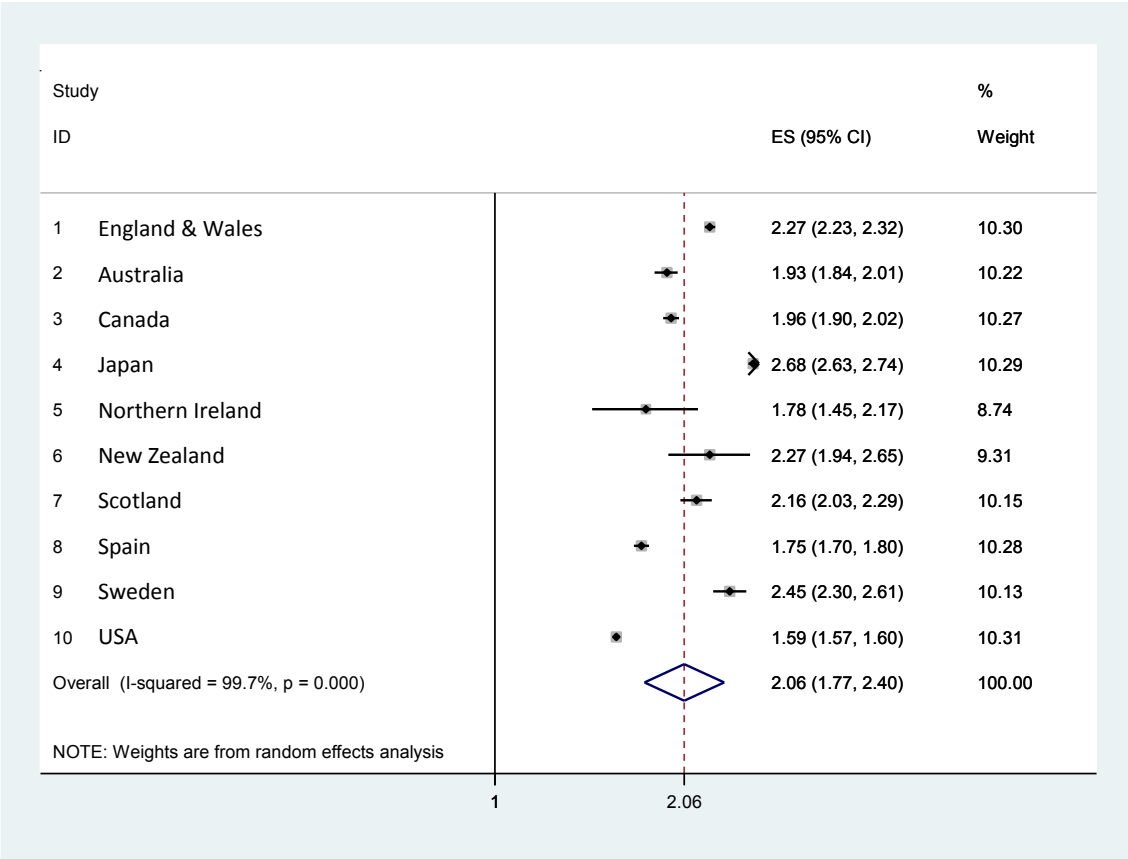

Figure E1: Meta-analysis of mortality rate ratios for male vs female sex, for J84 ('other interstitial pulmonary diseases') over time, using random effects model

Mortality using underlying cause of death data – J84.1 and J84.9 combined coding

Using J84.1+J84.9 combined coding ('other interstitial pulmonary diseases with fibrosis' and 'interstitial pulmonary disease, unspecified'), crude and age-standardised mortality rates were higher than more specific J84.1 coding (Table E1 / Figure E2). Age-standardised mortality rates increased to 9.76 per 100,000 (England & Wales, 2012), 7.72 per 100,000 (USA, 2010), 7.45 per 100,000 (Canada, 2011), 6.38 per 100,000 (Australia, 2011), and 5.25 per 100,000 (Spain, 2011). Rate ratios over time were essentially equivalent to J84 figures. Meta-analysis again showed an overall 3% increase over time (rate ratio 1.03, 95% CI 1.01-1.04, p<0.001) (Figure E3).

Table E1: Crude and age-standardised mortality (standardised to 2013 European Standard Population) per 100,000 population from J84.1+J84.9 ('other interstitial pulmonary diseases with fibrosis' and 'interstitial pulmonary disease, unspecified') over time

Country	Crude mortality rates per 100,000 population over time												
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
England & Wales		4.50	4.71	4.87	5.21	5.20	5.40	5.85	6.19	6.15	6.72	7.57	8.15
Australia	3.07	3.39	3.61	3.33	3.41	3.05	3.71	3.77	4.18	3.99	4.63	4.36	
Canada	3.51	3.75	3.70	3.60	4.55	4.92	4.60	4.79	4.82	5.08	5.22	5.37	
Spain	2.93	3.19	3.43	3.58	3.57		3.74	4.28	4.01	4.11	4.47	4.63	
USA	4.33	4.52	4.10	4.31	5.04	4.81	4.86	4.95	5.09	5.13	5.20		
Country	**Age-standardised mortality rates per 100,000 population over time**												
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
England & Wales		6.33	6.15	6.35	6.76	6.66	6.89	7.47	7.83	7.74	8.37	9.33	9.76
Australia	5.08	5.57	5.78	5.28	5.31	4.74	5.64	5.65	6.35	5.93	6.79	6.38	
Canada	5.88	6.23	6.00	5.74	7.26	7.69	7.03	7.13	7.06	7.29	7.48	7.45	
Spain	3.69	4.04	4.31	4.43	4.45		4.60	5.20	4.82	4.86	5,24	5.25	
USA	6.93	7.13	6.46	6.77	7.86	7.43	7.47	7.55	7.69	7.63	7.72		

Age-standardised to 2013 European Standard Population

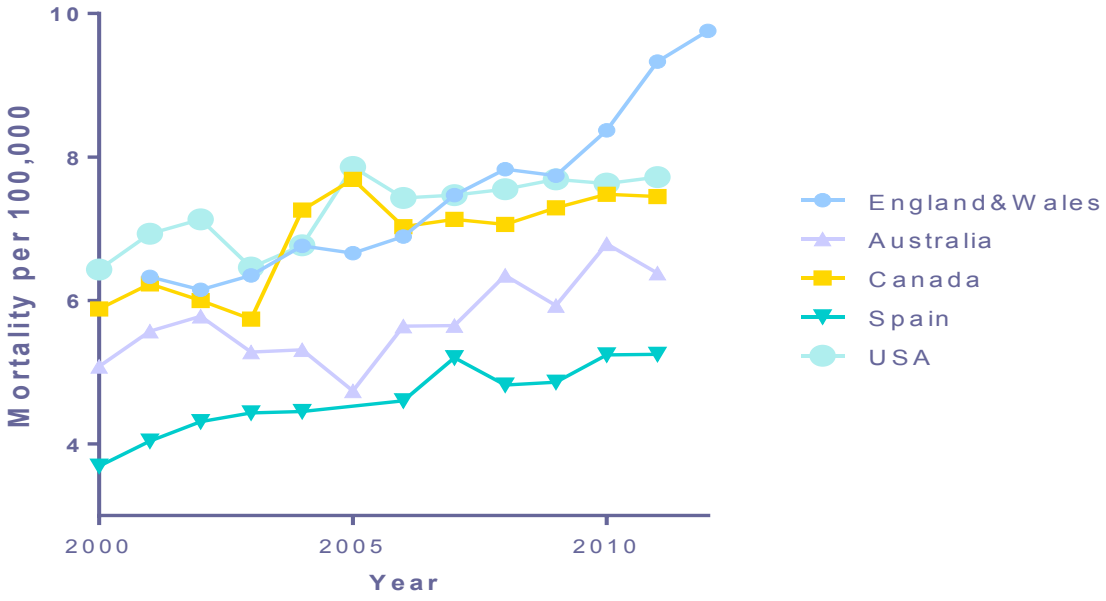

Figure E2: Age-standardised mortality rates from J84.1+J84.9 ('other interstitial pulmonary diseases with fibrosis' and 'interstitial pulmonary disease, unspecified') for selected countries by year, using underlying cause of death data. Age-standardised to 2013 European Standard Population.

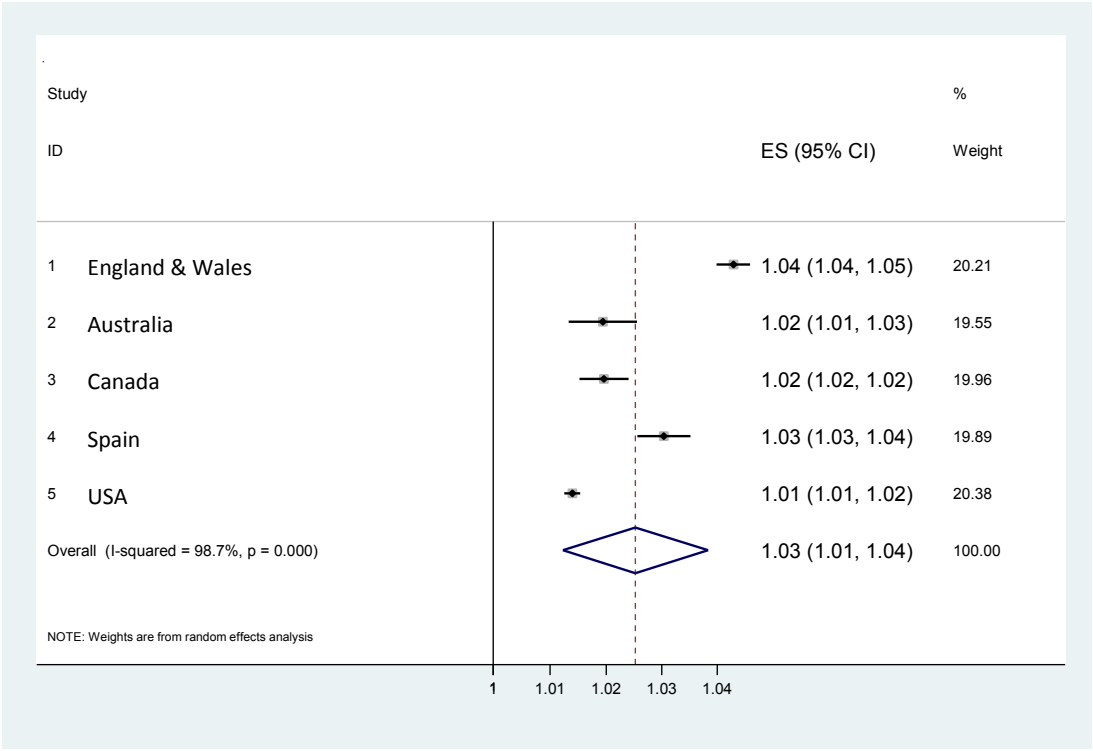

Figure E3: Meta-analysis of mortality rate ratios for annual increase in mortality from J84.1+J84.9 ('other interstitial pulmonary diseases with fibrosis' and 'interstitial pulmonary disease, unspecified') over time, using random effects model.

<u>Mortality using multiple cause of death data – J84.1 and J84.9 combined coding</u>

Using multiple cause of death data from the USA, Australia and England & Wales, age-standardised mortality rates from J84.1+J84.9 were highest in England & Wales – 14.65 per 100,000 in 2010, compared to 11.99 per 100,000 in Australia, and 11.73 per 100,000 in the USA (Figure E4).

As with J84.1 coding, mortality rate ratios over time were similar to underlying cause of death data for England & Wales, but the rate of increase was less for Australia, with no increase over time in the USA. Using Poisson regression for combined USA, Australia and England & Wales data (years where data was available for all three countries) there was a

marginally reduced chance of having a diagnostic code of either J84.1 or J84.9 in the USA (rate ratio 0.98, 95% CI 0.97-0.99, p<0.001) and a slightly greater reduced chance in Australia (rate ratio 0.90, 95% CI 0.88-0.91, p<0.001) (Table E2a). The mutually adjusted (for age and sex) mortality rate ratio for annual change for J84.1+J84.9 was 1.01 (95% CI 1.007-1.009, p for trend<0.001). Meta-analysis using the random effects method (including all years with data available) showed individual rates of 1.04 for England & Wales (95% CI 1.038-1.043, p<0.001), 1.01 for Australia (95% CI 1.01-1.02, p<0.001), and 1.00 for USA (95% CI 1.00-1.01, p<0.001), with an overall rate of 1.02 (95% CI 0.99-1.04, p<0.001) (Table E2b).

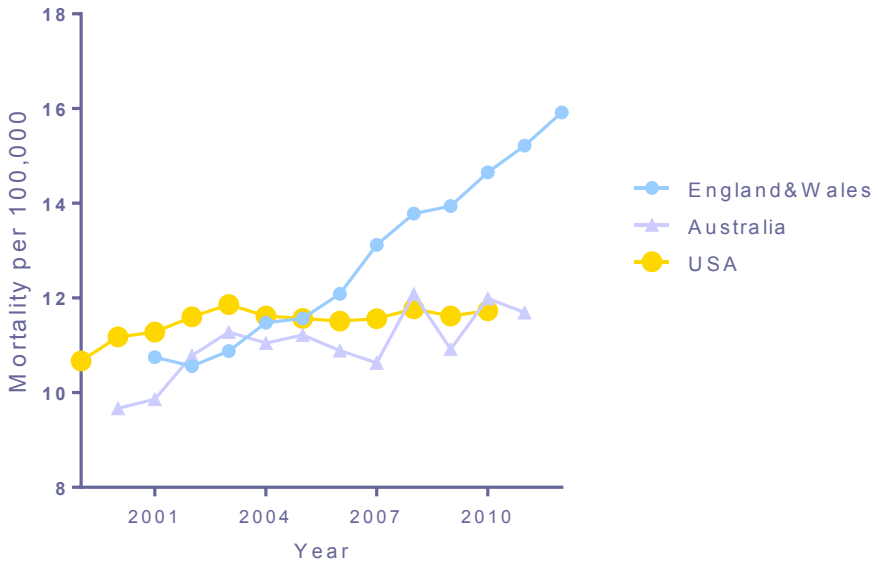

Figure E4: Age-standardised mortality rates from J84.1+J84.9 ('other interstitial pulmonary diseases with fibrosis' and 'interstitial pulmonary disease, unspecified') for England & Wales, Australia and USA, using multiple cause of death data, over time. Age-standardised to 2013 European Standard Population.

Table E2a: Deaths, crude and age-standardised mortality rates, and Poisson regression modelling for J84.1+J84.9 ('other interstitial pulmonary diseases with fibrosis' and 'interstitial pulmonary disease, unspecified') for England & Wales (E&W), Australia and USA, using multiple cause of death data, from 2001-2010

	Deaths	Person years (millions)	Crude mortality rate (per 100,000 population)	Age-standardised mortality rate (per 100,000 population)	Mutually adjusted mortality rate ratio (95% confidence intervals)	
Sex						
Female	132728	1887.95	7.03	7.83	1.00	
Male	157565	1825.06	8.63	15.48	1.73	(1.72-1.74)*
Age group (years)						
0-44	5623	2308.71	0.24	0.18	0.01	(0.01-0.01)
45-54	9803	524.15	1.87	1.47	0.07	(0.07-0.07)
55-64	26356	394.75	6.68	6.12	0.26	(0.26-0.27)
65-74	64119	254.38	25.21	25.41	1.00	
75-84	112026	168.54	66.47	71.81	2.71	(2.69-2.74)
85+	72366	62.47	115.84	129.95	5.01	(4.96-5.07)†
Country						
E&W	51234	537.91	9.52	12.28	1.00	
Australia	14611	204.85	7.13	11.07	0.90	(0.88-0.91)*
USA	224448	2970.25	7.56	11.61	0.98	(0.97-0.99)*

Age-standardised to 2013 European Standard Population. *p<0.001, †p for trend<0.001

Table E2b: Rate ratios for annual increase in mortality from J84.1+J84.9 ('other interstitial pulmonary diseases with fibrosis' and 'interstitial pulmonary disease, unspecified') for England & Wales, Australia and USA, using multiple cause of death data, from 2001-10

Country	Rate ratio	95% Confidence Intervals	p value
England & Wales	1.04	1.038-1043	<0.001
Australia	1.01	1.01-1.02	<0.001
USA	1.00	1.00-1.01	<0.001

Subnational data from the USA using J84.1+J84.9 multiple cause of death data showed *crude* mortality rates ranging from 3.85 per 100,000 (Nevada) to 13.26 per 100,000 (Vermont). Looking at the top 5 most populous states (California, Texas, New York, Florida, Illinois) with full age-specific data and only few missing values, the highest rates were in Texas (crude rate 6.25 per 100,000, age-standardised rate 12.20 per 100,000) and lowest in New York (crude rate 5.32 per 100,000, age standardised rate 7.93 per 100,000) (Table E3a).

While crude mortality rates increased over time, age-standardised rates remained relatively stable. Rate ratios for annual increase over time showed a 1% increase for Florida, Illinois and New York, a marginal increase for California and a marginal decrease for Texas (Table E3b), with an overall rate ratio by meta-analysis of 1.00 (95% CI 1.00-1.01).

Table E3a: Deaths, crude and age-standardised mortality rates, and Poisson regression modelling for J84.1+J84.9 ('other interstitial pulmonary diseases with fibrosis' and 'interstitial pulmonary disease, unspecified') for five most populous states in USA, using multiple cause of death data, from 2001-2010

	Deaths	Person years (millions)	Crude mortality rate (per 100,000 population)	Age-standardised mortality rate (per 100,000 population)	Mutually adjusted mortality rate ratio (95% confidence intervals)	
Sex						
Female	37577	603.45	6.23	8.04	1.00	
Male	40567	585.56	6.93	12.69	1.57	(1.55-1.59)*
Age group (years)						
0-44	360	762.01	0.05	0.04	0.01	(0.00-0.01)
45-54	2773	164.39	1.69	1.64	0.07	(0.07-0.08)
55-64	7557	117.28	6.44	6.43	0.28	(0.27-0.28)
65-74	17358	75.89	22.87	23.22	1.00	
75-84	29954	50.79	58.98	61.55	2.65	(2.60-2.70)
85+	20142	18.66	107.96	115.06	5.07	(4.97-5.17)†
State						
California	25969	392.97	6.61	11.66	1.00	
Florida	16134	193.81	8.32	9.70	0.84	(0.82-0.85)*
Illinois	9046	138.90	6.51	10.35	0.90	(0.87-0.92)*
New York	11218	210.81	5.32	7.93	0.68	(0.66-0.69)*
Texas	15777	252.51	6.25	12.20	1.06	(1.04-1.08)*

Age-standardised to 2013 European Standard Population. *p<0.001, †p for trend<0.001

Table E3b: Rate ratios for annual increase in mortality from J84.1+J84.9 ('other interstitial pulmonary diseases with fibrosis' and 'interstitial pulmonary disease, unspecified') for five most populous states in USA, using multiple cause of death data, from 2001-2010

Country	Rate ratio	95% Confidence Intervals	p value
California	1.00	1.00-1.01	0.433
Florida	1.01	1.00-1.01	0.001
Illinois	1.01	1.01-1.02	<0.001
New York	1.01	1.00-1.02	<0.001
Texas	0.99	0.99-1.00	<0.001