The Mortality Burden of Idiopathic Pulmonary Fibrosis in the United Kingdom

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To the Editor,

We have previously demonstrated that mortality from idiopathic pulmonary fibrosis (IPF) is on the rise in the UK (1) and globally.(2) Although numerous clinical trials, genetic and metabolomics studies have provided insight, large epidemiological studies on disease burden remains limited. This is particularly important now that therapeutic options for IPF are available. Despite its limitations, registered deaths from IPF are a pragmatic and validated(3) way of assessing and providing reliable estimates of disease burden in terms of mortality. The aim of our study was to provide up to date IPF mortality rate estimates and changes to trends in the UK.

Methods

Data source

We used routine mortality data from England and Wales obtained from the Office of National Statistics (ONS) (4) which is derived from registered death certificates and coded for the underlying cause of death.(5) The accuracy of coding of underlying cause of deaths is high.(6)

We used the term IPF clinical syndrome (IPF-CS) (1, 7) when using routinely collected clinical data, to acknowledge the difficulty in demonstrating that our study population meets ATS/ERS diagnostic criteria. (8)

Statistical analysis

We obtained annual number of deaths from IPF-CS stratified by age and sex for the years 1979 to 2016. During our study period, deaths were coded using different International Classification of Diseases (ICD) codes; from 1979 to 2000 ICD-9 codes 515 (post inflammatory fibrosis) and 516.3 (idiopathic fibrosing alveolitis) were used and from 2001 onwards it was ICD-10 code J84.1 (idiopathic pulmonary fibrosis). We extracted general population estimates for the same period. All

data were grouped into 5-6 year periods, but without combining the different ICD codes, and 5 year age groups over the age of 55.

Crude mortality rates stratified by age, sex and calendar period were estimated. We used direct standardization to calculate age-standardized mortality rates, standardized to the 2016 population of England and Wales. We performed a sub-analysis of the two different ICD-9 codes for IPF-CS (ICD-9 code 515 and ICD-9 code 516.3). Poisson regression was used to estimate mortality rate ratios, adjusting for age and sex. We explored effect modification between trends in annual mortality rates with age and sex. Likelihood ratio tests were used for hypothesis testing. Stata v15 (StataCorp, College Station, TX) was used for all statistical analyses.

Results

A total of 82,702 deaths were attributed to IPF-CS in England and Wales from 1979 to 2016. The overall age-standardized mortality rate for this period was 4.68 per 100,000 person-years (95% Confidence Interval [CI] 4.64 to 4.71). Age-standardized mortality rates increased from 1.66 (95% CI 1.54 to 1.79) in 1979 to 8.29 (95% CI 8.06 to 8.53) per 100,000 person-years in 2016 (see Figure 1). The annual increase in the number of IPF-CS deaths, after adjusting for age and sex was approximately 5% (Rate Ratio [RR] 1.050, 95% CI 1.049 to 1.051; $p<0.001$). Age-standardized mortality rates were higher in men and the elderly (See Table 1). There was also strong evidence of effect modification by age ($p<0.001$) and sex ($p<0.001$). The increase in annual mortality rates was highest amongst men (RR per year 1.052, 95% CI 1.051 to 1.053) and over 85s (RR per year 1.094, 95% CI 1.092 to 1.096).

Sub-analysis of ICD-9 codes

From 1979 to 2000 there were 12,989 deaths from post-inflammatory fibrosis (ICD-9 code 515) and 16,989 deaths from idiopathic fibrosing alveolitis (ICD-9 code 516.3). The age-standardized mortality rates for both ICD-9 codes increased during this period. For post-inflammatory fibrosis, the age-standardized mortality rate increased from 0.92 (95% CI 0.88 to 0.97) per 100,000 person-years in the 1979 to 1983 calendar period to 1.77 (95% CI 1.72 to 1.82) per 100,000 person-years in the 1995 to 2000 calendar period. Age-standardized mortality rates for idiopathic fibrosing alveolitis increased from 0.88 (95% CI 0.84 to 0.92) to 2.41 (2.35 to 2.47) per 100,000 person-years for the same calendar periods. Yearly mortality increased by 4.4% (RR 1.044, 95% CI 1.041 to 1.047) for post-inflammatory fibrosis and 6.3% (RR 1.063, 95% CI 1.060 to 1.066) for idiopathic fibrosing alveolitis, after controlling for age and sex.

Figure 1: Age-standardized mortality rates for idiopathic pulmonary fibrosis clinical syndrome (IPF-CS) in England and Wales from 1979 to 2016.

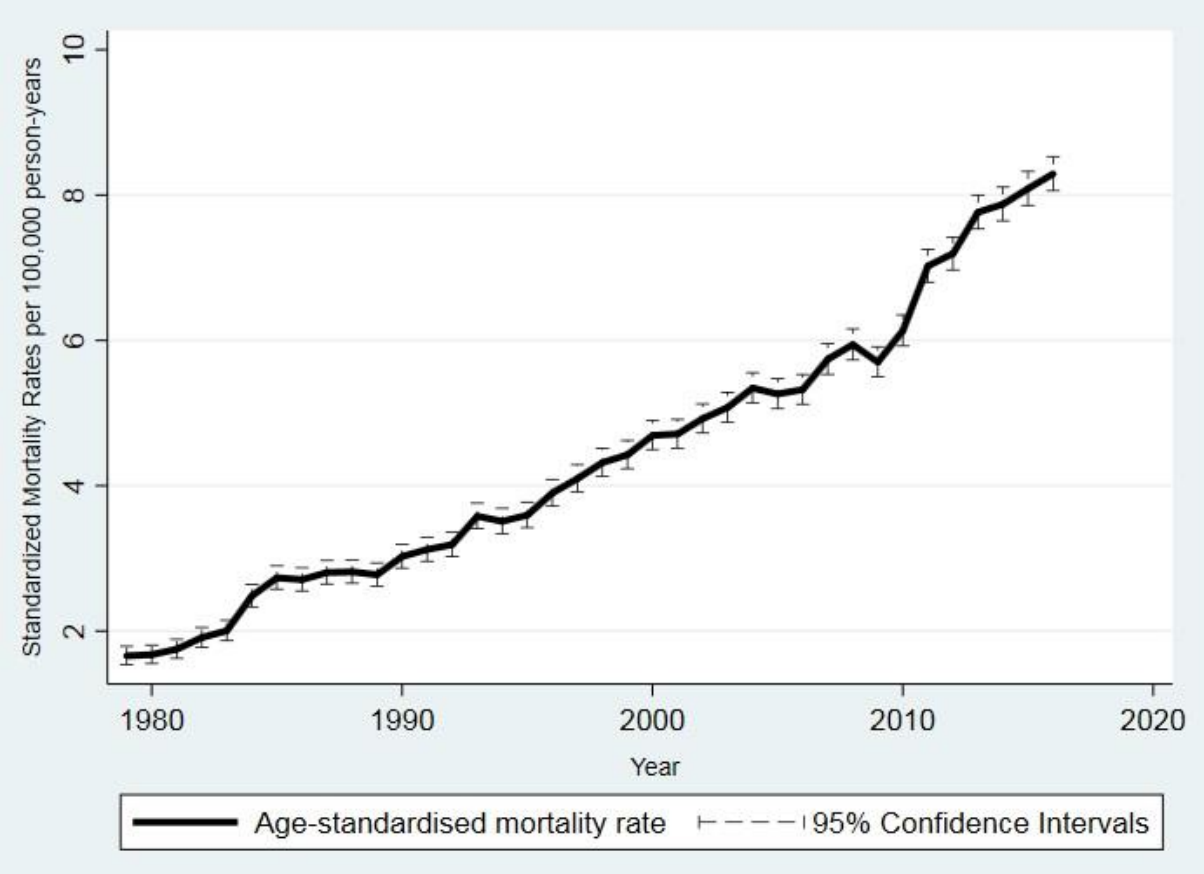

Table 1: Age-standardized mortality rates and mortality rate ratios of deaths from idiopathic pulmonary fibrosis clinical syndrome

	Number of deaths	**Person-years (million)**	**Crude mortality rate per 100,000 person-years (95% CI)**	**Age- standardized mortality rate per 100,000 person - years (95% CI)**	**Adjusted mortality rate ratio (95% CI)***
Calendar period					
ICD-9					
1979-1983	3858	248	1.56 (1.51-1.61)	1.81 (1.75-1.86)	**1.00**
1984-1988	5888	250	2.36 (2.30-2.42)	2.71 (2.64-2.78)	1.53 (1.47-1.59)
1989-1994	8640	305	2.84 (2.78-2.90)	3.21 (31.4-3.28)	1.87 (1.80-1.94)
1995-2000	11577	310	3.73 (3.67-3.80)	4.18 (4.10-4.25)	2.50 (2.41-2.59)
ICD-10					
2001-2005	12197	265	4.61 (4.53-4.69)	5.07 (4.98-5.16)	3.16 (3.05-3.28)
2006-2010	14677	274	5.35 (5.27-5.44)	5.77 (5.68-5.87)	3.80 (3.67-3.94)
2011-2016	25865	343	7.53 (7.44-7.63)	7.71 (7.62-7.81)	5.59 (5.40-5.78)
Sex					
Male	50912	975	5.22 (5.18-5.27)	7.41 (7.34-7.48)	2.03 (1.99-2.05)
Female	31790	1020	3.12 (3.08-3.15)	2.99 (2.96-3.02)	**1.00**
Age group (years)					
<54	2499	1460	0.17 (0.16-0.18)	0.17 (0.16-0.18)	0.002 (0.001-0.003)
55-59	2599	113	2.30 (2.21-2.39)	2.30 (2.21-2.39)	0.26 (0.25-0.28)
60-64	4952	105	4.71 (4.58-4.85)	4.71 (4.59-4.84)	0.58 (0.56-0.60)
65-69	8837	95.3	9.27 (9.08-9.47)	9.27 (9.08-9.47)	**1.00**
70-74	13294	81	16.41 (16.13-16.69)	16.41 (16.13-16.69)	1.93 (1.87-1.98)
75-79	17030	64.4	26.45 (26.05-26.84)	26.45 (26.05-26.84)	3.31 (3.23-3.40)
80-84	16541	44.2	37.45 (36.88-38.02)	37.45 (36.88-38.02)	4.38 (4.27-4.49)
≥85	16950	35.5	47.78 (47.06-48.50)	47.78 (47.06-48.50)	4.83 (4.71-4.95)

*Mortality rate ratios adjusted for all other variables in the table

Discussion

This study demonstrates that mortality from IPF-CS continues to rise by 5% per year after accounting for an ageing population. We found a marked increase in IPF-CS deaths from 2010 onwards, with IPF-CS mortality in 2016 being 51% higher than 2010. Sub-analysis of the ICD-9 codes showed that age-standardized mortality rates increased for both codes. Registered deaths were highest in men and the elderly, which is consistent with previous studies.(1, 2) Based on these findings we estimate that approximately 5,500 people die from IPF-CS in the UK each year.

One strength of our study is the large number of registered deaths and long study period, which enabled us to estimate precise changes to mortality trends and stratify our results by sex, age and calendar period. We were also able to explore if the annual increase in mortality was modified by age or sex. A possible limitation is the validity of diagnosis of IPF. However, previous studies have demonstrated a high diagnostic accuracy for death certification of lung fibrosis.(2, 3, 9) Furthermore, we recently showed that only two-thirds of people with IPF have it recorded as their underlying cause of death and 80% had it mentioned anywhere on their death certificate (2) suggesting that our results are an under-estimate of the mortality burden and incidence of IPF in the UK. We were not able to evaluate how changes from ICD-9 to ICD-10 coding impacted mortality trends. Data from the ONS suggest that the number of deaths assigned to the respiratory chapter as a whole decreased by 22% as a result of the introduction of ICD-10 codes, largely driven by the decrease in number of deaths assigned to pneumonia.(10) It is possible that this may have resulted in further under-estimating the actual number of IPF-CS related deaths.

These findings are consistent with our work demonstrating a progressive rise in IPF mortality in the UK. (1, 2, 11) Increased case ascertainment could be a contributing factor to the trends seen, but it is also possible that the true incidence of IPF has continued to increase. If the marked increase in number of deaths is purely due to increased disease recognition, there is no evidence that ascertainment is complete, and continued upward trends in mortality are likely to be seen.

In summary, IPF-CS now accounts for almost 7% of all respiratory deaths in the UK (4) and carries the same mortality burden as liver, bladder and intracranial malignancies. Despite increasing research investment, it remains an important cause of respiratory mortality and a growing public health problem.

(1050 words)

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Author Contributions VN and RBH conceived and designed the study. VN prepared and analyzed the data. VN and RBH were involved in the interpretation of the data and in writing or revising the manuscript before submission. VN takes responsibility for the integrity of the work in this manuscript and is the guarantor of the manuscript.

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