INTERNATIONAL COMPARATIVE EPIDEMIOLOGY OF IDIOPATHIC PULMONARY FIBROSIS

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Contents

Abstract

Background

Evidence from the UK suggests the incidence of idiopathic pulmonary fibrosis is increasing, but there is a lack of data from elsewhere in the World. The cause of the disease remains unknown. New anti-fibrotic therapies may increase the use of surgical lung biopsy for accurate diagnosis, although the risks of this (and other surgery) are not clear.

Methods

Collated international mortality statistics and a systematic review of the literature were used to assess the incidence and mortality of idiopathic pulmonary fibrosis worldwide. Primary care data from the United Kingdom were used to assess the association between recent major surgery and a new diagnosis of idiopathic pulmonary fibrosis. Secondary care data from the United States and United Kingdom were used to assess the risk of surgical lung biopsy for the diagnosis of interstitial lung disease, and the risk of other major surgery in those with idiopathic pulmonary fibrosis.

Results

Mortality from idiopathic pulmonary fibrosis in increasing steadily worldwide. Incidence varies worldwide but is in the range of 3-9 per 100,000 in the West. No association was identified between recent major surgery and a new diagnosis of idiopathic pulmonary fibrosis. Surgical lung biopsy for the diagnosis of interstitial lung disease has an in-hospital mortality of under 2% for elective procedures, but this is higher for non-elective surgery, and in those who are older with co-morbidities. In those with idiopathic pulmonary fibrosis undergoing major surgery, in-hospital mortality was higher than the general population.

Conclusion

Idiopathic pulmonary fibrosis seems to be increasingly common worldwide. Surgery has risks, particularly in unwell older patients, and less invasive diagnostic methods are needed.

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Publications arising from this thesis

Surgical lung biopsy for the diagnosis of interstitial lung disease in England: 1997-2008.

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List of Tables

List of Figures

List of Abbreviations

95% CI	95% Confidence Intervals
AE	Acute exacerbation
AHRQ	Agency for Healthcare Research and Quality
AIP	Acute interstitial pneumonia
ALAT	Latin American Thoracic Association
ANA	Antinuclear antibody
ATS	American Thoracic Society
BTS	British Thoracic Society
CABG	Coronary artery bypass graft
CDC	Centers for Disease Control and Prevention
CFA	Cryptogenic fibrosing alveolitis
COP	Cryptogenic organising pneumonia
CPRD	Clinical Practice Research Datalink
CT	Computed tomography
CTD	Connective tissue disease
CTD-ILD	Connective tissue disease associated interstitial lung disease
DAD	Diffuse alveolar damage
DIP	Desquamative interstitial pneumonia
DPLD	Diffuse parenchymal lung disease
EAA	Extrinsic allergic alveolitis
ERS	European Respiratory Society
FDA	Food and Drug Administration
FVC	Forced vital capacity
GOR(D)	Gastro-oesophageal reflux (disease)
GP	General Practice *or* General practitioner
HES	Hospital Episode Statistics
HCUP	Healthcare Cost and Utilization Project
HP	Hypersensitivity pneumonitis
HRCT	High resolution computed tomography

HSCIC	Health and Social Care Information Centre
ICD (CM)	International Classification of Diseases (Clinical Modification)
ICU	Intensive care unit
IFA	Idiopathic fibrosing alveolitis
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
IMD	Index of Multiple Deprivation
IPAF	Interstitial pneumonia with autoimmune features
IPF (-CS)	Idiopathic pulmonary fibrosis (-clinical syndrome)
JRS	Japanese Respiratory Society
LAM	Lymphangioleiomyomatosis
LCH	Langerhans cell histiocytosis
LIP	Lymphoid interstitial pneumonia
LRTI	Lower respiratory tract infection
LSOA	Lower super output area
MCTD	Mixed connective tissue disease
MDT	Multi-disciplinary team
MV	Mechanical ventilation
NAC	N-acetylcisteine
NCHS	National Center for Health Statistics
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIS	Nationwide / National Inpatient Sample
NOS	Not otherwise specified
NSIP	Non-specific interstitial pneumonia
n/a	Not available
n/s	Not specified
OLB	Open lung biopsy
ONS	Office of National Statistics
OP	Organising pneumonia
OPCS-4	Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (4th Revision)

OR	Odds ratio
PF	Pulmonary fibrosis
PIF	Post-inflammatory pulmonary fibrosis
PTCA	Percutaneous transluminal coronary angioplasty
PTX	Pneumothorax
RA (-ILD)	Rheumatoid arthritis (-interstitial lung disease)
RB-ILD	Respiratory bronchiolitis associated interstitial lung disease
RR	Rate ratio
SE	Surgical emphysema
SLB	Surgical lung biopsy
SLE	Systemic lupus erythematosus
SNOMED CT	Systematised Nomenclature of Human Medicine-Clinical Terms
TA	Technology appraisal
THIN	The Health Improvement Network
THR	Total hip replacement
TKR	Total knee replacement
UIP	Usual interstitial pneumonia
UK	United Kingdom of Great Britain and Northern Ireland
US(A)	United States (of America)
VATS	Video-assisted thoracoscopic surgery
WHO	World Health Organisation

Chapter 1 : Introduction

This chapter outlines the current classification of interstitial lung disease (ILD), with particular focus on the changing terminology and diagnostic proposals for idiopathic pulmonary fibrosis (IPF). The clinical coding systems used to classify IPF and other ILD in large datasets are described, leading on to an overview of IPF epidemiology so far, specifically focussing on incidence and mortality. The chapter then explores the aetiology of IPF, its clinical presentation, and methods of diagnosis, including the role of surgical lung biopsy, before a brief overview of management options and prognosis. Finally, the aims and objectives of this thesis are put forward, with an outline of the chapters to follow.

1.1 – Defining idiopathic pulmonary fibrosis (IPF)

Idiopathic pulmonary fibrosis (IPF) is a disease of the lung parenchyma that tends to occur in older people and causes progressive breathlessness. It is one of the most common forms of interstitial lung diseases (ILD), yet its aetiology remains unclear. This section outlines how IPF fits into the spectrum of ILD, how definitions and terminology have evolved over time, and how cases are identified in epidemiological studies.

1.1.1 – Classification of interstitial lung disease

Interstitial lung disease, also known as diffuse parenchymal lung disease, describes a group of conditions that primarily affect the interstitium of the lungs between the airways and the pulmonary circulation. Different types of ILD can have a variety of clinico-pathological manifestations, including fibrosis, inflammation and nodules, and the various types have different clinical presentations, treatments and prognoses. In broad terms, ILD can be divided into disease which is idiopathic (no clear cause), the main group of which is termed idiopathic interstitial pneumonias, and disease which can be attributed to an alternative explanation such as another medical condition, inhaled exposures, or as a side-effect of prescribed medications.

1.1.1.1 – The idiopathic interstitial pneumonias

A multidisciplinary consensus classification of the idiopathic interstitial pneumonias was published in 2002 by the American Thoracic Society (ATS) and European Respiratory Society (ERS) (1), and updated in 2013 (2). This proposed seven clinico-pathologic entities, in order of relative frequency: idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP), cryptogenic organising pneumonia (COP), acute interstitial pneumonia (AIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), and lymphoid interstitial pneumonia (LIP). The distinction between these is summarised in Table 1-1.

Table 1-1: Typical features of the idiopathic interstitial pneumonias

Name	Clinical features	Radiological features	Histopathological features	Management approaches and prognosis
Idiopathic pulmonary fibrosis (IPF)	Progressive breathlessness and cough in older adults.	Reticulation, honeycombing and traction bronchiectasis in a peripheral basal distribution.	Usual interstitial pneumonia pattern. Architectural destruction with fibroblastic foci.	Consider anti-fibrotics. Supportive care. Progressive.
Non-specific interstitial pneumonia (NSIP)	Breathlessness and cough. Younger age than IPF.	Ground glass opacification and consolidation, irregular lines.	Cellular and fibrosing patterns. Interstitial chronic inflammation. Interstitial fibrosis less heterogeneous than IPF.	Consider immunosuppression. Better prognosis than IPF.
Cryptogenic organising pneumonia (COP)	Cough and breathlessness. Constitutional symptoms. Younger age than IPF.	Patchy bilateral consolidation and / or nodules.	Organising pneumonia, preservation of lung architecture, mild interstitial chronic inflammation.	Corticosteroids. Observation. Usually good outcome but can relapse.
Acute interstitial pneumonia (AIP)	Rapidly progressive breathlessness and hypoxia.	Progressive diffuse consolidation and ground glass changes.	Diffuse alveolar damage, airspace organisation, alveolar septal thickening.	Consider corticosteroids. Empirical antimicrobials. Ventilatory support. High early mortality.

(Continued)

Table 1-1: Typical features of the idiopathic interstitial pneumonias (continued)

Name	Clinical features	Radiological features	Histopathological features	Management approaches and prognosis
Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD)	Mild symptoms (breathlessness) in smokers.	Bronchial wall thickening, centrilobular nodules, patchy ground glass changes.	Bronchiolocentric alveolar macrophage accumulation, chronic inflammation.	Smoking cessation. Good outcome.
Desquamative interstitial pneumonia (DIP)	Insidious breathlessness and cough in smokers.	Ground glass opacification, lower zone predominance.	Diffuse macrophage accumulations in distal airspaces, fibrotic thickening of alveolar septa.	Smoking cessation. Corticosteroids. Usually good outcome.
Lymphoid interstitial pneumonia (LIP)	Insidious cough and breathlessness. May have constitutional symptoms. Females>males.	Diffuse reticular opacities, centrilobular nodules, ground-glass change, thin-walled cysts.	Dense interstitial lymphoid infiltrate, alveolar septal distribution, lymphoid hyperplasia.	Corticosteroids. Can progress or resolve.

Each of the clinical and radiological/pathological patterns seen in the idiopathic interstitial pneumonias can also be due to an alternative cause: for example, lymphoid interstitial pneumonia is only rarely idiopathic and is more commonly associated with underlying autoimmune disease or immunodeficiency. Similarly, the usual interstitial pneumonia pattern typical of IPF can also be seen in patients with rheumatoid arthritis. Identifying any possible underlying cause is therefore important in all cases of interstitial lung disease.

1.1.1.2 – Interstitial lung disease due to other medical conditions

A number of medical conditions have been associated with the development of interstitial lung disease, the largest group being rheumatological conditions, known as connective tissue disease or collagen vascular disease. These include rheumatoid arthritis, systemic sclerosis (scleroderma), systemic lupus erythematosus (SLE), Sjögren's syndrome and dermato- and polymyositis (3). People with these autoimmune multi-system diseases may have extensive lung involvement or none at all, and the lung disease can sometimes precede manifestations in other areas. A number of serological markers can help identify these conditions, and most are treated with immunosuppression if appropriate. The distinction between them is summarised in Table 1-2.

The distinction between various types of connective tissues disease related ILD (CTD-ILD) can be challenging. Mixed connective tissue disease (MCTD) is a term used to describe a constellation of features that overlaps several of the other conditions, and commonly has associated ILD. Interstitial pneumonia with autoimmune features (IPAF) is a new label proposed by an ERS/ATS statement that can be applied to people with an idiopathic interstitial pneumonia and features suggestive of connective tissue disease that do not meet established criteria for CTD (4): an example would be a non-specific interstitial pneumonia pattern with Raynaud's phenomenon and a positive non-specific autoimmune serology result.

Table 1-2: Typical features of the connective tissue disease associated interstitial lung diseases

Name of connective tissue disease	Extra-pulmonary features	Pulmonary features	Radiological pattern of ILD	Serological markers
Rheumatoid arthritis (RA)	Inflammatory polyarthritis. Rheumatoid nodules. Constitutional symptoms.	Common. ILD, nodules, bronchiectasis.	UIP (most common). NSIP, LIP, OP.	Rheumatoid factor Anti-CCP antibodies.
Systemic sclerosis (scleroderma)	Scleroderma (skin thickening). Raynaud's phenomenon. Oesophageal dysmotility. Renal disease.	Common in diffuse disease. ILD and pulmonary hypertension.	NSIP (most common). UIP.	Anti-nuclear antibody (ANA). Anti-Scl 70 and Anti-centromere antibodies.
Systemic lupus erythematosus (SLE)	Arthralgia. Rash. Constitutional symptoms. Neuropsychiatric symptoms. Renal disease. Pericarditis.	Less common. ILD. Pneumonitis. Pleuritis. Shrinking lung syndrome.	NSIP (most common). OP, LIP, UIP, DIP, DAD.	ANA. Anti-dsDNA and Anti-SM antibodies.
Sjögren's syndrome	Dry eyes, dry mouth.	Less common. ILD. Airways disease.	NSIP, LIP.	Rheumatoid factor. ANA. Anti-Ro, Anti-La antibodies.
Dermatomyositis / polymyositis	Proximal muscle weakness and pain.	ILD – may precede myositis. Can be rapidly progressive.	NSIP, OP, UIP, DAD.	Creatinine kinase. Myositis-specific antibodies eg Anti-Jo1, Anti-MDA5.

ILD: interstitial lung disease; UIP: usual interstitial pneumonia; NSIP: non-specific interstitial pneumonia; OP: organising pneumonia; LIP: lymphoid interstitial pneumonia; DIP: desquamative interstitial pneumonia; DAD: diffuse alveolar damage.

1.1.1.3– Interstitial lung disease due to inhaled substances

Interstitial lung disease has long been described in patients with certain occupational exposures, such as coal miners. These conditions, also known as occupational ILD, include pneumoconiosis, asbestosis, silicosis and berylliosis. A careful history is important to decide whether the ILD can be attributed to the exposure in question. Radiological appearances may mimic idiopathic ILD: for example, asbestosis typically has a usual interstitial pneumonia pattern similar to IPF (5, 6). People may not correctly recall exposures, and job titles may be more helpful in deciding the final diagnosis (7).

Organic dust exposure, via employment or hobbies, can lead to hypersensitivity pneumonitis (previously termed extrinsic allergic alveolitis), an inflammatory condition that can either occur acutely and resolve spontaneously (acute hypersensitivity pneumonitis) or develop insidiously with progressive fibrosis (chronic hypersensitivity pneumonitis) (8). Common variants include bird-fancier's lung (due to avian proteins, in those who keep birds such as pigeons) and famer's lung (due to bacteria in mouldy hay). Again, a careful exposure history is crucial but the cause may not always be identified. Radiological findings can vary but advanced chronic disease can look very similar to IPF (9).

1.1.1.4– Interstitial lung disease due to other known causes

A number of medications have been associated with interstitial lung disease. Common culprits include antibiotics (such as nitrofurantoin, sometimes used long-term to prevent urinary tract infections), anti-rheumatic drugs (such as methotrexate, commonly used to treat rheumatoid arthritis), cardiovascular drugs (such as amiodarone, used for atrial fibrillation), and chemotherapeutic agents (such as bleomycin, used to treat lymphoma and other cancers). Drug-induced lung disease can present in a variety of ways, from acute severe pneumonitis to more insidious pulmonary fibrosis. An online repository of causative agents is available at www.pneumotox.com (10).

Other known causes of interstitial lung disease include radiotherapy to the thoracic region (for example, to treat breast or lung cancer), previous infections (for example, following a severe pneumonia), advanced cancer (termed lymphangitis carcinomatosis) and following acute respiratory distress syndrome.

1.1.1.5 – Other interstitial lung disease

A number of other forms of interstitial lung disease are known that do not fit neatly into standard classifications. Sarcoidosis is a granulomatous multi-system disease of unknown aetiology that commonly affects the lungs, with a wide spectrum of presentation from isolated hilar lymphadenopathy to diffuse parenchymal changes and fibrosis (11). Chronic advanced disease can mimic IPF radiologically although additional typical characteristics and extra-pulmonary features are usually present.

Lymphangioleiomyomatosis (LAM) is a rare systemic disease affecting mainly women that can cause a number of pulmonary manifestations including pneumothoraces and cystic parenchymal lung disease. Langerhans cell histiocytosis is another rare multi-system disease that can present with interstitial lung disease including irregular cysts and nodules (12).

In some cases the clinical presentation and test results are not typical for any of the known causes of interstitial lung disease and there is no obvious causative factor from the clinical history. These people may be labelled as having ‘unclassified’ interstitial lung disease, or ‘unclassifiable interstitial pneumonia’ (1).

1.1.2 – Changing definitions and terminology of IPF

Nomenclature used to describe IPF has varied between regions and over time (1). The original descriptor used in the United Kingdom was cryptogenic fibrosing alveolitis (CFA), with 'lone' CFA sometimes used to exclude the presence of associated connective tissue disease. The term idiopathic pulmonary fibrosis has been in use for longer in the United States, and idiopathic interstitial pneumonia has been favoured in Japan.

It is likely that terms have become more precise over time: a diagnosis of IPF or CFA in the 1980s might have been achieved using clinical examination and chest radiography, and was likely to have encompassed some of the other types of idiopathic interstitial pneumonia and possibly connective tissue disease related ILD. Increased availability of high-resolution computed tomography imaging and observations of varying disease courses dependent on radiological and histological patterns led to proposals by Katzenstein and Myers in 1998 that recommended the term IPF be used more narrowly to describe patients with a usual interstitial pneumonia (UIP) pattern on histology, in the absence of other causes (13). This was followed by more formal diagnostic criteria from the ATS and ERS in 2000 (14) and 2011 (15) (see Table 1-3); the latter criteria reflecting advances in imaging and reluctance by some patients and clinicians to consider surgical biopsy. The current definition of IPF is therefore likely to be a more specific one than might have existed in earlier studies.

UIP is described as the histological correlate of IPF, and a UIP pattern can be described on imaging (further explanation of this is provided in Section 1.4.3). While UIP may therefore be seen as synonymous with IPF, in reality this pattern can be seen in other ILD with known causes as well (for example, asbestosis and rheumatoid arthritis associated ILD), hence the proviso that alternative causes must be excluded to diagnose IPF.

Table 1-3: Diagnostic criteria for idiopathic pulmonary fibrosis (IPF)

Source	Diagnostic criteria
ATS/ERS 2000 (14)	Definite IPF: - Surgical lung biopsy showing usual interstitial pneumonia (UIP) - Exclusion of other known causes of ILD - Abnormal pulmonary function tests with evidence of restriction and decreased diffusing capacity of the lung - Characteristic abnormalities (bibasal reticular abnormalities with minimal ground-glass opacities) on chest x-ray or high-resolution computer tomography (HRCT) If no surgical lung biopsy, IPF is likely in the presence of the three other 'major' criteria above plus: - No features to support an alternative diagnosis on transbronchial lung biopsy or bronchoalveolar lavage …plus 3 of the following 4 minor criteria: - Age >50 years - Insidious onset of otherwise unexplained exertional dyspnoea - Duration of illness ≥3 months - Bibasilar inspiratory crackles
ATS/ERS/JRS/ALAT 2011 (15)	- Exclusion of other known causes of ILD - Presence of UIP pattern on HRCT in patients not subject to surgical lung biopsy - Specific combinations of HRCT and surgical lung biopsy in patients subjected to surgical lung biopsy o Definite UIP on HRCT and possible UIP or unclassifiable fibrosis on surgical lung biopsy o Possible UIP on HRCT and at least probable UIP on surgical lung biopsy Probable IPF: - Possible UIP on HRCT with possible UIP or unclassifiable fibrosis on lung biopsy. Possible IPF: - HRCT inconsistent with UIP but definite UIP on lung biopsy.

ATS: American Thoracic Society; ERS: European Respiratory Society; JRS: Japanese Respiratory Society; ALAT: Latin American Thoracic Association.
IPF: idiopathic pulmonary fibrosis; ILD: interstitial lung disease; UIP: usual interstitial pneumonia; HRCT: high-resolution computer tomography.

The term ‘pulmonary fibrosis’ is a more generic descriptor for scar tissue in the lungs and could be applied to a number of types of interstitial lung disease: ideally this should be quantified with the cause. Post-inflammatory pulmonary fibrosis is another broad term that was used predominantly in the United States to refer to patients with more generic disease than IPF, although some studies have suggested that many of these patients actually had IPF (16, 17). This term has been abandoned in updated classification processes in favour of more specific terms.

In summary, IPF is currently well defined based on international consensus statements, however previous terminology and classification was less precise and may have included a wider range of pathologies.

1.1.3 – Clinical coding of IPF and other ILD

Given the changes in terminology and disease classification for IPF over time, it is unsurprising that clinical coding in healthcare databases has adapted at a similar pace. Most sources classify diseases using the World Health Organisation (WHO) International Classification of Diseases (ICD) system (18), which has undergone a number of revisions over time and been modified for more precise clinical use in the United States. In the United Kingdom however, primary care providers have used an alternative coding system known as Read codes.

This section describes the ICD-9 and ICD-10 coding systems approach to IPF and other ILDs, introduces the upcoming ICD-11 system, and outlines the Read code system used in UK general practice.

1.1.3.1 – ICD-9 and ICD-9-CM

Respiratory diseases are allocated ICD-9 codes 460-519. Most ILD is classed under 'other diseases of the respiratory system', although hypersensitivity pneumonitis is grouped alongside chronic obstructive pulmonary disease; occupational diseases such as pneumoconiosis are grouped separately; and sarcoidosis is listed with infectious disease. ICD-10 was officially endorsed as a replacement for ICD-9 in 1990, however the more detailed US clinical modification of the system (ICD-9-CM) has only recently been superseded by ICD-10-CM and is therefore still of relevance to epidemiological studies.

Selected relevant ICD-9-CM codes are highlighted in Table 1-4. Idiopathic fibrosing alveolitis (516.3) is the most specific for IPF, although the less specific post-inflammatory pulmonary fibrosis (515) may include some cases as well.

Table 1-4: International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes for interstitial lung disease

ICD-9-CM code	Descriptor	Disease synonyms
515	Post-inflammatory pulmonary fibrosis	Not available
516.3	Idiopathic fibrosing alveolitis	- Diffuse (idiopathic) (interstitial) pulmonary fibrosis. - Hamman-Rich syndrome. - Cryptogenic fibrosing alveolitis. - Chronic fibrosing alveolitis. - Diffuse alveolar fibrosis.
517.2	Lung involvement in systemic sclerosis	- Lung disease with systemic sclerosis. Scleroderma of lung.
714.81	Rheumatoid lung	- Rheumatoid lung disease. - Rheumatoid fibrosing alveolitis. - Rheumatoid pneumoconiosis.
517.8	Lung involvement in disease classified elsewhere	- Juvenile dermatopolymyositis with lung involvement. - Lung disease due to connective tissue disorder. - Lung disease with polymyositis. - Lung disease with Sjogren's disease. - Lung disease with systemic lupus erythematosus. - Lung disorder due to autoimmune disorder. - Lung sarcoidosis. - Pulmonary amyloidosis.

(Continued)

Table 1-4: ICD-9-CM codes for interstitial lung disease (continued)

ICD-9-CM code	Descriptor	Disease synonyms
495	Extrinsic allergic alveolitis	Includes subdivisions of: - Farmers' lung - Bagassosis - Bird-fanciers' lung - Suberosis - Malt workers' lung - Maple bark-strippers' lung - Ventilation pneumonitis - Other specified allergic alveolitis and pneumonitis - Unspecified allergic alveolitis and pneumonitis.
500	Coal workers' pneumoconiosis	
501	Asbestosis	
502	Pneumoconiosis due to silica or silicates	
503	Pneumoconiosis due other inorganic dust	*Lung disease caused by exposure to metallic beryllium or its soluble salts*
504	Pneumopathy due to inhalation of other dust	*Airway obstruction due to the dust inhaled during the processing of cotton*
505	Pneumoconiosis unspecified	
135	Sarcoidosis	

1.1.3.2 – ICD-10

ICD-10 was endorsed by the WHO in 1990 and has been in use since, particularly for national mortality statistics. The system organises various chapters based on organ systems: respiratory diseases are re-classified in Chapter X (ten) with the prefix 'J'. Interstitial lung disease is mainly found under subheading J84 (other interstitial pulmonary disease), with J84.1 (other interstitial pulmonary disease with fibrosis) the most specific for IPF. Occupational ILD and hypersensitivity pneumonitis are both grouped under the subsection 'lung disease due to external agents', while sarcoidosis is re-classified with various immune disorders in chapter III. Connective tissue disease related ILD is coded under 'respiratory disorders in diseases classified elsewhere', with additional codes linked in the musculoskeletal system chapter.

Selected relevant ICD-10 codes are highlighted in Table 1-5.

1.1.3.3 – ICD-10-CM and ICD-11

The clinical modification of ICD-10 (ICD-10-CM) was made effective from October 2015, and therefore not in use for most of the work in this thesis. Notable changes include the clear allocation of the idiopathic interstitial pneumonias as sub-categories of J84.1 (with IPF specifically allocated J84.112).

ICD-11 is currently under development by the World Health Organisation, with formal implementation expected in 2018 (19). Current proposals (as of 8 September 2016) list respiratory diseases in chapter 12, with the idiopathic interstitial pneumonias specifically classified under CA83, and with IPF specifically allocated code CA83.5: this classification may well change before final approval.

Table 1-5: International Classification of Diseases, 10th Revision (ICD-10) codes for interstitial lung disease

ICD-10 code	Descriptor	Disease synonyms
J84	Other interstitial pulmonary diseases	
J84.0	Alveolar and parietoalveolar conditions	- Alveolar proteinosis - Pulmonary alveolar microlithiasis
J84.1	Other interstitial pulmonary diseases with fibrosis	- Diffuse pulmonary fibrosis - Fibrosing alveolitis (cryptogenic) - Hamman-Rich syndrome - Idiopathic pulmonary fibrosis - Usual interstitial pneumonia
J84.8	Other specified interstitial pulmonary diseases	
J84.9	Interstitial pulmonary disease, unspecified	- Interstitial pneumonia not otherwise specified
J99.0	Rheumatoid lung disease	(also classified under M05.1)
J99.1	Respiratory disorders in other diffuse connective tissue disorders	Respiratory disorders in: - Dermatomyositis - Polymyositis - Sjogren's syndrome - Systemic lupus erythematosus - Systemic sclerosis - Wegener granulomatosis

(Continued)

Table 1-5: ICD-10 codes for interstitial lung disease (continued)

ICD-10 code	Descriptor	Disease synonyms
J60	Coalworker pneumoconiosis	- Anthracosilicosis, Anthracosis, Coalworker lung
J61	Pneumoconiosis due to asbestos and other mineral fibres	- Asbestosis
J62	Pneumoconiosis due to dust containing silica	- Silicosis
J63	Pneumoconiosis due to other inorganic dusts	Includes sub-categories for: - Aluminosis - Bauxite fibrosis - Berylliosis - Graphite fibrosis - Siderosis - Stannosis - Due to other specified inorganic dusts
J64	Unspecified pneumoconiosis	
J67	Hypersensitivity pneumonitis due to organic dust	Includes sub-categories for: - Farmer lung - Bagassosis - Bird fancier lung - Suberosis - Maltworker lung - Mushroom-worker lung - Maple-bark-stripper lung - Air-conditioner and humidifier lung - Due to other organic dusts - Due to unspecified organic dust
D86	Sarcoidosis	Includes sub-categories for: - Sarcoidosis of lung - Sarcoidosis of lymph nodes - Sarcoidosis of lung and lymph nodes - Sarcoidosis of skin - Sarcoidosis of other and combined sites - Sarcoidosis, unspecified

1.1.3.4 – Read codes

Read codes are a highly detailed coding system employed widely across UK general practice (20). Codes used for IPF include H563.00 (idiopathic fibrosing alveolitis), H563.12 (cryptogenic fibrosing alveolitis) and H563100 (diffuse pulmonary fibrosis). Read code dictionaries are updated regularly with new codes, although the system is currently under revision and due to be replaced by a new system called SNOMED CT. More information on Read codes is available in Chapter 4.

1.2 – Epidemiology of IPF

This section examines some of the landmark studies of incidence, prevalence and mortality of IPF. In view of the changes in definitions of IPF over time, it is important to consider the limitations of older studies based on previous classification systems when comparing to contemporaneous findings.

1.2.1 – Incidence

Early studies attempting to identify the burden of IPF tended to involve clinicians collating cases from their local area or asking interested colleagues to contribute to registries. Subsequently, the use of large databases collected for administrative reasons or clinical care enabled far greater numbers to be examined, albeit with some concern about case validity, coding reliability and generalisability to the wider population.

One of the earliest and most important studies was by Coultas *et al* (21), from New Mexico, USA. The authors established a population-based registry of patients with ILD in Bernalillo County, the most populous area of the state, using a combination of hospital discharge letters, autopsy and other pathology reports, death certificates, and contact with general and specialist physicians who might encounter patients with ILD. Diagnoses were verified by chart review to identify appropriate terminology and expert opinion if there was any ambiguity. The authors identified 63 incident cases of idiopathic pulmonary fibrosis (ICD-9 code 516.3) over a two year period (1988-1990), and 28 incident cases of post-inflammatory pulmonary fibrosis (ICD-9 code 515). The incidence of IPF specifically was 10.7 per 100,000 for males, and 7.4 per 100,000 for females. IPF was the largest individual ILD diagnosis (31% of incident cases) followed by post-inflammatory fibrosis (14%), unspecified ILD (10%), and sarcoidosis (8%). Incidence was highest in older patients.

A later study by Fernandez-Perez *et al* (22) identified patients with IPF in Olmsted County, Minnesota, USA, from 1997-2005. This study made use of

the local comprehensive medical records linkage system, with cases identified using ICD-9 code 516.3, then expert review according to ATS/ERS diagnostic criteria. Broad and narrow criteria were defined, where the former allowed 'possible' UIP on imaging, in contrast to the latter requiring definite UIP on either imaging or histology. The authors identified 47 'broad' cases and 24 'narrow' cases, and reported an incidence in residents aged 50 years or older of 17.4 per 100,000 (broad criteria), and 8.8 per 100,000 (narrow criteria).

In terms of database studies, Gribbin *et al* (23) and Navaratnam *et al* (24) both used The Health Improvement Network (THIN), a collection of representative primary care records from the UK, to explore the incidence of IPF from 1991 through to 2008. Cases were identified using relevant Read codes, with exclusion of those aged under 40 or with alternative diagnoses, to aid specificity. Gribbin *et al* identified over 900 cases up until 2003, with a crude incidence of 4.6 per 100,000 (by sex, 5.69 per 100,000 in men, and 3.44 per 100,000 in women), while Navaratnam *et al* reported over 2,000 patients from 2000-2008, with an overall incidence of 7.44 per 100,000. Both studies confidently showed an increase in incidence over time.

A comparable study from the USA by Raghu *et al* (25) used records from a large US health plan from 1996-2000. Incident cases were identified using ICD-9 code 516.3, with a broad definition excluding reference to other types of ILD, and a narrow definition requiring in addition a code for a relevant diagnostic test (surgical lung biopsy, transbronchial lung biopsy, or computed tomography of the thorax) prior to diagnosis. 295 incident cases were identified as meeting the broad definition, and 120 as meeting the narrow definition; when these proportions were extrapolated to the overall US population, incidence rates were estimated at 16.3 per 100,000 (broad definition) and 6.8 per 100,000 (narrow definition).

Details of further studies addressing incidence of IPF are given in Chapter 3 of this thesis.

1.2.2 – Prevalence

Some studies also report prevalence of IPF. While this gives a flavour of the burden of disease, incidence remains the more useful measure, by allowing dynamic assessment that reflects variation over time, and by better reflecting a disease which typically has low survival (by preventing bias due to a minority of patients living longer).

The study by Coultas *et al* reported a prevalence of IPF of 20.2 per 100,000 in males, and 13.2 per 100,000 in females (21), while Fernandez-Perez *et al* noted a prevalence in those aged 50 years or older of 63 per 100,000 (broad criteria) and 27.9 per 100,000 (narrow criteria) – albeit with low numbers (22). Raghu *et al* estimated overall prevalence at 42.7 per 100,000 (broad definition) and 14.0 per 100,000 (narrow definition) from their database study (25).

Prevalence was not reported in the two UK primary care studies, however it was noted in two Scandinavian studies: von Plessen estimated a prevalence of hospitalised cryptogenic fibrosing alveolitis of 23.4 per 100,000 in Bergen, Norway by 1998 (26), and Hodgson *et al* estimated a prevalence of idiopathic fibrosing alveolitis of 16-18 per 100,000 in Finland at the same time (27).

1.2.3 – Mortality

A number of studies have examined mortality due to IPF, mainly using routine mortality statistics. These statistics give an estimate of disease burden, although with the caveat that death certification may not be completely reliable, either due to miscoding or poor capture of the cause of death (16, 28, 29).

A study by Johnston *et al* from the UK showed a dramatic increase in numbers of deaths from cryptogenic fibrosing alveolitis, from 336 in 1979, to 702 in 1988 (29). A subsequent study by Hubbard *et al* examined mortality statistics from seven countries and noted some variation: mortality from IPF increased

over time in England & Wales, Scotland, Australia and Canada, but there was no trend in Germany and New Zealand and a fall in the USA (30). In contrast, mortality increased notably for post-inflammatory fibrosis in the USA, perhaps implying differing coding practice. A further mortality analysis from the UK was part of the study by Navaratnam *et al* (24), where deaths increased to 3,019 in 2008, with an age-standardised rate of 5.10 per 100,000 from 2005-2008. All three of these studies revealed higher mortality among men than women.

Mannino *et al* (31) and Olson *et al* (17) both used national mortality statistics to assess deaths from pulmonary fibrosis in the USA. The Mannino study examined data from 1979-1991 and reported age-adjusted mortality for men as 4.86 per 100,000 in 1979, rising to 5.09 per 100,000 in 1991, and for women as 2.14 per 100,000 in 1979, rising to 2.72 per 100,000 in 1991. Olson *et al* used similar data from 1992-2003 and showed a 28% increase in age-adjusted mortality over time in men, and a 41% increase over time in women. These studies used ICD-9 codes 516.3 and 515, and ICD-10 code J84.1 (Olson study only).

Mortality studies consistently show an increase in deaths due to IPF, although it is unclear how much this relates to increased awareness and coding of disease, and how much reflects increasing incidence over time. Similarly, the reliability of various codes for conveying IPF or more non-specific disease is not clear.

Further exploration of the global incidence and mortality of IPF will be addressed by Chapters 2 and 3 of this thesis.

1.3 – Aetiology of IPF

The aetiology of IPF is unclear, although a number of risk factors have been investigated (32). These include occupational exposures, cigarette smoking, infectious agents, diabetes, and gastro-oesophageal reflux. Studies have also shown links with clotting pathways, and there is likely to be a genetic component. It is therefore likely that disease occurs in genetically predisposed individuals who are exposed to certain risk factors or triggers. These risk factors are discussed briefly in this section.

1.3.1 – Occupational exposures

Evidence supporting the role of occupational inhaled exposures in the development of IPF is limited by a number of factors including poor recall and quantification of exposures and misdiagnosis of IPF. However, a number of case-control studies have suggested associations with wood dust, metal dust, textile dust, livestock, stone/sand/silica, wood fires, agriculture and hairdressing (33-39) (see Table 1-6, re-produced with permission of the American Thoracic Society). These studies are supported by epidemiological studies suggesting higher rates of IPF in areas with more manufacturing industry (40), autopsy studies identifying metal particles in lymph nodes of patients with IPF (41), and animal models demonstrating a fibrotic response in response to inhaled particles (33). Furthermore, well-established conditions where pulmonary fibrosis is known to follow occupational exposure (such as asbestosis) make it plausible that other substances could have a similar effect (32). It has been theorised that unrecognised or low-level asbestos exposure itself may contribute to some cases of IPF (42-44).

Table 1-6: Summary of case-control studies of occupational and environmental risk factors for idiopathic pulmonary fibrosis

Exposure	United Kingdom		United States		Japan	
	Scott, 1990 (34) (40/106) *	Hubbard, 1996 (35) (218/569) *	Mullen, 1998 (36) (17/94) *	Baumgartner, 2000 (37) (248/491) *	Iwai, 1994 (38) (86/172) *	Miyake, 2005 (39) (102/59)*
Agriculture/farming	-	-	-	1.60 (1.0-2.5)	3.01 (1.29-7.43)	-
Livestock	10.89 (1.24-96.0)	-	-	2.70 (1.30-5.50)	-	-
Wood dust	2.94 (0.87-9.9)	1.71 (1.01-2.92)	3.3 (0.42-25.8)	1.60 (0.80-3.30)	-	6.71 (0.37-123.59)
Textile dust	0.9 (0.24-3.44)	1.80 (1.10-2.96)	-	1.90 (0.80-4.40)	-	-
Mould	-	-	16.0 (1.62-158)	-	-	0.98 (0.48-2.01)
Metal dust	10.97 (2.34-52.4)	1.68 (1.07-2.65)	-	2.00 (1.00-4.00)	1.34 (1.14-1.59)	9.55 (1.68-181.12)
Stone/sand/silica	1.59 (0.52-4.79)	1.76 (1.01-3.07)	11.0 (1.05-115)	3.90 (1.20-12.70)	-	-
Wood fires	12.55 (1.40-114.0)	-	-	0.80 (0.40-1.60)	-	-
Smoking	1.11 (0.13-1.40)	1.57 (1.01-2.43)	-	1.60 (1.10-2.40)	2.94 (1.37-6.3)	3.23 (1.01-10.84)

Values are shown as odds ratios (95% confidence intervals).
* Number in parenthesis represent number of cases/number of controls.
- represents associations not examined in a certain study.

Taskar VS, Coultas DB. 2006. Is idiopathic pulmonary fibrosis an environmental disease? Proc Am Thorac Soc. Vol3. Pp 203-298.
The Annals of the American Thoracic Society is an official journal of the American Thoracic Society.

1.3.2 – Tobacco smoking

Several case-control studies from the UK, USA and Japan have shown an association between tobacco smoking and the development of IPF (35, 37-39, 45) (see Table 1-6). As with studies of occupational exposures, these have limitations (such as reduced response from smoking controls) but have biological plausibility. Furthermore, epidemiological variation between males and females has been linked to historical smoking patterns, with longstanding higher rates in men and more recent rises in women matching previous population smoking data (17).

1.3.3 – Infectious agents

A large number of studies have examined the role of viruses in the aetiology of IPF, including Epstein-Barr virus, hepatitis C, and human herpesvirus (46-49). While some studies have detected evidence of viral DNA in lung tissue, results have been inconclusive (15). A limitation of these studies is the fact that patients with IPF were often taking immunosuppressive medication which would have increased susceptibility to virus infection (reverse causation).

1.3.4 – Diabetes

There is some support for the theory that diabetes may be a risk factor for IPF, based on case-control studies from Japan and the UK (50, 51). In the UK study, this association persisted after adjusting for prednisolone exposure, and was strongest for those using insulin. However, another Japanese study did not find an association (52).

1.3.5 – Gastro-oesophageal reflux

Gastro-oesophageal reflux disease (GORD) has been shown to be more common in patients with IPF (51, 53, 54), and there is evidence that its

presence (and treatment) affects progression and survival (55, 56). However, the evidence for causation is unclear. The presumed mechanism is chronic micro-aspiration of gastric contents leading to a fibrotic response in the lung; an alternative theory could be that the non-compliant lung affects intrathoracic pressures with subsequent precipitation of abnormal reflux (15). Studies suggest GORD is often asymptomatic in those with IPF (53, 54).

1.3.6 – Coagulopathy

Both epidemiological and basic science studies have suggested a link between dysfunction of clotting pathways and IPF (57). In a population-based case-control study, Navaratnam *et al* showed that people with IPF were more likely to have a pro-thrombotic state than the general population, and these people had a higher risk of death (58). Other studies have reported a higher incidence of venous thrombosis and acute coronary syndromes in people with IPF (59-61). A small open-label trial from Japan suggested that treatment of people with IPF with anticoagulation (warfarin) might be beneficial (62), however a larger blinded randomised controlled trial from North America showed a higher mortality in the warfarin arm – suggesting interfering with abnormal coagulation was harmful (63). Whether this risk applies to treatment with a clear indication for warfarin (such as atrial fibrillation) is unclear, although a post hoc analysis of anticoagulant use in IPF clinical trials suggested a higher mortality in those treated with warfarin (64). It has been suggested that low molecular weight heparins or the newer direct oral anticoagulants may not have this effect (65, 66).

1.3.7 – Genetics

A number of observations underlie the link between genetics and the development of pulmonary fibrosis, including cases in closely-related family members, the presence of pulmonary fibrosis in certain genetic syndromes, and the differential rates of disease in workers with similar exposures to

known culprit dusts (67). A distinction can be made between familial and sporadic IPF: the former describes IPF affecting two or more members of the same family that is clinically indistinguishable from sporadic IPF but may develop at a younger age (15, 68, 69). Familial IPF is likely to represent less than 5% of total cases of IPF (32).

Both familial and sporadic forms have been associated with various gene mutations, with varying frequencies. Mutations in genes coding for surfactant proteins C and A2, as well as the gene ELMOD2, have been noted in familial cases (70-72), while genes affecting the length of telomeres, such as TERT and TERC, have been identified in sporadic cases as well, albeit to a lesser extent (32, 73). More recently, a common variant in the promoter region of the MUC5B gene was identified in 34% of cases of familial interstitial pneumonia, 38% of cases with IPF, and 9% of controls (74): this association has been replicated elsewhere in the US and Europe (75, 76), and it seems that the presence of this variant is associated with improved survival in those with IPF compared to those without the variant (77). A subsequent genome-wide association study using multiple cohorts identified a further gene, TOLLIP, with a similar mortality association (78), and interest has arisen as to whether the effect of various pharmacotherapies might vary according to genetic characteristics (79).

1.4 – Diagnosis of IPF

1.4.1 – Clinical presentation of IPF

Idiopathic pulmonary fibrosis typically presents with chronic exertional breathlessness and cough. Onset is usually in middle to later life, typically in the sixth and seventh decades (with a median age of onset of 66 years) and more commonly in males (15, 80, 81).

Signs of IPF on clinical examination typically include bilateral basal inspiratory crackles, finger clubbing, and exertional hypoxia. The differential diagnosis for clinicians usually includes more common conditions such as congestive cardiac failure and chronic obstructive pulmonary disease, however the combination of features above should prompt consideration of an interstitial lung disease.

1.4.2 – The diagnostic pathway for ILD

The diagnosis of IPF requires investigations to confirm the presence of an interstitial lung disease, and then a multi-disciplinary team consensus as to whether the findings are consistent with IPF, or alternatively another ILD (80). Standard investigations include chest radiography, pulmonary function tests (spirometry, lung volumes and gas transfer), and high resolution computed tomography of the chest (HRCT). Additional tests to exclude other causes of ILD may include blood tests (to identify connective tissue disease or hypersensitivity pneumonitis), bronchoalveolar lavage (where a lymphocytosis may suggest hypersensitivity pneumonitis or sarcoidosis) and transbronchial biopsies. If there is uncertainty after HRCT then a surgical lung biopsy may be appropriate.

The role of the multi-disciplinary team (MDT) in confirming a diagnosis of IPF has been endorsed by various bodies and is now standard practice (15, 80). The ideal MDT would include a respiratory physician, ILD specialist nurse, radiologist, histopathologist and thoracic surgeon, with the latter two

members most involved when consideration is being given to invasive testing after HRCT.

1.4.3 – The role of high resolution computed tomography

People with IPF typically have bilateral basal reticular changes on chest radiography, with restrictive spirometry, reduced lung volumes and decreased gas transfer. However, high resolution computed tomography (HRCT) is now the key diagnostic test, both to confirm findings characteristic of IPF and exclude findings that may suggest alternative diagnoses (2).

Diagnostic criteria for IPF require a usual interstitial pneumonia (UIP) pattern on HRCT (15). This comprises reticular opacification, honeycombing with or without traction bronchiectasis, and a predominantly subpleural and basal distribution. A number of features are considered inconsistent with a UIP pattern, including upper or mid-lung predominance, extensive ground glass change (more than the reticular abnormality), profuse micronodules, and diffuse mosaic attenuation. The presence of reticular change in a subpleural basal distribution, without honeycombing, and without any of the 'inconsistent with UIP' features, has been termed 'possible UIP'.

The positive predictive value of a UIP pattern on HRCT has been estimated at 90-100% (15), however, ATS/ERS guidelines recommend surgical lung biopsy where radiological appearances are not definitive.

1.4.4 – The role of surgical lung biopsy

Surgical lung biopsy has traditionally been viewed as the 'gold standard' test for the diagnosis of IPF (82), particularly in the United States. However, improvements in imaging and the perceived risks of the procedure mean that it is not deemed necessary for everyone with suspected IPF (1, 15, 83). A key question is whether the information obtained by a lung biopsy will change clinical management to an extent that outweighs the potential risks of the

surgery. This question has been considered even prior to the revised diagnostic criteria for IPF: in 1999, Temes *et al* examined all diagnostic lung biopsies for suspected ILD at three hospitals over a six year period, and proposed that while elective and urgent biopsies had acceptable mortality risks with frequent changes in subsequent clinical care, emergency biopsies had higher risks with fewer changes to care and should therefore be avoided (84). This section considers the use of surgical lung biopsy for IPF, and evidence for benefits and harms of the procedure from the literature.

1.4.4.1 – Frequency of use of surgical lung biopsy for IPF

There is variable data on how frequently surgical lung biopsy is utilised to diagnose IPF, and it is likely this has changed over time and varies between countries. Epidemiological studies from Europe covering the period 1992-2001 suggest 28-33% of patients with IPF received a surgical biopsy (27, 85, 86), while a US series from 1997-2005 had a similar rate of 29% (22). However, a medical benefits based study from Japan covering 2003-2007 revealed only 11% of those with IPF had undergone surgical biopsy (87), and a Swedish registry starting in 2014 reported 14% of patients had biopsy-confirmation (88). Further data is available from clinical trials in IPF, where biopsy rates vary from 18-25% in the two INPULSIS trials (89), 21-26% in the Japanese pirfenidone trials (90, 91) and 30% in the ASCEND trial (92), to 47-55% in the multicentre CAPACITY trials (93). Overall, the range of patients receiving surgical lung biopsy appears to vary considerably.

1.4.4.2 – Benefits of surgical lung biopsy

The value of adding surgical lung biopsy to standard tests in the evaluation of suspected IPF has been examined in a number of studies. NICE guidance from 2013 (80) evaluated sixteen studies (post 1994), although these were low-moderate quality and only three yielded enough data to calculate sensitivity, specificity, and positive and negative predictive values (94-96) (see Table 1-7). NICE also reported the diagnostic yield from fourteen studies (whether IPF

was diagnosed or not), although some of these studies included all ILD and others only IPF. Overall, the guideline group recommended surgical lung biopsy if a confident diagnosis could not be made from clinical and radiological findings, acknowledging that surgical lung biopsy increased the likelihood of a confident diagnosis, but with increased risks (80).

Surgical lung biopsy may identify other pathology that has an improved prognosis and alternative treatment options. In a 2001 prospective study by Hunninghake *et al* (97), 91 patients with suspected IPF underwent surgical lung biopsy after clinical assessment: in nine patients (10%), a certain diagnosis of IPF was overturned, and in eleven (12%), IPF was confirmed having been thought unlikely. Most studies of the effectiveness of surgical lung biopsy have considered patients with undifferentiated ILD, and although many do not specify the most likely diagnosis pre-operatively, several state that histology resulted in a change in treatment plans in over 50% (84, 98-104). However, many of these are older studies where treatment options differed, and it is unclear if these treatments would have been given empirically in the absence of histology (for example, if the patient declined a biopsy).

Although lung biopsy is useful for diagnosis, it is not always conclusive. Problems include inter-observer variation in interpretation (105), varying pathology in different areas of the lung (106, 107), and the possibility of no clear diagnosis (or unclassifiable disease) despite biopsy (with rates of over 18% reported) (108-111).

Table 1-7: Diagnostic accuracy of surgical lung biopsy for interstitial lung disease

Study author / year	Study details	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Aalokken, 2012 (94)	• 64 patients with IIP, all with HRCT/SLB • Independent review of images ➢ Histology result compared to MDT consensus opinion of both tests	73%	74%	83%	61%
Coutinho, 2008 (95)	• 120 patients with DPLD, all with HRCT/SLB ➢ Clinical/HRCT diagnosis compared to final histology	67%	90%	76%	85%
Peckham, 2004 (96)	• 26 patients with suspected ILD ➢ Clinical (ATS/ERS criteria) compared to final histology	71%	67%	71%	76%
	➢ HRCT diagnosis compared to final histology	71%	75%	77%	73%

ILD: interstitial lung disease; IIP: idiopathic interstitial pneumonia; DPLD: diffuse parenchymal lung disease; HRCT: high resolution computed tomography; SLB: surgical lung biopsy; MDT: multi-disciplinary team; ATS: American Thoracic Society; ERS: European Respiratory Society.

Sensitivity: proportion of those with the disease (based on reference or 'gold standard' test) who are positive on the test being assessed (for example, HRCT).

Specificity: proportion of those without the disease (based on reference or 'gold standard' test) who are negative on the test being assessed (for example, HRCT).

Positive predictive value: probability of having the disease (based on reference or 'gold standard' test) in a patient with a positive test result (of the test being assessed, for example, HRCT). Dependent on pre-test probability so needs to be interpreted with knowledge of disease prevalence.

Negative predictive value: probability of not having the disease (based on reference or 'gold standard' test) in a patient with a negative test result (of the test being assessed, for example, HRCT). Dependent on pre-test probability so needs to be interpreted with knowledge of disease prevalence.

Based on NICE (2013) (80)

1.4.4.3 – Risks of surgical lung biopsy

A large number of studies have considered the risks of surgical lung biopsy for interstitial lung disease. Risks include prolonged air leak, pneumonia, pneumothorax, and most notably acute exacerbations of the underlying ILD, which can lead to mortality (82). Most studies focus on undifferentiated ILD, while some have selected only those with suspected IPF, subsequently confirmed IPF, or usual interstitial pneumonia (UIP) on histology. Older studies have included a greater number of open lung biopsies, while later studies have been dominated by video-assisted thoracoscopic surgery (VATS). Finally, outcomes have varied, in part due to the different research aims, for example safety studies are more likely to report mortality and morbidity data than studies of diagnostic yield.

One of the earliest studies to raise awareness of the risk of lung biopsy for ILD was a study by Utz *et al* from the Mayo Clinic, USA (112). The authors examined 60 patients with an ultimate diagnosis of UIP over a ten year period (1986-1995), and reported a 30-day mortality of 17% (10 deaths, all patients with IPF rather than connective tissue disease associated UIP). Limitations of this study include the difference in clinical practice at the time, for example less than 50% of patients underwent a pre-operative CT scan, and might not have required biopsy if this had been available. Other earlier studies included a large number of patients who were immunocompromised (104, 113-115), and variable numbers of patients who were on mechanical ventilation pre-operatively, and later studies have reported lower mortality rates. In a 2005 study by Lettieri *et al* (116), it was noted that almost half of those undergoing lung biopsy were on oxygen pre-operatively, with 17% on immunosuppression: excluding those with mechanical ventilation or immune compromise reduced 90-day mortality from 6% to under 2%. Supporting the argument of Temes *et al* (84) that emergency biopsies have higher risks, a number of studies specifically of those with acute respiratory failure pre-operatively report very high mortality of up to 50% (117-119).

A recent review by Nguyen and Meyer of 30 studies reported overall 30-day mortality of 4.3% for open lung biopsy and 2.1% for VATS; however included studies were heterogeneous and included data from as far back as the 1950s (120). A subsequent systematic review and meta-analysis by Han *et al* reported a composite post-operative mortality of 3.6% (95% confidence interval (CI) 2.1-5.5), with pooled 30- and 90-day mortality rates of 2.2% (95% CI 1.0-4.0) and 3.4% (95% CI 1.8-5.5) respectively, however significant heterogeneity was again noted (121).

A summary of studies from after the year 2000 that report risks following surgical lung biopsy for ILD is shown in Table 1-8. Studies including indications other than ILD (for example, pulmonary nodules) have been excluded. All case series include some degree of bias (for example, case selection) and may not be applicable to other centres. Abstracts have been included but are shown in italics to acknowledge the reduced information on cases included.

In summary, numerous mostly single-centre studies have examined the mortality risk from surgical lung biopsy for interstitial lung disease, which ranges from 0% to far higher, and in many cases may reflect how 'well' the person is pre-operatively.

Further notes on Table 1-8

Last search completed using Medline and Embase on 31 July 2016. % VATS reflects the procedure performed, not intention, so will be reduced in cases of conversion to open surgery (assuming this was documented). % IPF is presented to aid interpretation of mortality data rather than assess yield: some series may have included *only* cases of IPF. Morbidity documentation requires specific figures as a single patient may have had multiple complications: it was unclear from all studies if morbidity records included deaths.

Table 1-8: Studies reporting risk of surgical lung biopsy for diagnosis of interstitial lung disease (year 2000 onwards)

Study author/year	Location	Number patients	Mean age	Years of data	% VATS	% IPF	Mortality	Morbidity	Comments
*Akyil, 2015** (122)	*Istanbul, Turkey*	*202*	*49*	*2007-2014*	*57%*	*n/a*	*2.0% (30d)*	*12.9%*	
*Bertolaccini, 2015** (123)	*Verona, Italy*	*87*	*n/a*	*2008-2014*	*100%*	*UIP 38%*	*0% (n/s)*	*3.5% (major)* *5.8% (minor)*	*Risk factors: ↑age, pre-operative oxygen requirement*
*Bond, 2015** (124)	*Birmingham, UK*	*35*	*n/a*	*2013*	*100%*	*n/a*	*3% (30d)*	*29%*	*Wound infection and pain common*
*Nicol, 2015** (125)	*Edinburgh, UK*	*166*	*n/a*	*2007-2013*	*100%*	*n/a*	*3.6% (p-o)*	*n/a*	
*Raza, 2015** (126)	*Southampton, UK*	*101*	*57‡*	*2008-2014*	*95%*	*n/a*	*1% (90d)*	*8% (minor)*	
Rotolo, 2015 (127)	Varese, Italy	161	55	1997-2014	94%	IPF 24%	3.1% (30d)	11.8%	Prolonged air leak in 5%. Deaths due to post-op acute respiratory failure. Risk factors: pre-op oxygen, UIP
*Findikcioğlu, 2014** (108)	*Adana, Turkey*	*45*	*50.5*	*n/a*	*69%*	*IIP 40%*	*4.4% (p-o)*	*18%*	*Risk factors: ↑age, MV*
Morris, 2014 (109)	Edinburgh, UK	66	59	2011-2013	100%	UIP 21%	1.5% (30d)	28.8%	PTX in 11%, LRTI 6%, SE 5%
*Quarantotto, 2014** (128)	*Ferrara, Italy*	*47*	*59.3*	*2005-2010*	*100%*	*n/a*	*0% (p-o)*	*4%*	*Prolonged air leak: 4%*
Sonobe, 2014 (100)	Kyoto, Japan	64	57	2007-2013	98%	UIP 19%	0% (60d)	n/a	PTX in 6%
Blackhall, 2013 (129)	Glasgow, UK	103	58†	2008-2010	79%	UIP/NSIP 31%	4.9% (30d)	6.8% (major) 6.8% (minor)	21% conversion rate (to OLB) 4/5 deaths: respiratory failure
Luo, 2013 (130)	Guangzhou, China	32	52.2	2007-2011	100%	IPF 13%	0% (30d) 5.2% (90d)	65.6%	Infection in 56%, PTX 25%
*Sanna, 2013** (102)	*Forli, Italy*	*226*	*58.3*	*2003-2013*	*98%*	*UIP 42%*	*0.4% (p-o)*	*n/a*	*Prolonged air leak in 5%*

*Abstract only; † Median age; ‡ ambiguous data; n/a: not available; n/s: not specified; d/c: discharge; SLB: surgical lung biopsy; (Continued)
VATS: video-assisted thoracoscopic surgery; IPF: idiopathic pulmonary fibrosis; IIP: idiopathic interstitial pneumonia; UIP: usual interstitial pneumonia;
NSIP: non-specific interstitial pneumonia; p-o: post-operative (also reflects in-hospital or 'operation-related' mortality); 30d/60d/90d: 30-, 60- and 90-day mortality;
MV: mechanical ventilation; PTX: pneumothorax; LRTI: lower respiratory tract infection; SE: surgical emphysema; OLB: open lung biopsy; AE: acute exacerbation; ICU: intensive care unit.

Table 1-8: Studies reporting risk of surgical lung biopsy for diagnosis of interstitial lung disease (year 2000 onwards) (continued)

Study author/year	Location	Number patients	Mean age	Years of data	% VATS	% IPF	Mortality	Morbidity	Comments
Plones, 2013 (131)	Freiburg, Germany	45	61.4†	2000-2011	96%	UIP 100%	0% (30d)	n/a	Pneumonia in 4%
Blanco, 2012 (132)	Spain	171	57	1997-2011	82-90%‡	UIP 29%	5.8% (p-o)	n/a	12% conversion rate (to OLB) 7/10 deaths: respiratory failure
Fibla, 2012 (133)	Rochester, USA	311	60.9	2002-2009	90%	IPF 39%	9% (30d) 10.6% (90d)	11.5%	AE in 7%, need for ICU 6%. Risk factors: ↑age, OLB, pre-op ICU, immunosuppression
Fibla, 2012 (134)	Spain	224	57.1	2007-2009	100%	IPF 26%	0% (p-o)	6% (in-hospital) 5% (post-d/c)	Dyspnoea in 3%, PTX or air leak 2%. Pain in 3%, PTX 2%
*Gill, 2011** (135)	*California, USA*	*61*	*61.6*	*2004-2010*	*92%*	*UIP 46%*	*0% (p-o)*	*1.6%*	*1 case of post-op respiratory failure*
Sakamoto, 2011 (136)	Tokyo, Japan	20	n/a	2000-2006	n/a	IPF 40%	5% (p-o)	n/a	Mortality due to AE-IPF
Zhang, 2010 (137)	China	418	n/a	1999-2009	45%	IPF 15%	1.9% (p-o)	12%	5 deaths: respiratory failure and AE
Bando, 2009 (138)	Tochigi, Japan	113	59	1994-2006	100%	IIP 46%	1.8% (p-o)	n/a	Two deaths: both AE-IPF. 0% mortality at 30 days. Prolonged air leak in 15%.
*Guerra, 2009** (139)	*Porto, Portugal*	*53*	*47.2*	*1998-2007*	*70%*	*n/a*	*1.9% (p-o)*	*9.4%*	*Prolonged air leak in 6%*
*Ishie, 2009** (140)	*Florianopolis, Brazil*	*48*	*58.8*	*n/a*	*96%*	*UIP 29%*	*0% (p-o)*	*2%*	*1 case of residual pneumothorax*
Sigurdsson, 2009 (101)	Reykjavik, Iceland	73	57.3	1986-2007	38%	UIP 32%	2.7% (30d) 4% (90d)	16%	All deaths: respiratory failure. Prolonged air leak in 12%, AE 3%
*Gil Carbonell, 2008** (141)	*Alicante, Spain*	*17*	*50*	*1992-2007*	*58%*	*UIP 100%*	*11.7% (30d)*	*n/a*	*Risk factors: ↑age*
*Greenwood, 2008** (110)	*Liverpool, UK*	*224*	*54.6*	*2001-2008*	*73%*	*IPF 34%*	*0.9% (n/s)*	*11.2%*	

*Abstract only; † Median age; ‡ ambiguous data; n/a: not available; n/s: not specified; d/c: discharge; SLB: surgical lung biopsy; (Continued)

VATS: video-assisted thoracoscopic surgery; IPF: idiopathic pulmonary fibrosis; IIP: idiopathic interstitial pneumonia; UIP: usual interstitial pneumonia;

NSIP: non-specific interstitial pneumonia; p-o: post-operative (also reflects in-hospital or 'operation-related' mortality); 30d/60d/90d: 30-, 60- and 90-day mortality;

MV: mechanical ventilation; PTX: pneumothorax; LRTI: lower respiratory tract infection; SE: surgical emphysema; OLB: open lung biopsy; AE: acute exacerbation; ICU: intensive care unit.

Table 1-8: Studies reporting risk of surgical lung biopsy for diagnosis of interstitial lung disease (year 2000 onwards) (continued)

Study author/year	Location	Number patients	Mean age	Years of data	% VATS	% IPF	Mortality	Morbidity	Comments
Kreider, 2007 (142)	Philadelphia, USA	68	58	1998-2004	100%	UIP 34%	4.4% (60d)	19.1%	All deaths: AE-IPF. Re-admissions in 11%. Risk factors: pre-op oxygen
Lee, 2007 (143)	Daejeon, South Korea	40	56.4	2001-2006	30%	UIP 10%	15% (30d) 20% (90d)	n/a	Prolonged air leak in 7.5% Risk factors: pre-op oxygen, MV
*Quadrelli, 2007** (144)	*Buenos Aires, Argentina*	*71*	*n/a*	*n/a*	*73%*	*n/a*	*11.2% (30d)*	*22.5%*	*Risk factors: immunocompromise, pre-op respiratory failure, acute symptoms*
Park, 2007 (145)	Seoul, South Korea	200	58	1990-2003	75%	IPF 70%	4% (30d) 8.5% (90d)	15%	Prolonged air leak in 8%. Risk factors: AE, low transfer factor
Canzian, 2006 (118)	Sao Paulo, Brazil	63	51†	1982-2003	n/a	UIP 11%	51% (p-o)	n/a	All patients: acute respiratory failure pre-op
Kondoh, 2006 (146)	Japan	236	n/a	1989-2000	58%	n/a	0.8% (p-o)	n/a	Primary focus on AE rate: 2.1%
*Sakamoto, 2006** (147)	*Nagoya, Japan*	*110*	*n/a*	*1989-2002*	*63%*	*n/a*	*6.4% (30d)*	*10.9%*	
Carrillo, 2005 (148)	Mexico	722	n/a	1986-1990	n/a	n/a	3% (30d)	n/a	Risk factors: ↑CO_2, ↓O_2, co-morbidity
Lee, 2005 (104)	Taiwan	196	48.5	1995-2003	62%	UIP 5%	24% (30d) 33.7% (p-o) ‡	6.6%	Prolonged air leak in 5.6% 49.5% patients immunocompromised
Lettieri, 2005 (116)	Washington DC, USA	83	57.3	1996-2002	72%	IPF 51%	4.8% (30d) 6% (90d)	8.4%	30-d mortality 7.1% in IPF patients Risk factors: MV, immunocompromise
Ooi, 2005 (111)	Cambridge, UK	70	56	1998-2003	79%	UIP 37%	1.4% (p-o)	7.1%	1 death: metastatic lung cancer
Parambil, 2005 (149)	Rochester, USA	58	n/a	1996-2002	n/a	IPF 100%	13.8% (p-o)	n/a	Focus on 7 with SLB during AE: 6/7 died
Soh, 2005 (117)	Taipei, Taiwan	32	50.6	1990-2002	0%	n/a	56.2% (p-o)	40.6%	All patients: acute respiratory failure pre-op

*Abstract only; † Median age; ‡ ambiguous data; n/a: not available; n/s: not specified; d/c: discharge; SLB: surgical lung biopsy; (Continued)
VATS: video-assisted thoracoscopic surgery; IPF: idiopathic pulmonary fibrosis; IIP: idiopathic interstitial pneumonia; UIP: usual interstitial pneumonia;
NSIP: non-specific interstitial pneumonia; p-o: post-operative (also reflects in-hospital or 'operation-related' mortality); 30d/60d/90d: 30-, 60- and 90-day mortality;
MV: mechanical ventilation; PTX: pneumothorax; LRTI: lower respiratory tract infection; SE: surgical emphysema; OLB: open lung biopsy; AE: acute exacerbation; ICU: intensive care unit.

Table 1-8: Studies reporting risk of surgical lung biopsy for diagnosis of interstitial lung disease (year 2000 onwards) (continued)

Study author/year	Location	Number patients	Mean age	Years of data	% VATS	% IPF	Mortality	Morbidity	Comments
Tiitto, 2005 (99)	Oulu, Finland	76	56.7	1973-2002	45%	IPF 84%	5.3% (30d)	n/a	Risk factor: OLB
*Jinbo, 2004** (150)	*Ube, Japan*	*34*	*n/a*	*1999-2003*	*100%*	*n/a*	*5.9% (p-o)*	*11.8%*	*2 deaths: AE*
Yamaguchi, 2004 (98)	Fukuoka, Japan	30	56.7	1994-2002	100%	IPF 40%	0% (p-o)	10%	Post-op acute respiratory failure: 6.7%
*Ayed, 2003** (151)	*Kuwait*	*79*	*38.9*	*1995-2001*	*100%*	*n/a*	*1.3% (p-o)*	*10.1%*	
Chuang, 2003 (119)	Taipei, Taiwan	34	43	n/a	0%	n/a	29.4% (p-o)	11.8%	Half cases had respiratory distress pre-op: all deaths in this group
Kayatta, 2003 (152)	Atlanta, USA	194	58	2003-2012	100%	IPF 43%	6.7% (30d)	n/a	Risk factors: ↑age, MV, pre-op O_2
Qureshi, 2003 (153)	Liverpool, UK	100	n/a	1995-1999	70%	n/a	0% (p-o)	n/a	
*Warzelhan, 2002** (154)	*Freiburg, Germany*	*68*	*53.1*	*1990-2002*	*69%*	*UIP 31%*	*5.8% (30d)*	*10.1%*	
*Enomoto, 2002** (155)	*Japan*	*9*	*n/a*	*1997-2001*	*100%*	*UIP 100%*	*n/a*	*22.2%*	*2/9 patients: AE. Small selected cohort. Risk factors: poor lung function*
Nicholson, 2002 (105)	London, UK	59	n/a	1979-1998	n/a	UIP 100%	1.7% (p-o)	n/a	
Blewett, 2001 (156)	Ontario, Canada	32	58	1997-1999	0%	UIP 81%	0% (p-o)	n/a	Ambulatory patients only
Hunninghake, 2001 (97)	USA	91	n/a	n/a	n/a	IPF 59%	1.1% (p-o)	18%	Prolonged air leak: 4.4%, PTX: 3.3%
Utz, 2001 (112)	Rochester, USA	60	63.4	1986-1995	27%	IPF 77%	16.7% (30d)	n/a	Risk factor: low transfer factor
Ayed, 2000 (157)	Kuwait	61	38‡	1996-1998	52%	n/a	3.3% (p-o)	14.8%	Prolonged air leak: 6.6%; post-op respiratory failure: 3.3%. Trial data
Miller, 2000 (158)	Canada and USA	42	56‡	1994-1997	43%	UIP 52%	2.4% (p-o)	19.0%	

*Abstract only; † Median age; ‡ ambiguous data; n/a: not available; n/s: not specified; d/c: discharge; SLB: surgical lung biopsy;
VATS: video-assisted thoracoscopic surgery; IPF: idiopathic pulmonary fibrosis; IIP: idiopathic interstitial pneumonia; UIP: usual interstitial pneumonia;
NSIP: non-specific interstitial pneumonia; p-o: post-operative (also reflects in-hospital or 'operation-related' mortality); 30d/60d/90d: 30-, 60- and 90-day mortality;
MV: mechanical ventilation; PTX: pneumothorax; LRTI: lower respiratory tract infection; SE: surgical emphysema; OLB: open lung biopsy; AE: acute exacerbation; ICU: intensive care unit.

1.5 – Management and prognosis of IPF

Management of idiopathic pulmonary fibrosis has changed considerably over recent years, as longstanding practices have been refuted and new medications have been introduced as a result of large randomised controlled clinical trials. However, the overall prognosis for those diagnosed with IPF remains poor. This section briefly considers management options – including disease-modifying and supportive therapies – and the outlook for those diagnosed with the disease.

1.5.1 – Treatment guidance for IPF

In the United Kingdom, there have been two major guidelines relevant to the treatment of IPF. In 2008, the British Thoracic Society (BTS) coordinated a comprehensive guideline that acknowledged the lack of proven medical therapies, and emphasised the role of best supportive care and recruitment to clinical trials (159). In 2013, the National Institute for Health and Care Excellence (NICE) guideline re-emphasised the role of best supportive care (80), while referencing the availability of the new anti-fibrotic therapy pirfenidone, examined separately in technology appraisal TA282 (160). A similar appraisal for another disease-modifying agent, nintedanib (TA379) was published in 2016 (161).

In the United States, there have been three treatment guidelines coordinated by the American Thoracic Society (ATS), which summarise changes in practice over a relatively short period of time. While acknowledging a lack of evidence, initial guidance from 2000 (14) suggested consideration of combined therapy with corticosteroids and azathioprine or cyclophosphamide. A major update from 2011 in conjunction with the European Respiratory Society and others strongly recommended against this option (15), but made only a weak recommendation against treatment with prednisolone, azathioprine and N-acetylcisteine, suggesting this therapy could be offered to a minority of

patients. This recommendation was based on the results of the IFIGENIA study (162), which showed benefit with regards to lung function versus prednisolone and azathioprine alone, although with a number of limitations including the absence of a true control group on no treatment. This treatment regimen had also been given a tentative low-key weak recommendation in the 2008 BTS guideline (159). At this stage, the ATS/ERS guidelines gave a similar weak recommendation against pirfenidone, based on two randomised controlled trials from Japan (90, 91) and earlier results from the two CAPACITY trials (93).

In 2015, an updated treatment guideline was produced by the ATS and others to reflect recent major advances in the field (163). Notably, this included a strong recommendation *against* combination therapy with prednisolone, azathioprine and N-acetylcisteine, based on the higher mortality observed versus placebo in the PANTHER study (164). There was also a conditional recommendation *for* treatment with pirfenidone and nintedanib, based on new randomised controlled trial evidence from the ASCEND (92) and INPULSIS (89) trials respectively. These treatments are discussed further below.

1.5.2 – Disease-modifying therapy

The introduction of disease-modifying anti-fibrotic medications has altered the therapeutic landscape in IPF dramatically. It is likely that progress will continue, with many experts speculating about the role of sequential or combination regimens and additional medications currently undergoing clinical trials (165-168).

Pirfenidone was licenced in Japan and Europe after clinical trial evidence suggested a reduction in rate of decline of forced vital capacity (FVC) over time (90, 91, 93). To satisfy additional US Food and Drug Administration (FDA) requirements, the large ASCEND trial was conducted: this trial randomised 555 patients to pirfenidone or placebo and showed a significant reduction in FVC decline from baseline to one year and improved progression-free survival for those on pirfendidone (92). There was no difference in secondary

endpoints such as dyspnoea scores or mortality, although a pre-specified pooled analysis using results from the earlier CAPACITY trials did suggest reduced all-cause and IPF-specific mortality. Pirfenidone was approved by NICE in the UK for patients with an FVC between 50% and 80% predicted (160). Side effects include photosensitivity, gastrointestinal upset and liver function test derangement: treatment discontinuation in 'real-world' case series has been reported as 13-19% (169).

Nintedanib was licenced by the FDA and recommended by NICE following the twin INPULSIS trials: these replicate studies randomised 1,066 patients to either nintedanib or placebo, and showed a similar reduction in FVC decline over one year (89). While one of the studies showed a reduction in time to first exacerbation, this was not shown in both, and there was no impact on secondary endpoints such as dyspnoea scores and mortality. The main side effect of treatment was diarrhoea, which was tolerated in most cases. As with pirfenidone, NICE recommended nintedanib for patients with an FVC between 50-80%, with cessation in the case of disease progression (161). A systematic review and meta-analysis of drug treatments for IPF did not show a clear advantage for either treatment in terms of mortality outcomes (170).

A number of other agents have been trialled in IPF but with disappointing results: latest ATS and/or NICE guidance currently recommend against treatment with warfarin, prednisolone, azathioprine. N-acetylcisteine, ambrisentan, bosentan, macitentan, imatinib, sildenafil, co-trimoxazole or mycophenolate mofetil (80, 163)

1.5.3 – Supportive therapy

While anti-fibrotic therapy may benefit patients with IPF, it is acknowledged that not everyone will be suitable or will tolerate treatment, and supportive care is recommended from the point of diagnosis (80). This includes patient education and support, relief of symptoms (for example, cough), management of co-morbidities and ultimately end-of-life care. Specific

interventions may include smoking cessation, influenza and pneumococcal vaccination, pulmonary rehabilitation, ambulatory or long-term oxygen therapy, and referral for consideration of lung transplantation. International guidelines suggest transplant referral should take place early for patients with IPF, acknowledging the likely progression in the absence of treatment (171).

1.5.4 – Prognosis of IPF

The natural history of IPF varies and is not reliably predictable at the time of diagnosis: some patients may have a slow progressive decline over many years, while others deteriorate more rapidly (15, 172). The phenomenon of acute exacerbations – rapid declines in respiratory function in the absence of infection, heart failure or another identifiable cause - has been well described: these may occur spontaneously or as a result of triggers such as lung biopsy, and may be either fatal or leave the patient with much worsened disease (172, 173). Overall, the disease is progressive, and the median survival has been reported as 2-4 years (15, 172, 174, 175), although the placebo arms of clinical trials of patients with milder disease show improved outcomes (15, 176). The most common cause of death in patients with IPF is progressive respiratory failure (177).

1.6 – Rationale, aims and objectives, and thesis outline

1.6.1 – Rationale for thesis

The advent of anti-fibrotic therapies (and their associated financial impact on healthcare budgets) means that it is crucial to understand the true burden of IPF in terms of incidence and mortality worldwide. Most current data originate from the US and Europe, and often predate updated diagnostic criteria which have steadily been adopted over time. There is also a need to identify new aetiological factors, to help guide our understanding of possible means of prevention and the targeting of new therapies. Finally, with an increased awareness of the importance of accurate diagnosis, the role of definitive tests such as surgical lung biopsy may become more prominent, and there is a pressing need to quantify the risk of this procedure in large populations. The risk of surgical procedures in people with established IPF – particularly given the theoretical risk of triggering acute exacerbations - is also unclear.

1.6.2 – Aims and objectives

This thesis will firstly aim to update the current knowledge base with regards incidence and mortality of IPF worldwide, by systematically and comprehensively reviewing the available literature. Secondly, it will explore the role of recent surgical intervention in the aetiology of IPF. Thirdly, it will consider the risks of surgical lung biopsy, in particular mortality, in the diagnosis of interstitial lung disease such as IPF. Finally, it will explore the risks of surgery in established disease, again focussing on mortality.

1.6.3 – Thesis outline

This section briefly outlines the content of each chapter.

Chapter 2: Mortality from idiopathic pulmonary fibrosis

This chapter will collate available global mortality statistics for IPF, with consideration of overall mortality, variation between regions and variation over time.

Chapter 3: Systematic review of incidence and mortality of idiopathic pulmonary fibrosis

This chapter will systematically review the literature to assess the incidence and mortality of IPF worldwide, with consideration given to the merits and limitations of various study designs, and an attempt to derive summary statistics if possible.

Chapter 4: The association between recent major surgery and the onset of idiopathic pulmonary fibrosis

This chapter will use primary care data from the United Kingdom to assess whether major surgery is associated with a subsequent new diagnosis of IPF, using a case-control study design.

Chapter 5: Risk of surgical lung biopsy for diagnosing interstitial lung disease in the United States

This chapter will use secondary care data from the USA to assess the risks of surgical lung biopsy – in particular, in-hospital mortality – when attempting to diagnose interstitial lung disease, with an assessment of factors associated with increased risk.

Chapter 6: Risk of surgical lung biopsy for diagnosing interstitial lung disease in the United Kingdom

This chapter will use secondary care data from the United Kingdom to assess the risks of surgical lung biopsy for diagnosing interstitial lung disease, with linked national mortality data allowing an assessment of 30-day and 90-day mortality as well as re-admissions and cause of death. As with the previous chapter, risk factors for early mortality will be assessed.

Chapter 7: Mortality of patients with idiopathic pulmonary fibrosis undergoing major surgery

This chapter will use secondary care data from the USA to assess the risks for patients with IPF undergoing major elective surgical procedures, with a focus on in-hospital mortality.

Chapter 8: Conclusions and recommendations for future research

This chapter will summarise the key findings of the thesis, and consider future research questions and challenges in the field.

1.6.4 – Summary of chapter

This chapter has addressed how idiopathic pulmonary fibrosis fits into the spectrum of interstitial lung disease, and how diagnostic criteria have changed over time: both these issues are relevant when identifying patients with IPF in large datasets using changing clinical coding systems. The chapter then introduced key studies of incidence, prevalence and mortality, before a brief overview of aetiological theories that have been previously investigated. The clinical assessment of patients with suspected IPF was then outlined, with consideration of the role of surgical lung biopsy, including both benefits and a comprehensive review of the literature regarding risks, notably post-operative mortality. A brief overview of management and prognosis followed, before a summary of the aims and objectives of the thesis and an outline of the structure to follow.

Chapter 2 : Mortality from idiopathic pulmonary fibrosis

This chapter compares mortality rates from idiopathic pulmonary fibrosis across countries using national mortality statistics, and considers the reliability of this approach to assessing global mortality from IPF.

This work was published in the Annals of the American Thoracic Society in 2014 (178).

2.1 – Introduction

2.1.1 – Background

There is good evidence from the United Kingdom that mortality from IPF is increasing (24), and similar evidence from the United States until 2003 (17, 31). However, evidence from elsewhere is limited and outdated (30). Mortality statistics are collated around the World and offer the opportunity to measure disease burden over time, although not all conditions will be recorded by national statistics agencies (179).

2.1.2 – Using death certificates to estimate mortality

Mortality statistics are usually obtained from death certificates, which are compiled by a physician after a person dies and outline the cause of death. This may be relatively simple (for example, myocardial infarction) or may be more complex (for example, gastro-intestinal haemorrhage due to chronic liver disease secondary to long-term alcohol abuse). Most statistics are based on the 'underlying cause of death': international guidance has recently changed so that this is more likely to reflect underlying conditions (for example, lung cancer) rather than a final event (for example, pneumonia) (18, 180). In some cases additional data on multiple causes of death are provided, which can be useful to assess disease burden in conditions such as IPF when the underlying cause of death may be unrelated (31). Data from death certification may be published in full or summary form by national statistics agencies for the benefit or researchers, policy-makers and public health organisations.

A limitation of using death certificates to estimate mortality is the possibility of either under-recognition or misclassification. This has been assessed previously in both the US and UK (16, 29), but these studies are from twenty years ago and may not reflect current practice.

2.1.3 – Rationale for the study

There are no contemporaneous published mortality data from outside the UK and USA, yet IPF is known to occur in countries worldwide (32). It is important to know whether previously described increases in mortality are maintained, and whether they are replicated elsewhere - both to enhance the epidemiological understanding of the disease but also to assess disease burden in an era of new treatments.

2.1.4 – Aims and Objectives

This chapter aims to examine mortality from IPF across a number of countries using death certification data. The objectives are to determine current mortality rates across regions, the extent of any changes over time, and whether any regional differences exist.

A further aim is to assess the reliability of death certification as a measure of IPF mortality, using data from a UK cohort. This would aim to estimate the extent to which mortality data would likely underestimate (or overestimate) the true burden of IPF.

2.2 – Methods

2.2.1 – Data searches

Cause of death data were obtained from the websites of national statistics agencies, which were identified by searching for 'statistics' and '[name of country]' using the Google search engine. Initial searches were undertaken of the major western English-speaking nations (United Kingdom, United States, Canada, Australia, and New Zealand), followed by the rest of Europe, and all other countries in the G20 group of major economies. The extent of searching was guided by the expected likelihood of finding data at a sufficient level of detail to include IPF: many agencies listed only deaths from 'influenza', 'pneumonia' and 'chronic lower respiratory diseases' in their respiratory section, in line with the WHO mortality database (179). Searches took place November 2013 – January 2014.

2.2.2 – Codes selection

Where possible, data were obtained for the four-digit ICD-10 codes J84.1 ('other interstitial pulmonary diseases with fibrosis') and J84.9 (interstitial pulmonary disease, unspecified): the first code being the most specific for IPF, and the combination of the two codes reflecting a broader definition. Where only three-digit ICD-10 codes were available, data were obtained for the umbrella code J84 ('other interstitial pulmonary diseases'). The other two sub-codes under this heading, J84.0 and J84.8, were only rarely used in more detailed datasets, and so it was felt that data from J84 would broadly approximate J84.1 and J84.9 codes. All identified cases were labelled as 'IPF-clinical syndrome' (IPF-CS), a term used previously that acknowledges a minority of such cases identified in large datasets may not be 'true' IPF (24, 181).

Where available, data were also collated on multiple cause of death (featuring all diseases mentioned on death certification), with the expectation that these would have an increased number of IPF cases due to occasions where it was listed as a secondary cause.

2.2.4 – Data preparation

For each country, the number of deaths from IPF-CS was grouped by year, sex, and age category (0-44 years, 45-54 years, 55-64 years, 65-74 years, 75-84 years, and 85 years and older). Crude mortality rates for each group 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 then calculated by standardising to the 2013 European Standard Population (182, 183).

2.2.5 – Data analysis

Numbers of deaths and crude and age-adjusted mortality rates were plotted for individual countries to assess change over time. Mortality rate ratios were calculated by Poisson regression modelling for sex, age and year, and used to calculate trend data for individual countries. The 65-74 age category was used as a baseline as this includes the average age of diagnosis of IPF (172). Meta-analysis using the random effects model was used to determine overall estimates of change in mortality over time and mortality differences by age and sex across countries. Graphs were created using GraphPad Prism 6 (GraphPad Software, La Jolla, California, USA) and data analysis was completed using Stata, version 11 (StataCorp, College Station, Texas, USA).

2.2.6 – Validation study

To assess the validity of death certification as a measure of mortality from IPF, cause of death data was obtained from a cohort study of 211 patients with IPF from the UK (58). All participants in this study were incident cases of IPF from England and Wales who had had imaging review by two experienced thoracic radiologists, and confirmation as definite or probably usual interstitial pneumonia according to 2011 ATS/ERS criteria (15). The aim of this study was to assess the presence of clotting factors in patients with IPF, with collection of mortality data as part of survival analysis. Mortality data was provided by the study team.

2.3 – Results

This section will first outline those countries providing data, and the numbers of deaths by each code for each country, with a comment on the overall use of different codes. Mortality rates by underlying cause of death will then be discussed for each country individually. This will be followed by an overall assessment with use of meta-analysis to compare countries. A similar structure will then be followed for those countries yielding multiple cause of death data. Finally, the validation study of UK death certificates will be reported.

2.3.1 – Geographical spread of data

Ten national statistics agencies yielded data on deaths from pulmonary fibrosis. Deaths by four-digit ICD-10 codes were available from five territories: England and Wales, Australia, Canada, Spain and the United States. Deaths by three-digit ICD-10 codes (J84) were available from an additional five territories: Japan, Northern Ireland, New Zealand, Scotland and Sweden. England and Wales, Australia and the United States provided data on multiple cause of death separately. Deaths were available for individual states in the USA, however values representing fewer than ten deaths were suppressed for confidentiality reasons, and therefore this limited the ability to calculate age-specific rates for younger patients in smaller states. Data were therefore analysed separately for the largest five states, where there was minimal data suppression, for multiple cause of death data only. Sources of data are listed in Appendix A. For clarity, reference to the United Kingdom includes its four constituent countries (with three statistics agencies): England and Wales, Scotland and Northern Ireland.

2.3.2 – Total deaths per country and outlier data

The number of years of data available for each country varied from three to twelve years, spanning 1999-2012. Table 2-1 displays the number of years available for each country, alongside total numbers of deaths for each ICD-10 code group. There were three years of data where erroneous data were suspected: Spain in 2005 (very few deaths recorded compared to adjacent years) and the United States multiple cause of death data from 2006 and 2007 (apparent excess of deaths from J84.8 in all states). These outlier years were not studied, and as all three countries with multiple cause of death data provided the more specific sub-codes, it was decided to omit analysis of the less-specific umbrella code J84 for this part of the project.

2.3.3 – Comparison between ICD-10 codes

For the five countries yielding data for both broad and specific ICD-10 codes, comparison was made between the relative frequencies of use of the four-digit sub-codes. J84.1 comprised 78-95% of all J84 codes for underlying cause of death for all the years available, with J84.9 comprising 4-20% of codes. A smaller proportion of deaths in the youngest age category were coded as J84.1. Both these codes combined comprised greater than 98% of the all J84 cases for almost all years of data.

For Japan, the majority of data were available only as three-digit ICD-10 codes (ie code J84) but there were overall totals available for each sub-code. While J84.1 and J84.9 comprised over 99% of the total codes, the majority of cases (70-75%) were classified as J84.9, in contrast to other countries where the majority were classified as J84.1.

Table 2-1: Countries included in mortality analysis, with years of data and number of deaths per available ICD-10 code

Country	Years of data analysed	Deaths from J84	Deaths from J84.1	Deaths from J84.1 + J84.9 (combined)
Underlying cause of death data				
England and Wales	2001-2012	38,861	34,473	38,426
Australia	2000-2011	9,325	7,754	9,182
Canada	2000-2011	17,792	15,350	17,588
Japan	2009-2011	40,928	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	4,341	n/a	n/a
Spain	2000-2004, 2006-2011	18,563	16,840	18,344
Sweden	2000-2012	4,153	n/a	n/a
USA	1999-2010	168,637	135,460	166,222
Multiple cause of death data				
England and Wales	2001-2012	65,770	59,734	65,643
Australia	2000-2011	17,588	14,829	17,501
USA	1999-2010	220,075*	214,794	262,595

* Excludes 2006/07 – outlier data.

ICD-10: International Classification of Diseases, 10th revision; J84: other interstitial pulmonary diseases; J84.1: other interstitial pulmonary diseases with fibrosis; J84.9: interstitial pulmonary disease, unspecified; n/a: not available

2.3.4 – Mortality using underlying causes of death data, by country

Numbers of deaths, crude mortality rates and age-standardised mortality rates are presented here for each country for the available codes, followed by summary data for all countries.

2.3.4.1 – England and Wales

Deaths from pulmonary fibrosis in England and Wales increased annually, from 2,346 in 2001 to 4,652 in 2012, based on J84 coding (see Table 2-2). Age-standardised mortality rates increased from 6.39 per 100,000 to 9.84 per 100,000. Over 98.4% of these cases were J84.1/J84.9 for all years, with a decrease in the proportion coded as J84.1 over time (84% in 2012, vs 95% in 2001) (Table 2-3, Table 2-4). The age-standardised mortality rate due to J84.1 specifically was 8.28 per 100,000 in 2012. Figure 2-1, Figure 2-2 and Figure 2-3 show mortality over time for codes J84, J84.1/J84.9 and J84.1 respectively.

Table 2-2: Mortality from idiopathic pulmonary fibrosis clinical syndrome in England and Wales (J84 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	331.27	14804	4.47	4.63	1.00	
Male	319.38	24057	7.53	10.47	2.27	(2.23-2.32)*
Age group						
0-44	385.40	333	0.09	0.09	0.00	(0.00-0.01)
45-54	85.73	741	0.86	0.87	0.05	(0.04-0.05)
55-64	75.03	3163	4.22	4.23	0.23	(0.22-0.24)
65-74	55.07	9848	17.88	18.14	1.00	
75-84	35.90	15994	44.56	47.07	2.59	(2.53-2.66)
85+	13.52	8782	64.95	75.50	4.17	(4.05-4.29) †
Year						
2001	51.61	2346	4.55	6.39	1.00	
2002	52.60	2497	4.75	6.19	0.98	(0.92-1.03)
2003	52.86	2605	4.93	6.42	1.01	(0.96-1.07)
2004	53.15	2798	5.26	6.82	1.08	(1.02-1.14)
2005	53.58	2819	5.26	6.72	1.07	(1.01-1.13)
2006	53.95	2949	5.47	6.97	1.10	(1.04-1.16)
2007	54.39	3221	5.92	7.57	1.18	(1.12-1.25)
2008	54.84	3442	6.28	7.93	1.25	(1.18-1.31)
2009	55.24	3452	6.25	7.85	1.23	(1.17-1.30)
2010	55.69	3790	6.81	8.47	1.32	(1.26-1.39)
2011	56.17	4290	7.64	9.41	1.47	(1.40-1.55)
2012	56.57	4652	8.22	9.84	1.55	(1.48-1.63) †

* p <0.001; † p for trend <0.001

Figure 2-1: Mortality from J84 in England and Wales, 2001-2012

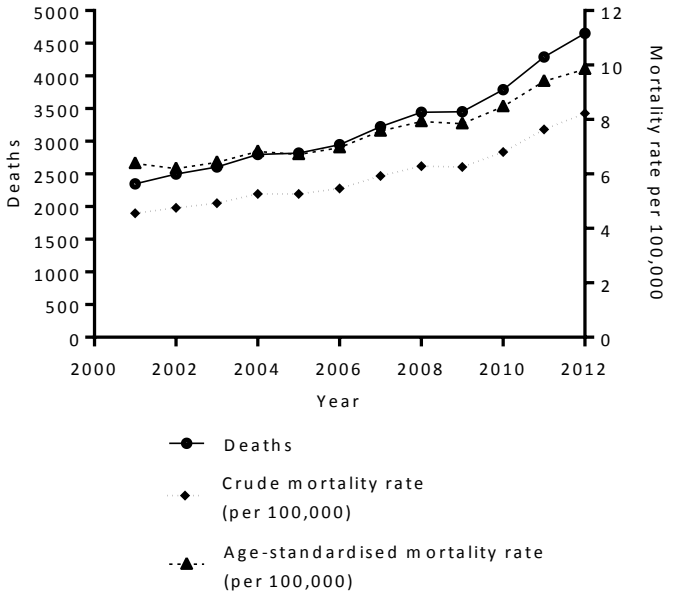


Table 2-3: Mortality from idiopathic pulmonary fibrosis clinical syndrome in England and Wales (J84.1/J84.9 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	331.27	14651	4.42	4.58	1.00	
Male	319.38	23775	7.44	10.36	2.27	(2.23-2.32)*
Age group						
0-44	385.40	273	0.07	0.07	0.00	(0.00-0.01)
45-54	85.73	702	0.82	0.82	0.05	(0.04-0.05)
55-64	75.03	3102	4.13	4.15	0.23	(0.22-0.24)
65-74	55.07	9735	17.68	17.93	1.00	
75-84	35.90	15878	44.23	46.73	2.61	(2.54-2.67)
85+	13.52	8736	64.61	75.07	4.19	(4.07-4.32) †
Year						
2001	51.61	2321	4.50	6.33	1.00	
2002	52.60	2480	4.71	6.15	0.98	(0.93-1.04)
2003	52.86	2573	4.87	6.35	1.01	(0.96-1.07)
2004	53.15	2770	5.21	6.76	1.08	(1.02-1.14)
2005	53.58	2788	5.20	6.66	1.07	(1.01-1.13)
2006	53.95	2913	5.40	6.89	1.10	(1.04-1.16)
2007	54.39	3179	5.85	7.47	1.18	(1.12-1.25)
2008	54.84	3397	6.19	7.83	1.24	(1.18-1.31)
2009	55.24	3398	6.15	7.74	1.22	(1.16-1.29)
2010	55.69	3745	6.72	8.37	1.32	(1.25-1.39)
2011	56.17	4252	7.57	9.33	1.47	(1.40-1.55)
2012	56.57	4610	8.15	9.76	1.55	(1.48-1.63) †

* p <0.001; † p for trend <0.001

Figure 2-2: Mortality from J84.1/J84.9 in England and Wales, 2001-2012

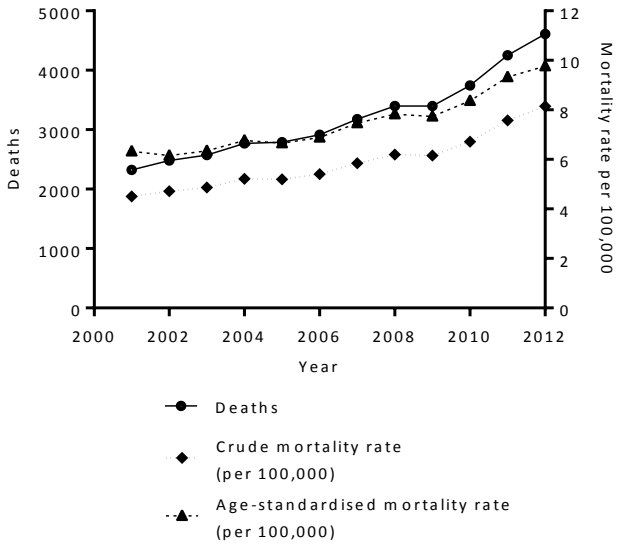
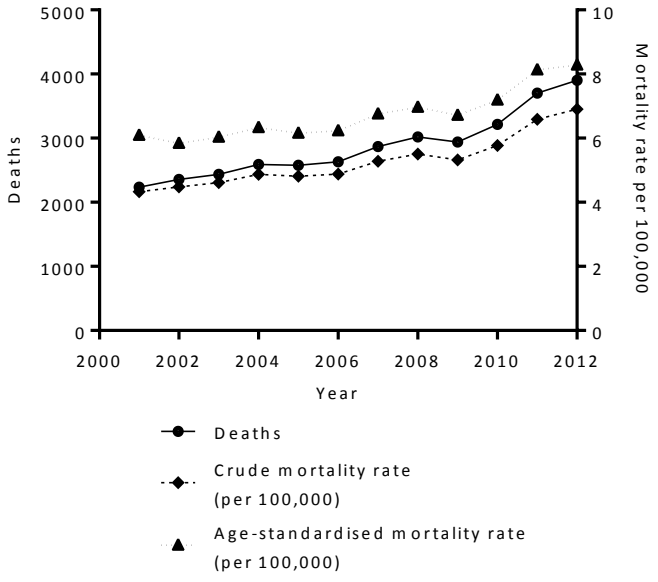


Table 2-4: Mortality from idiopathic pulmonary fibrosis clinical syndrome in England and Wales (J84.1 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	331.27	13123	3.96	4.11	1.00	
Male	319.38	21350	6.68	9.34	2.29	(2.24-2.34)*
Age group						
0-44	385.40	208	0.05	0.05	0.00	(0.00-0.00)
45-54	85.73	569	0.66	0.67	0.04	(0.04-0.05)
55-64	75.03	2677	3.57	3.59	0.22	(0.21-0.23)
65-74	55.07	8697	15.79	16.05	1.00	
75-84	35.90	14378	40.05	42.43	2.64	(2.57-2.71)
85+	13.52	7944	58.75	68.39	4.28	(4.15-4.42) †
Year						
2001	51.61	2234	4.33	6.09	1.00	
2002	52.60	2355	4.48	5.84	0.97	(0.91-1.03)
2003	52.86	2435	4.61	6.03	0.99	(0.94-1.05)
2004	53.15	2589	4.87	6.33	1.05	(0.99-1.11)
2005	53.58	2577	4.81	6.15	1.03	(0.97-1.08)
2006	53.95	2633	4.88	6.23	1.03	(0.98-1.09)
2007	54.39	2870	5.28	6.75	1.11	(1.05-1.17)
2008	54.84	3018	5.50	6.96	1.15	(1.08-1.21)
2009	55.24	2940	5.32	6.71	1.10	(1.04-1.16)
2010	55.69	3214	5.77	7.19	1.18	(1.12-1.24)
2011	56.17	3704	6.59	8.13	1.33	(1.26-1.40)
2012	56.57	3904	6.90	8.28	1.36	(1.30-1.44) †

* p <0.001; † p for trend <0.001

Figure 2-3: Mortality from J84.1 in England and Wales, 2001-2012



2.3.4.2 – Australia

Deaths from pulmonary fibrosis in Australia also increased over a similar time period, although crude and age-standardised mortality rates were lower than in England and Wales. Age-standardised mortality for J84 coding was 6.49 per 100,000 in 2012, compared to 5.11 per 100,000 in 2000. For J84.1, age-standardised mortality increased less, from 4.23 per 100,000 in 2000 to 5.08 per 100,000 in 2011 – see Table 2-5, Table 2-6, Table 2-7, Figure 2-4, Figure 2-5, and Figure 2-6.

2.3.4.3 – Canada

Data from Canada demonstrated an apparent jump in deaths after 2003 and then a more steady increase until 2010-11. Over 98.6% of J84 cases were sub-classified as J84.1 or J84.9, with 84-88% coded as J84.1 alone. Mortality rates were intermediate between Australia and England and Wales, with adjusted rates in 2011 of 7.52 per 100,000 (J84 coding) and 6.38 per 100,000 (J84.1 coding) – see Table 2-8, Table 2-9, Table 2-10, Figure 2-7, Figure 2-8 and Figure 2-9.

2.3.4.4 – Japan

Only limited data were available from Japan, for the broad J84 code and for just three years, however there were a large number of deaths reflecting the large population, and a clear increase in mortality over the three years. Age-adjusted mortality was amongst the highest out of the countries studied, at 10.26 per 100,000 – see Table 2-11, Figure 2-10.

Table 2-5: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Australia (J84 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	123.86	3866	3.12	3.96	1.00	
Male	122.36	5459	4.46	7.63	1.93	(1.85-2.01)*
Age group						
0-44	154.17	85	0.06	0.05	0.00	(0.00-0.01)
45-54	33.77	188	0.56	0.56	0.05	(0.04-0.06)
55-64	26.18	680	2.60	2.62	0.22	(0.20-0.24)
65-74	17.17	2010	11.71	11.78	1.00	
75-84	11.11	4008	36.07	37.41	3.20	(3.03-3.37)
85+	3.82	2354	61.59	67.58	5.84	(5.50-6.20) †
Year						
2000	19.03	588	3.09	5.11	1.00	
2001	19.27	660	3.42	5.63	1.08	(0.97-1.21)
2002	19.50	714	3.66	5.89	1.14	(1.02-1.27)
2003	19.72	665	3.37	5.33	1.03	(0.93-1.16)
2004	19.93	695	3.49	5.41	1.05	(0.94-1.18)
2005	20.18	621	3.08	4.78	0.91	(0.82-1.02)
2006	20.45	771	3.77	5.72	1.11	(0.99-1.23)
2007	20.83	788	3.78	5.69	1.10	(0.99-1.22)
2008	21.25	905	4.26	6.46	1.23	(1.11-1.36)
2009	21.69	894	4.12	6.11	1.18	(1.06-1.31)
2010	22.03	1032	4.68	6.87	1.32	(1.19-1.46)
2011	22.34	992	4.44	6.49	1.23	(1.11-1.36) †

* p <0.001; † p for trend <0.001

Figure 2-4: Mortality from J84 in Australia, 2000-2011

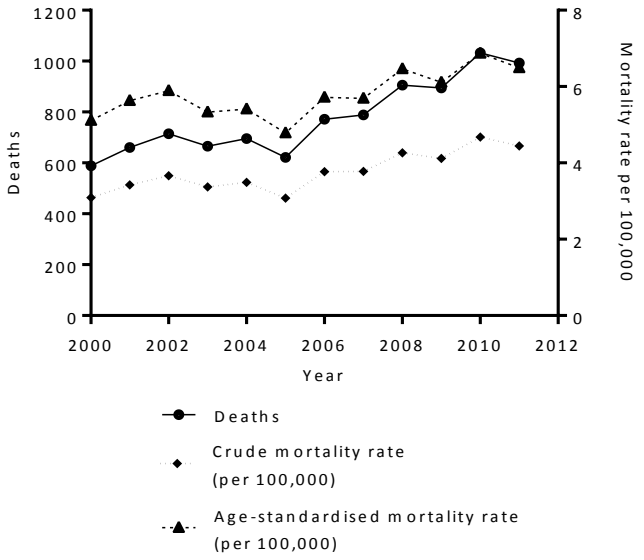


Table 2-6: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Australia (J84.1/J84.9 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	123.86	3802	3.07	3.89	1.00	
Male	122.36	5380	4.40	7.52	1.93	(1.85-2.02)*
Age group						
0-44	154.17	95	0.06	0.06	0.01	(0.00-0.01)
45-54	33.77	169	0.50	0.50	0.04	(0.04-0.05)
55-64	26.18	655	2.50	2.53	0.22	(0.20-0.23)
65-74	17.17	1979	11.53	11.59	1.00	
75-84	11.11	3954	35.58	36.92	3.21	(3.04-3.38)
85+	3.82	2330	60.97	66.84	5.88	(5.53-6.24) †
Year						
2000	19.03	585	3.07	5.08	1.00	
2001	19.27	653	3.39	5.57	1.08	(0.96-1.20)
2002	19.50	703	3.61	5.78	1.13	(1.01-1.26)
2003	19.72	657	3.33	5.28	1.03	(0.92-1.15)
2004	19.93	680	3.41	5.31	1.04	(0.93-1.16)
2005	20.18	615	3.05	4.74	0.91	(0.81-1.02)
2006	20.45	759	3.71	5.64	1.09	(0.98-1.22)
2007	20.83	785	3.77	5.65	1.10	(0.99-1.22)
2008	21.25	888	4.18	6.35	1.21	(1.09-1.34)
2009	21.69	865	3.99	5.93	1.15	(1.03-1.27)
2010	22.03	1019	4.63	6.79	1.31	(1.18-1.45)
2011	22.34	973	4.36	6.38	1.21	(1.09-1.34) †

* p <0.001; † p for trend <0.001

Figure 2-5: Mortality from J84.1/J84.9 in Australia, 2000-2011

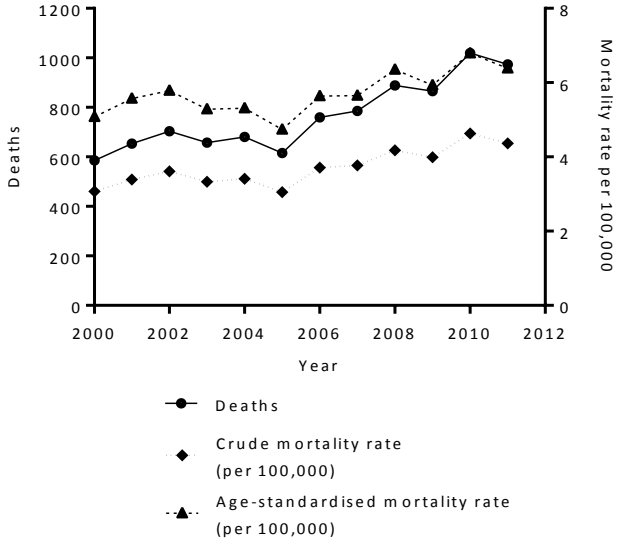


Table 2-7: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Australia (J84.1 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	123.86	3209	2.59	3.30	1.00	
Male	122.36	4545	3.71	6.39	1.95	(1.86-2.04)*
Age group						
0-44	154.17	53	0.03	0.03	0.00	(0.00-0.00)
45-54	33.77	107	0.32	0.32	0.03	(0.03-0.04)
55-64	26.18	537	2.05	2.08	0.21	(0.19-0.23)
65-74	17.17	1675	9.76	9.84	1.00	
75-84	11.11	3372	30.34	31.53	3.23	(3.04-3.42)
85+	3.82	2010	52.59	57.53	6.00	(5.63-6.41) †
Year						
2000	19.03	487	2.56	4.23	1.00	
2001	19.27	558	2.89	4.80	1.11	(0.98-1.25)
2002	19.50	612	3.14	5.04	1.18	(1.05-1.33)
2003	19.72	571	2.90	4.60	1.07	(0.95-1.21)
2004	19.93	592	2.97	4.65	1.08	(0.96-1.22)
2005	20.18	533	2.64	4.13	0.95	(0.84-1.07)
2006	20.45	641	3.13	4.74	1.11	(0.98-1.25)
2007	20.83	672	3.23	4.84	1.13	(1.00-1.27)
2008	21.25	758	3.57	5.44	1.24	(1.10-1.39)
2009	21.69	718	3.31	4.97	1.14	(1.02-1.28)
2010	22.03	837	3.80	5.59	1.29	(1.15-1.44)
2011	22.34	775	3.47	5.08	1.16	(1.03-1.30) †

* p <0.001; † p for trend <0.001

Figure 2-6: Mortality from J84.1 in Australia, 2000-2011

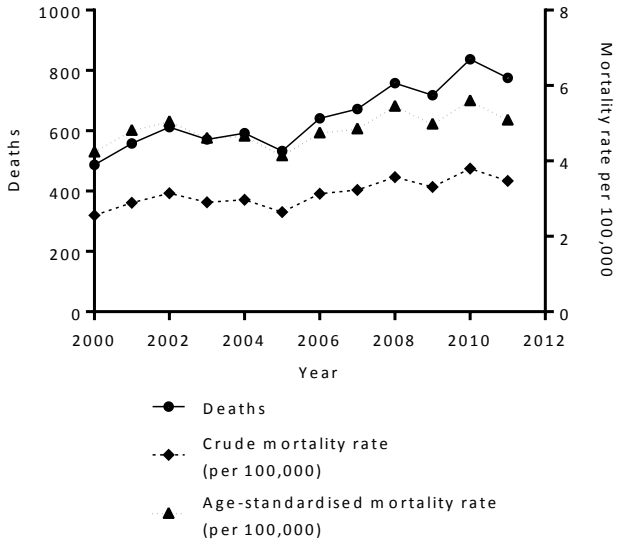


Table 2-8: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Canada (J84 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	196.55	7507	3.82	4.66	1.00	
Male	193.02	10285	5.33	9.18	1.96	(1.90-2.02)*
Age group						
0-44	234.88	198	0.08	0.08	0.01	(0.00-0.01)
45-54	59.62	484	0.81	0.81	0.06	(0.05-0.06)
55-64	43.28	1589	3.67	3.69	0.25	(0.24-0.27)
65-74	27.91	4017	14.39	14.58	1.00	
75-84	17.83	7071	39.66	41.79	2.86	(2.75-2.97)
85+	6.05	4433	73.32	82.07	5.68	(5.44-5.93) †
Year						
2000	30.69	1088	3.55	5.93	1.00	
2001	31.02	1178	3.80	6.30	1.06	(0.97-1.15)
2002	31.36	1175	3.75	6.05	1.02	(0.94-1.11)
2003	31.64	1159	3.66	5.81	0.98	(0.91-1.07)
2004	31.94	1464	4.58	7.31	1.21	(1.12-1.31)
2005	32.24	1598	4.96	7.74	1.28	(1.19-1.38)
2006	32.57	1517	4.66	7.11	1.18	(1.09-1.27)
2007	32.89	1595	4.85	7.21	1.20	(1.11-1.30)
2008	33.25	1626	4.89	7.14	1.19	(1.10-1.28)
2009	33.63	1728	5.14	7.36	1.22	(1.14-1.32)
2010	34.01	1801	5.30	7.57	1.24	(1.15-1.34)
2011	34.34	1863	5.42	7.52	1.25	(1.16-1.34) †

* p <0.001; † p for trend <0.001

Figure 2-7: Mortality from J84 in Canada, 2000-2011

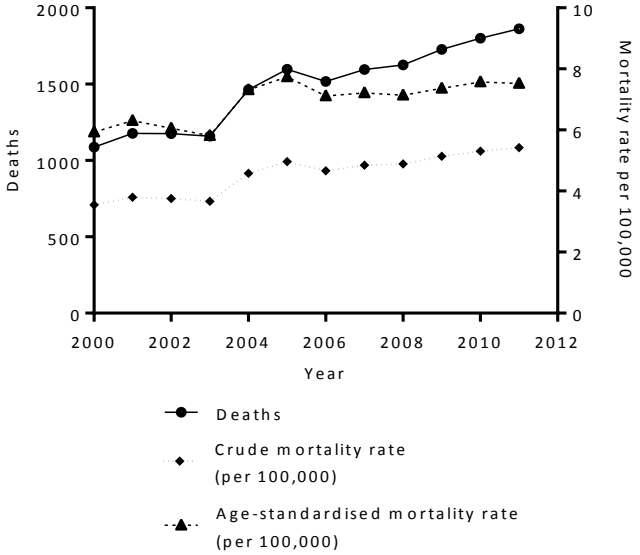


Table 2-9: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Canada (J84.1/J84.9 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	196.55	7414	3.77	4.61	1.00	
Male	193.02	10174	5.27	9.10	1.97	(1.91-2.03)*
Age group						
0-44	234.88	161	0.07	0.07	0.00	(0.00-0.01)
45-54	59.62	457	0.77	0.77	0.05	(0.05-0.06)
55-64	43.28	1554	3.59	3.61	0.25	(0.23-0.26)
65-74	27.91	3975	14.24	14.43	1.00	
75-84	17.83	7029	39.42	41.54	2.87	(2.76-2.99)
85+	6.05	4412	72.97	81.70	5.72	(5.48-5.97) †
Year						
2000	30.69	1078	3.51	5.88	1.00	
2001	31.02	1163	3.75	6.23	1.05	(0.97-1.14)
2002	31.36	1161	3.70	6.00	1.02	(0.94-1.11)
2003	31.64	1140	3.60	5.74	0.98	(0.90-1.06)
2004	31.94	1454	4.55	7.26	1.21	(1.12-1.31)
2005	32.24	1585	4.92	7.69	1.28	(1.19-1.39)
2006	32.57	1498	4.60	7.03	1.17	(1.08-1.27)
2007	32.89	1574	4.79	7.13	1.19	(1.11-1.29)
2008	33.25	1604	4.82	7.06	1.18	(1.09-1.28)
2009	33.63	1710	5.08	7.29	1.22	(1.13-1.32)
2010	34.01	1776	5.22	7.48	1.23	(1.14-1.33)
2011	34.34	1845	5.37	7.45	1.24	(1.15-1.34) †

* p <0.001; † p for trend <0.001

Figure 2-8: Mortality from J84.1/J84.9 in Canada, 2000-2011

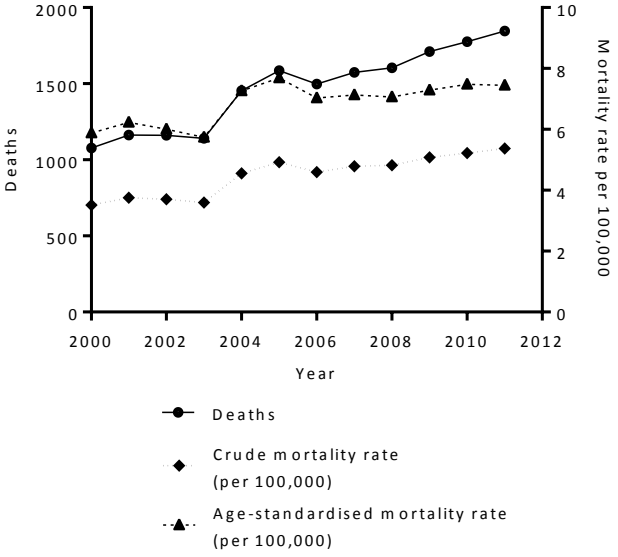


Table 2-10: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Canada (J84.1 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	196.55	6466	3.29	4.02	1.00	
Male	193.02	8884	4.60	7.97	1.98	(1.92-2.04)*
Age group						
0-44	234.88	109	0.05	0.05	0.00	(0.00-0.00)
45-54	59.62	375	0.63	0.63	0.05	(0.04-0.06)
55-64	43.28	1304	3.01	3.03	0.24	(0.22-0.25)
65-74	27.91	3455	12.38	12.56	1.00	
75-84	17.83	6210	34.83	36.72	2.92	(2.80-3.04)
85+	6.05	3897	64.45	72.01	5.82	(5.56-6.09) †
Year						
2000	30.69	938	3.06	5.09	1.00	
2001	31.02	997	3.21	5.40	1.04	(0.95-1.13)
2002	31.36	1036	3.30	5.36	1.05	(0.96-1.14)
2003	31.64	1006	3.18	5.09	0.99	(0.91-1.08)
2004	31.94	1292	4.05	6.47	1.24	(1.14-1.35)
2005	32.24	1398	4.34	6.82	1.30	(1.20-1.41)
2006	32.57	1338	4.11	6.29	1.20	(1.11-1.31)
2007	32.89	1374	4.18	6.25	1.20	(1.10-1.30)
2008	33.25	1401	4.21	6.16	1.19	(1.09-1.29)
2009	33.63	1485	4.42	6.33	1.22	(1.12-1.32)
2010	34.01	1506	4.43	6.33	1.20	(1.11-1.30)
2011	34.34	1579	4.60	6.38	1.22	(1.13-1.32) †

* p <0.001; † p for trend <0.001

Figure 2-9: Mortality from J84.1 in Canada, 2000-2011

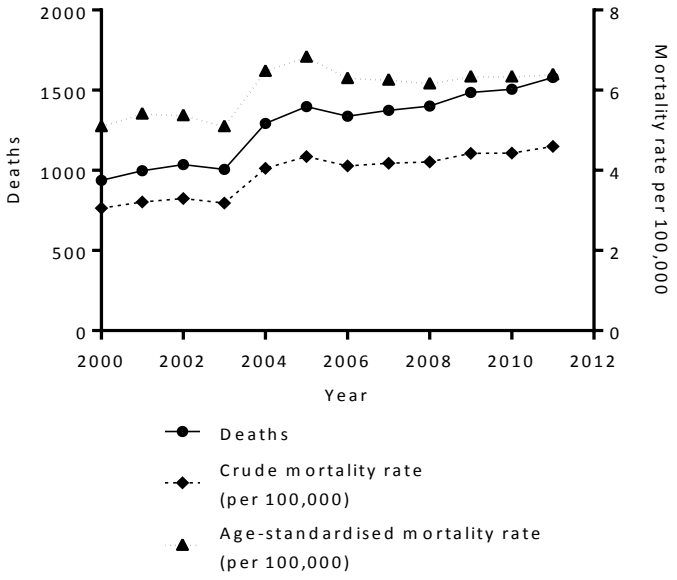
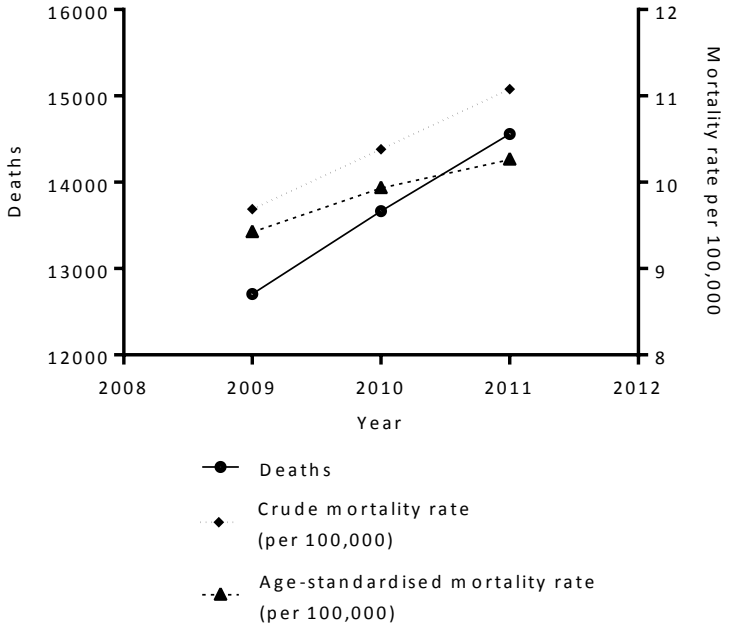


Table 2-11: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Japan (J84 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	201.74	15047	7.46	5.36	1.00	
Male	192.47	25881	13.45	14.39	2.68	(2.63-2.74)*
Age group						
0-44	204.07	212	0.10	0.10	0.01	(0.00-0.01)
45-54	46.31	353	0.76	0.76	0.04	(0.03-0.04)
55-64	55.95	2336	4.18	4.21	0.21	(0.20-0.22)
65-74	45.41	8787	19.35	19.92	1.00	
75-84	30.95	18329	59.22	63.97	3.22	(3.14-3.31)
85+	11.52	10911	94.70	117.39	5.97	(5.80-6.14) †
Year						
2009	131.14	12705	9.69	9.42	1.00	
2010	131.64	13664	10.38	9.93	1.05	(1.02-1.07)
2011	131.44	14559	11.08	10.26	1.09	(1.06-1.11) †

* p <0.001; † p for trend <0.001

Figure 2-10: Mortality from J84 in Japan, 2009-2011



2.3.4.5 – Northern Ireland

Northern Ireland provides statistics separately to the rest of the United Kingdom. Data were available for code J84 only, for three years from 2009-2011. Although numbers were low due to the small population, age-standardised mortality was among the highest of all countries assessed, and increased over the three years, to 13.36 per 100,000 in 2011 – see Table 2-12 and Figure 2-11.

2.3.4.6 – New Zealand

Data from New Zealand were available for five years for the J84 code. There was an initial sharp increase in deaths from 2006-2007 and then a more steady rise. Age-standardised mortality increased overall but appeared to plateau later at around 5.5 per 100,000 – see Table 2-13 and Figure 2-12.

2.3.4.7 – Scotland

Like Northern Ireland, Scotland provides its own statistical service, which yielded twelve years of data for the broad J84 code. Mortality from pulmonary fibrosis clearly increased over the time period studied, with an age-standardised mortality rate of 6.43 per 100,000 in 2001, rising to 10.71 per 100,000 in 2012 – see Table 2-14 and Figure 2-13.

2.3.4.8 – Spain

Spain provided data for all codes, from 2000-2011 (with outlier data in 2005 – omitted). Mortality was lower than in the United Kingdom, Canada and Japan, but steadily increased for all codes across the time period studied. Age-standardised mortality rose from 3.73 to 5.38 per 100,000 for the broader J84 code, and from 3.51 to 4.64 per 100,000 for the more specific J84.1 code – see Table 2-15, Table 2-16, Table 2-17, Figure 2-14, Figure 2-15 and Figure 2-16.

Table 2-12: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Northern Ireland (J84 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	2.76	177	6.41	7.49	1.00	
Male	2.65	221	8.33	13.43	1.78	(1.45-2.17)*
Age group						
0-44	3.33	6	0.18	0.18	0.01	(0.00-0.02)
45-54	0.73	8	1.09	1.09	0.04	(0.02-0.09)
55-64	0.57	42	7.31	7.31	0.30	(0.21-0.43)
65-74	0.43	103	24.00	24.31	1.00	
75-84	0.23	150	58.30	61.13	2.52	(1.96-3.24)
85+	0.09	89	96.40	110.89	4.44	(3.33-5.91) †
Year						
2009	1.81	106	5.91	8.22	1.00	
2010	1.80	122	6.76	9.80	1.12	(0.87-1.46)
2011	1.81	170	9.37	13.36	1.53	(1.20-1.95) †

* p <0.001; † p for trend <0.001

Figure 2-11: Mortality from J84 in Northern Ireland, 2009-2011

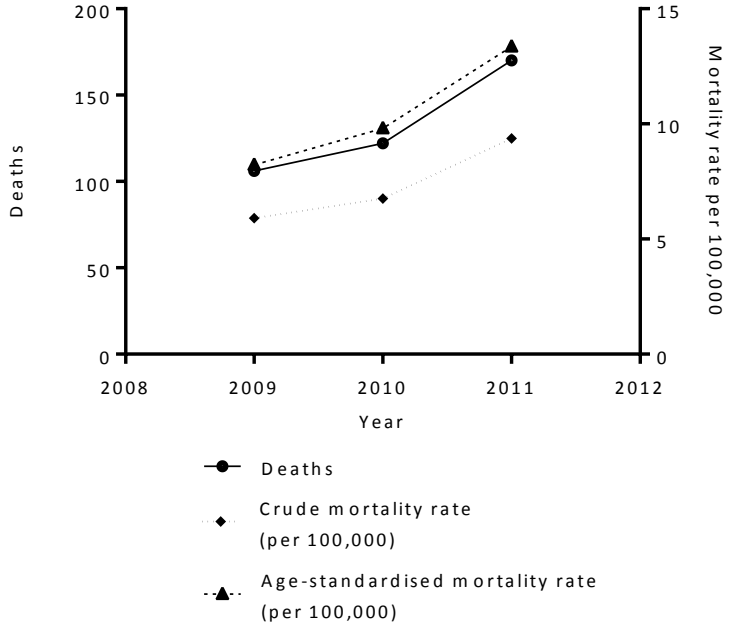


Table 2-13: Mortality from idiopathic pulmonary fibrosis clinical syndrome in New Zealand (J84 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	10.90	264	2.42	3.28	1.00	
Male	10.48	435	4.15	7.50	2.27	(1.94-2.65)*
Age group						
0-44	13.43	7	0.05	0.05	0.01	(0.00-0.01)
45-54	2.97	9	0.30	0.30	0.03	(0.02-0.06)
55-64	2.28	52	2.28	2.31	0.24	(0.18-0.33)
65-74	1.47	137	9.33	9.38	1.00	
75-84	0.91	300	32.97	34.39	3.65	(2.98-4.47)
85+	0.32	194	60.82	72.44	7.42	(5.96-9.25) †
Year						
2006	4.19	115	2.75	4.79	1.00	
2007	4.23	142	3.36	5.74	1.20	(0.94-1.53)
2008	4.27	145	3.40	5.52	1.19	(0.93-1.52)
2009	4.32	143	3.31	5.35	1.14	(0.89-1.46)
2010	4.37	154	3.52	5.55	1.19	(0.94-1.52) ‡

* p <0.001; † p for trend <0.001; ‡ p for trend 0.31

Figure 2-12: Mortality from J84 in New Zealand, 2006-2010

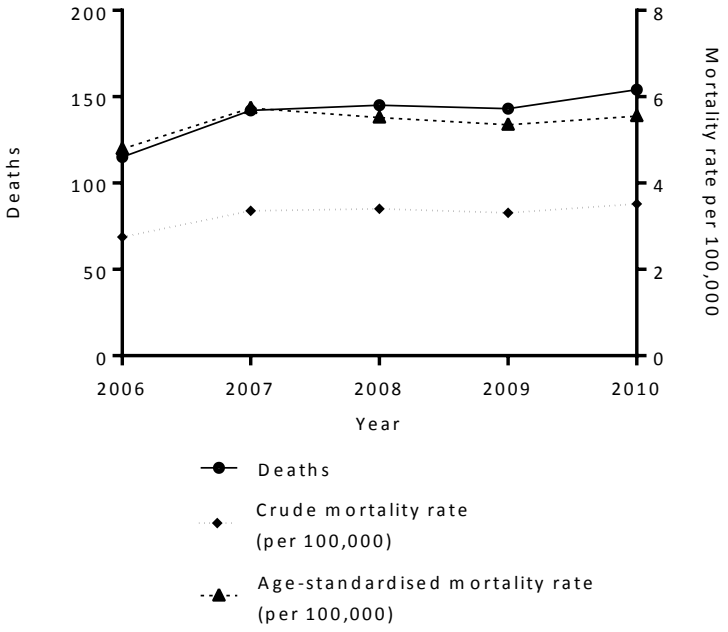


Table 2-14: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Scotland (J84 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	31.96	1780	5.57	5.64	1.00	
Male	29.85	2561	8.58	12.25	2.16	(2.03-2.29)*
Age group						
0-44	35.41	23	0.06	0.06	0.00	(0.00-0.00)
45-54	8.74	77	0.88	0.88	0.04	(0.03-0.05)
55-64	7.45	398	5.34	5.39	0.26	(0.23-0.29)
65-74	5.57	1138	20.43	20.96	1.00	
75-84	3.48	1818	52.28	56.02	2.68	(2.49-2.89)
85+	1.16	887	76.56	90.82	4.26	(3.90-4.65) †
Year						
2001	5.06	236	4.66	6.43	1.00	
2002	5.05	285	5.64	7.47	1.19	(1.00-1.41)
2003	5.06	295	5.83	7.84	1.22	(1.03-1.45)
2004	5.08	295	5.81	7.67	1.20	(1.01-1.43)
2005	5.09	338	6.63	8.82	1.36	(1.15-1.60)
2006	5.12	346	6.76	8.82	1.37	(1.16-1.61)
2007	5.14	374	7.27	9.26	1.45	(1.24-1.71)
2008	5.17	399	7.72	9.55	1.53	(1.30-1.80)
2009	5.19	401	7.72	9.72	1.51	(1.29-1.77)
2010	5.22	407	7.79	9.70	1.51	(1.28-1.77)
2011	5.30	493	9.30	11.34	1.79	(1.53-2.09)
2012	5.31	472	8.88	10.71	1.67	(1.43-1.95) †

* p <0.001; † p for trend <0.001

Figure 2-13: Mortality from J84 in Scotland, 2001-2012

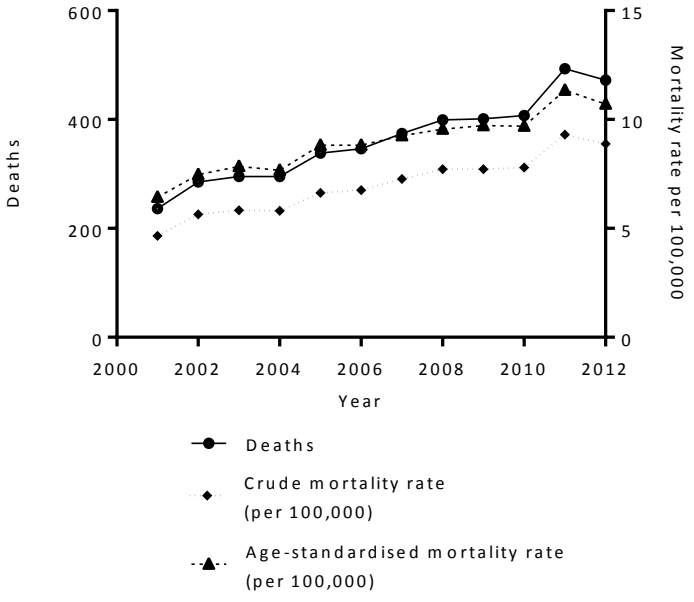


Table 2-15: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Spain (J84 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	242.90	8477	3.49	3.40	1.00	
Male	235.19	10086	4.29	5.97	1.75	(1.70-1.80)*
Age group						
0-44	284.94	188	0.07	0.07	0.01	(0.01-0.01)
45-54	62.66	362	0.58	0.58	0.05	(0.05-0.06)
55-64	50.04	1195	2.39	2.42	0.22	(0.21-0.24)
65-74	42.27	4447	10.52	10.77	1.00	
75-84	28.92	8298	28.69	29.81	2.78	(2.68-2.89)
85+	9.27	4073	43.96	47.75	4.48	(4.29-4.67) †
Year						
2000	40.59	1202	2.96	3.73	1.00	
2001	41.05	1322	3.22	4.07	1.07	(0.99-1.16)
2002	40.96	1425	3.48	4.37	1.15	(1.07-1.25)
2003	41.66	1503	3.61	4.47	1.19	(1.10-1.28)
2004	42.35	1531	3.62	4.51	1.18	(1.10-1.27)
2006	43.76	1648	3.77	4.63	1.21	(1.12-1.30)
2007	44.47	1913	4.30	5.23	1.37	(1.27-1.47)
2008	45.28	1833	4.05	4.87	1.28	(1.19-1.37)
2009	45.83	1904	4.15	4.91	1.30	(1.21-1.39)
2010	45.99	2095	4.56	5.33	1.40	(1.30-1.50)
2011	46.15	2187	4.74	5.38	1.43	(1.33-1.53) †

* p <0.001; † p for trend <0.001

Figure 2-14: Mortality from J84 in Spain, 2000-2011

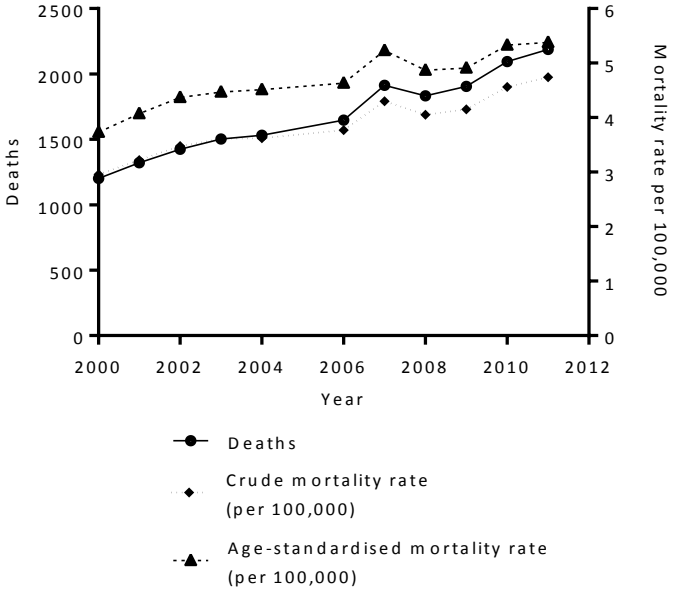


Table 2-16: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Spain (J84.1/J84.9 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	242.90	8392	3.45	3.36	1.00	
Male	235.19	9952	4.23	5.89	1.75	(1.70-1.80)*
Age group						
0-44	284.94	182	0.06	0.06	0.01	(0.01-0.01)
45-54	62.66	353	0.56	0.57	0.05	(0.05-0.06)
55-64	50.04	1184	2.37	2.40	0.22	(0.21-0.24)
65-74	42.27	4379	10.36	10.60	1.00	
75-84	28.92	8213	28.40	29.51	2.80	(2.70-2.90)
85+	9.27	4033	43.53	47.31	4.50	(4.31-4.70) †
Year						
2000	40.59	1188	2.93	3.69	1.00	
2001	41.05	1311	3.19	4.04	1.08	(0.99-1.16)
2002	40.96	1406	3.43	4.31	1.15	(1.07-1.24)
2003	41.66	1491	3.58	4.43	1.19	(1.11-1.29)
2004	42.35	1513	3.57	4.45	1.18	(1.09-1.27)
2006	43.76	1638	3.74	4.60	1.22	(1.13-1.31)
2007	44.47	1904	4.28	5.20	1.38	(1.28-1.48)
2008	45.28	1814	4.01	4.82	1.28	(1.19-1.38)
2009	45.83	1885	4.11	4.86	1.30	(1.21-1.40)
2010	45.99	2057	4.47	5.24	1.39	(1.29-1.49)
2011	46.15	2137	4.63	5.25	1.41	(1.31-1.51) †

* p <0.001; † p for trend <0.001

Figure 2-15: Mortality from J84.1/J84.9 in Spain, 2000-2011

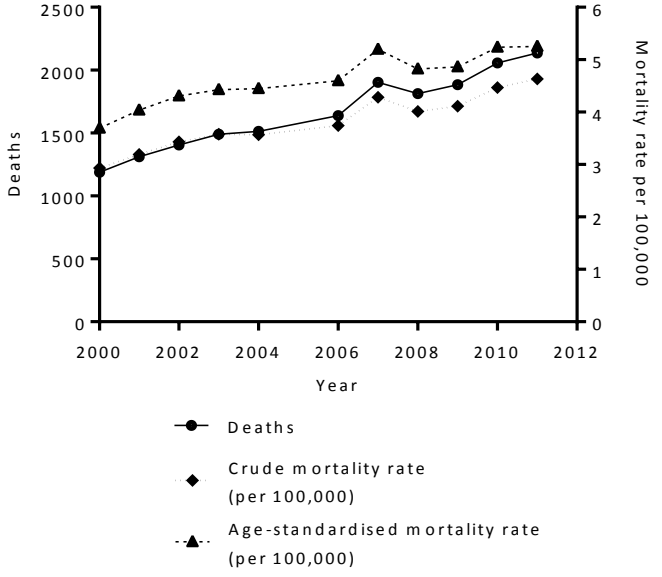
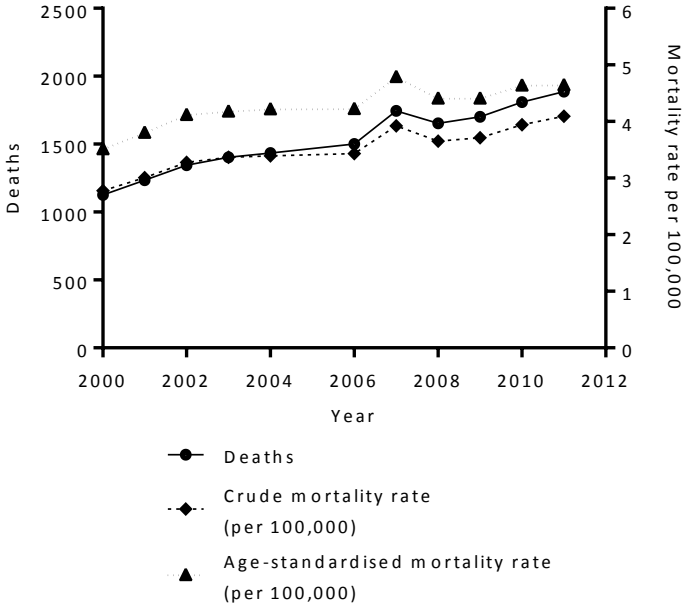


Table 2-17: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Spain (J84.1 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	242.90	7678	3.16	3.08	1.00	
Male	235.19	9162	3.90	5.44	1.76	(1.71-1.82)*
Age group						
0-44	284.94	152	0.05	0.05	0.01	(0.00-0.01)
45-54	62.66	306	0.49	0.49	0.05	(0.04-0.06)
55-64	50.04	1078	2.15	2.19	0.22	(0.21-0.24)
65-74	42.27	4011	9.49	9.71	1.00	
75-84	28.92	7572	26.18	27.30	2.83	(2.72-9.24)
85+	9.27	3721	40.16	43.77	4.56	(4.36-4.77) †
Year						
2000	40.59	1127	2.78	3.51	1.00	
2001	41.05	1235	3.01	3.80	1.07	(0.99-1.16)
2002	40.96	1345	3.28	4.11	1.16	(1.07-1.26)
2003	41.66	1404	3.37	4.17	1.18	(1.09-1.28)
2004	42.35	1434	3.39	4.21	1.18	(1.09-1.28)
2006	43.76	1500	3.43	4.22	1.17	(1.09-1.27)
2007	44.47	1744	3.92	4.78	1.33	(1.23-1.43)
2008	45.28	1653	3.65	4.40	1.23	(1.14-1.32)
2009	45.83	1702	3.71	4.40	1.24	(1.15-1.33)
2010	45.99	1810	3.94	4.63	1.28	(1.19-1.38)
2011	46.15	1886	4.09	4.64	1.31	(1.22-1.41) †

* p <0.001; † p for trend <0.001

Figure 2-16: Mortality from J84.1 in Spain, 2000-2011



2.3.4.9 – Sweden

Data from Sweden were available by broad code J84 for 13 years. Mortality from pulmonary fibrosis was lower than other countries, but increased steadily over time. Age-standardised mortality was 4.68 per 100,000 in 2012, up from 2.84 per 100,000 in 2000 – see Table 2-18 and Figure 2-17.

2.3.4.10 – United States

Mortality from pulmonary fibrosis in the USA increased slowly over the available time period (1999-2010), although rates did seem to plateau from 2004 onwards, particularly for the more specific J84.1 code. This comprised 78-82% of all J84 codes; over 97.7% were either J84.1 or J84.9. In 2010, age-standardised mortality was 7.80 per 100,000 for the J84 code, and 6.16 per 100,000 for the J84.1 code – see Table 2-19, Table 2-20, Table 2-21, Figure 2-18, Figure 2-19 and Figure 2-20.

Table 2-18: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Sweden (J84 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	59.96	1509	2.52	2.29	1.00	
Male	59.15	2644	4.47	5.59	2.45	(2.30-2.61)*
Age group						
0-44	67.23	37	0.06	0.06	0.01	(0.00-0.01)
45-54	15.61	65	0.42	0.41	0.05	(0.04-0.06)
55-64	15.14	310	2.05	2.04	0.23	(0.21-0.27)
65-74	10.75	930	8.65	8.74	1.00	
75-84	7.37	1801	24.43	26.25	3.01	(2.78-3.26)
85+	3.01	1010	33.59	38.84	4.50	(4.12-4.93) †
Year						
2000	8.88	226	2.54	2.84	1.00	
2001	8.91	240	2.69	3.10	1.05	(0.88-1.26)
2002	8.94	276	3.09	3.59	1.21	(1.01-1.44)
2003	8.98	292	3.25	3.72	1.27	(1.07-1.51)
2004	9.02	319	3.54	4.01	1.37	(1.16-1.63)
2005	9.05	321	3.55	4.07	1.37	(1.15-1.62)
2006	9.11	320	3.51	4.04	1.35	(1.14-1.60)
2007	9.18	314	3.42	3.90	1.31	(1.10-1.55)
2008	9.26	339	3.66	4.13	1.40	(1.18-1.65)
2009	9.34	345	3.69	4.14	1.40	(1.18-1.66)
2010	9.42	387	4.11	4.60	1.55	(1.31-1.82)
2011	9.48	368	3.88	4.37	1.45	(1.23-1.71)
2012	9.56	406	4.25	4.68	1.57	(1.34-1.85) †

* p <0.001; † p for trend <0.001

Figure 2-17: Mortality from J84 in Sweden, 2000-2012

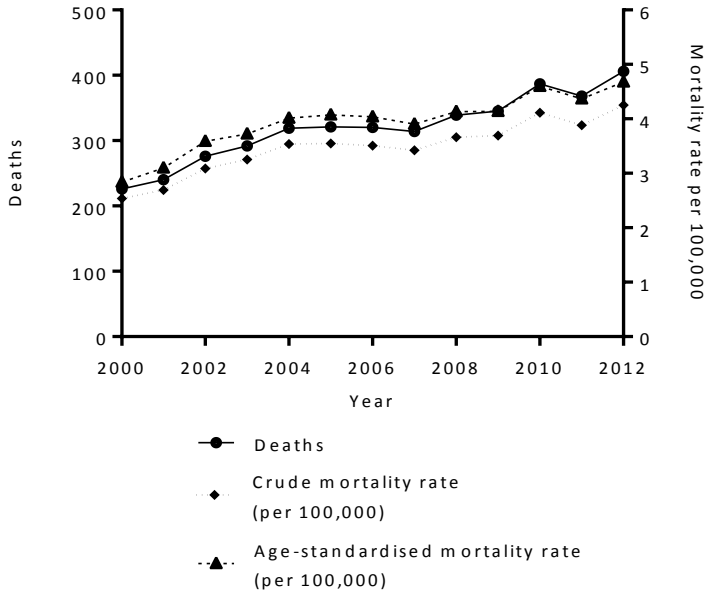


Table 2-19: Mortality from idiopathic pulmonary fibrosis clinical syndrome in the USA (J84 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	1796.48	81003	4.51	5.64	1.00	
Male	1734.22	87634	5.05	9.04	1.59	(1.57-1.60)*
Age group						
0-44	2228.67	3754	0.17	0.17	0.01	(0.01-0.01)
45-54	500.14	6513	1.30	1.31	0.08	(0.08-0.08)
55-64	358.92	16084	4.48	4.52	0.27	(0.27-0.28)
65-74	231.99	37566	16.19	16.54	1.00	
75-84	154.25	64159	41.59	43.61	2.64	(2.60-2.67)
85+	56.74	40561	71.48	77.30	4.74	(4.67-4.80) †
Year						
1999	279.04	11358	4.07	6.51	1.00	
2000	281.42	12373	4.40	7.01	1.08	(1.05-1.10)
2001	284.97	13067	4.59	7.22	1.12	(1.09-1.15)
2002	287.63	12017	4.18	6.57	1.01	(0.99-1.04)
2003	290.11	12699	4.38	6.86	1.05	(1.03-1.08)
2004	292.81	14975	5.11	7.95	1.22	(1.19-1.25)
2005	295.52	14375	4.86	7.50	1.15	(1.12-1.18)
2006	298.38	14834	4.97	7.63	1.17	(1.14-1.19)
2007	301.23	15084	5.01	7.62	1.16	(1.13-1.91)
2008	304.09	15665	5.15	7.76	1.18	(1.15-1.21)
2009	306.77	15929	5.19	7.71	1.18	(1.15-1.21)
2010	308.75	11358	5.27	7.80	1.18	(1.16-1.21) †

* p <0.001; † p for trend <0.001

Figure 2-18: Mortality from J84 in USA 1999-2010

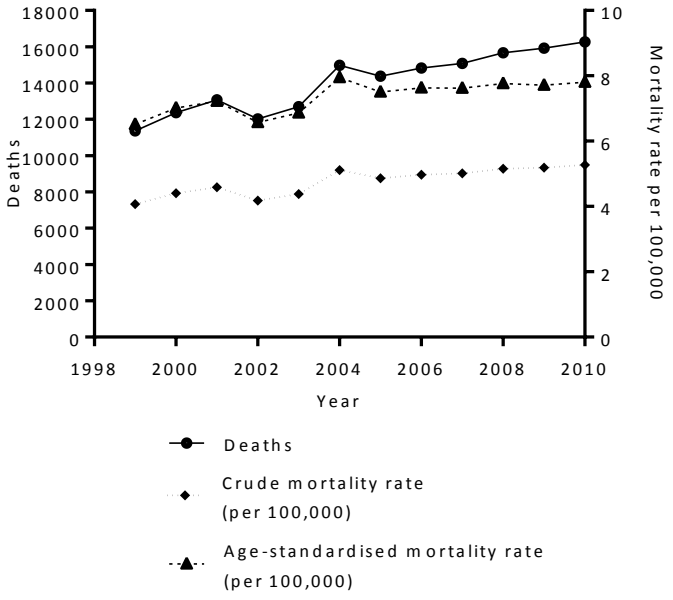


Table 2-20: Mortality from idiopathic pulmonary fibrosis clinical syndrome in the USA (J84.1/J84.9 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	1796.48	79904	4.45	5.57	1.00	
Male	1734.22	86318	4.98	8.94	1.59	(1.58-1.61)*
Age group						
0-44	2228.67	3279	0.15	0.15	0.01	(0.01-0.01)
45-54	500.14	6148	1.23	1.23	0.08	(0.07-0.08)
55-64	358.92	15641	4.36	4.40	0.27	(0.26-0.27)
65-74	231.99	37059	15.97	16.32	1.00	
75-84	154.25	63683	41.29	43.29	2.65	(2.62-2.69)
85+	56.74	40412	71.22	76.99	4.79	(4.72-4.85) †
Year						
1999	279.04	11189	4.01	6.43	1.00	
2000	281.42	12195	4.33	6.93	1.08	(1.05-1.10)
2001	284.97	12871	4.52	7.13	1.12	(1.09-1.15)
2002	287.63	11793	4.10	6.46	1.01	(0.98-1.03)
2003	290.11	12509	4.31	6.77	1.05	(1.03-1.08)
2004	292.81	14772	5.04	7.86	1.22	(1.19-1.25)
2005	295.52	14200	4.81	7.43	1.15	(1.13-1.18)
2006	298.38	14502	4.86	7.47	1.16	(1.13-1.19)
2007	301.23	14913	4.95	7.55	1.17	(1.14-1.20)
2008	304.09	15488	5.09	7.69	1.19	(1.16-1.22)
2009	306.77	15735	5.13	7.63	1.18	(1.15-1.21)
2010	308.75	16055	5.20	7.72	1.19	(1.16-1.22)

* p <0.001; † p for trend <0.001

Figure 2-19: Mortality from J84.1/J84.9 in USA, 1999-2010

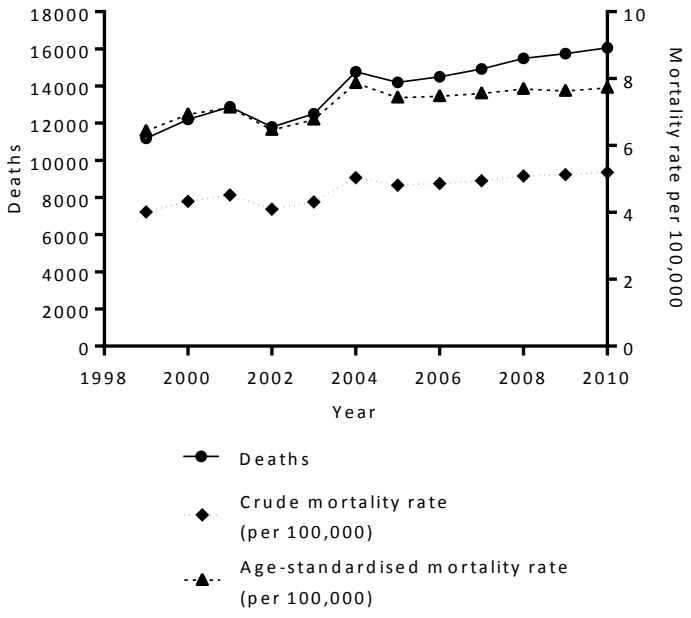
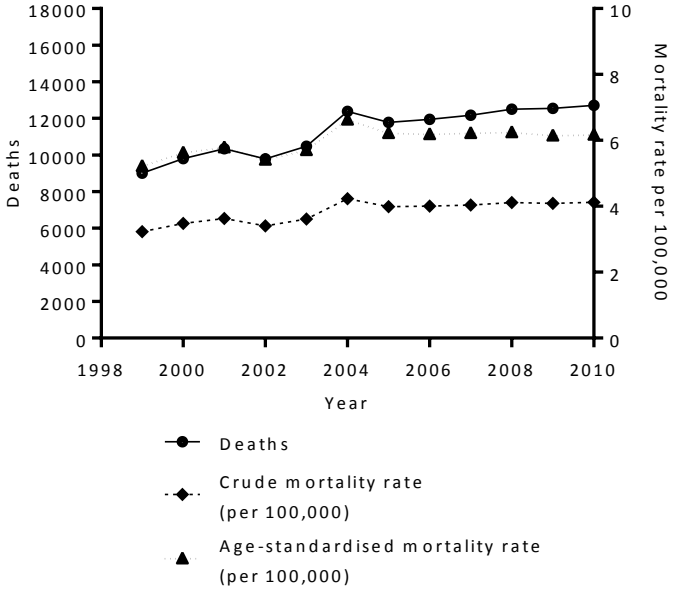


Table 2-21: Mortality from idiopathic pulmonary fibrosis clinical syndrome in the USA (J84.1 coding, for underlying cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	1796.48	64497	3.59	4.51	1.00	
Male	1734.22	70963	4.09	7.40	1.63	(1.61-1.65)*
Age group						
0-44	2228.67	1760	0.08	0.08	0.01	(0.01-0.01)
45-54	500.14	4519	0.90	0.91	0.07	(0.07-0.07)
55-64	358.92	12261	3.42	3.46	0.26	(0.25-0.26)
65-74	231.99	30358	13.09	13.40	1.00	
75-84	154.25	52917	34.31	36.03	2.69	(2.65-2.73)
85+	56.74	33645	59.29	64.24	4.88	(4.81-4.96) †
Year						
1999	279.04	9004	3.23	5.21	1.00	
2000	281.42	9806	3.48	5.62	1.08	(1.05-1.11)
2001	284.97	10348	3.63	5.78	1.12	(1.09-1.15)
2002	287.63	9792	3.40	5.40	1.04	(1.01-1.07)
2003	290.11	10475	3.61	5.70	1.09	(1.06-1.13)
2004	292.81	12375	4.23	6.62	1.27	(1.24-1.31)
2005	295.52	11788	3.99	6.21	1.19	(1.16-1.22)
2006	298.38	11941	4.00	6.18	1.18	(1.15-1.22)
2007	301.23	12169	4.04	6.21	1.18	(1.15-1.22)
2008	304.09	12496	4.11	6.24	1.19	(1.16-1.22)
2009	306.77	12551	4.09	6.14	1.17	(1.14-1.20)
2010	308.75	12715	4.12	6.16	1.17	(1.14-1.20) †

* p <0.001; † p for trend <0.001

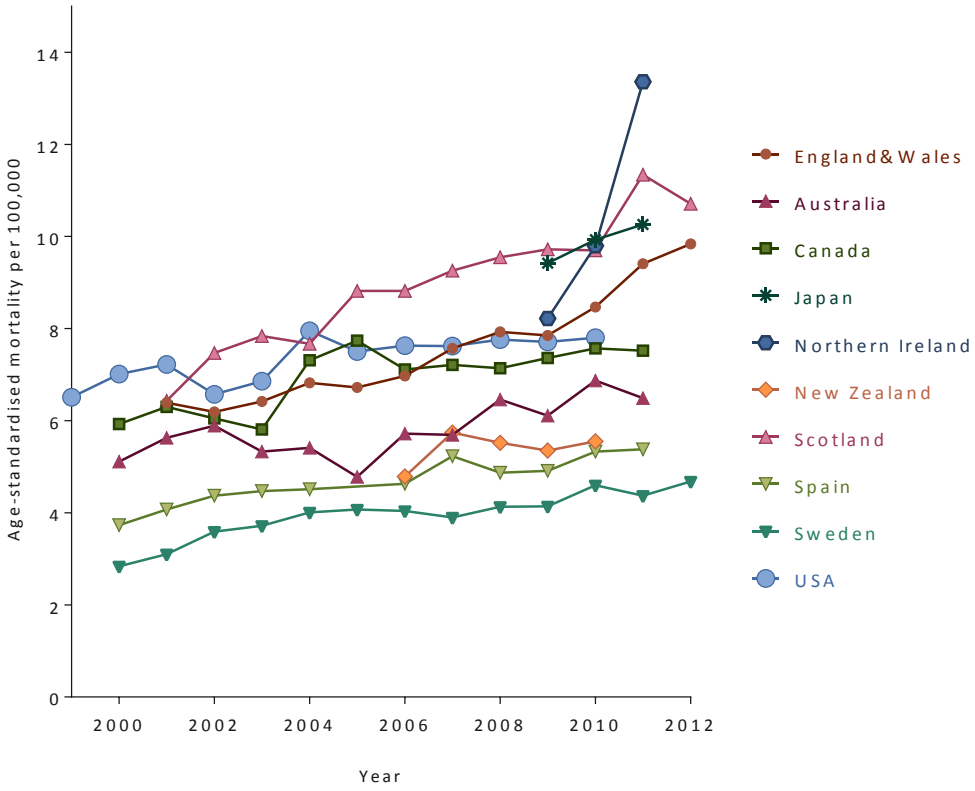
Figure 2-20: Mortality from J84.1 in USA, 1999-2010



2.3.5 – Mortality using underlying causes of death data – all countries

Using the broad J84 code, crude mortality varied across countries from 2.54 per 100,000 (Sweden, 2000) to 11.08 per 100,000 (Japan, 2011). Age-standardised rates were lowest in Sweden, Spain and New Zealand, and highest in Northern Ireland, Scotland, and Japan, varying from 4.68 to 13.36 per 100,000 for the latest years of data available (see Figure 2-21).

Figure 2-21: Age-standardised mortality rates for J84 for selected countries by year, using underlying cause of death data



Mortality was consistently higher in males, with mortality rate ratios for male sex ranging from 1.59 (United States) to 2.68 (Japan). Meta-analysis of rate ratios for sex showed an overall estimate of 2.06 (95% confidence intervals (CI) 1.77-2.40, p<0.001) for male versus female sex (Figure 2-22). Mortality was also significantly higher for increasing age, with rate ratios for >85 years versus 65-74 years ranging from 4.17 (England & Wales) to 7.42 (New Zealand). By meta-analysis of rate ratios, the overall estimate was 5.03 (95 % CI 4.59-5.51, p<0.001) (Figure 2-23).

Figure 2-22: Meta-analysis of mortality rate ratios for male vs female sex, for J84 code over time, for underlying cause of death data (random effects model)

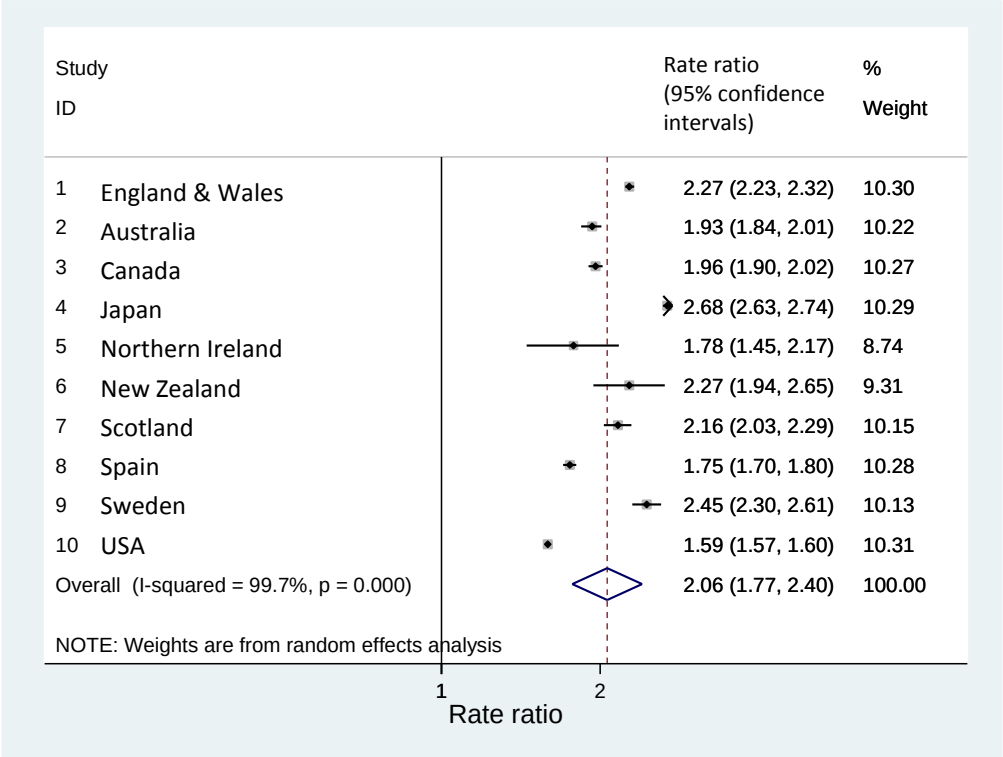
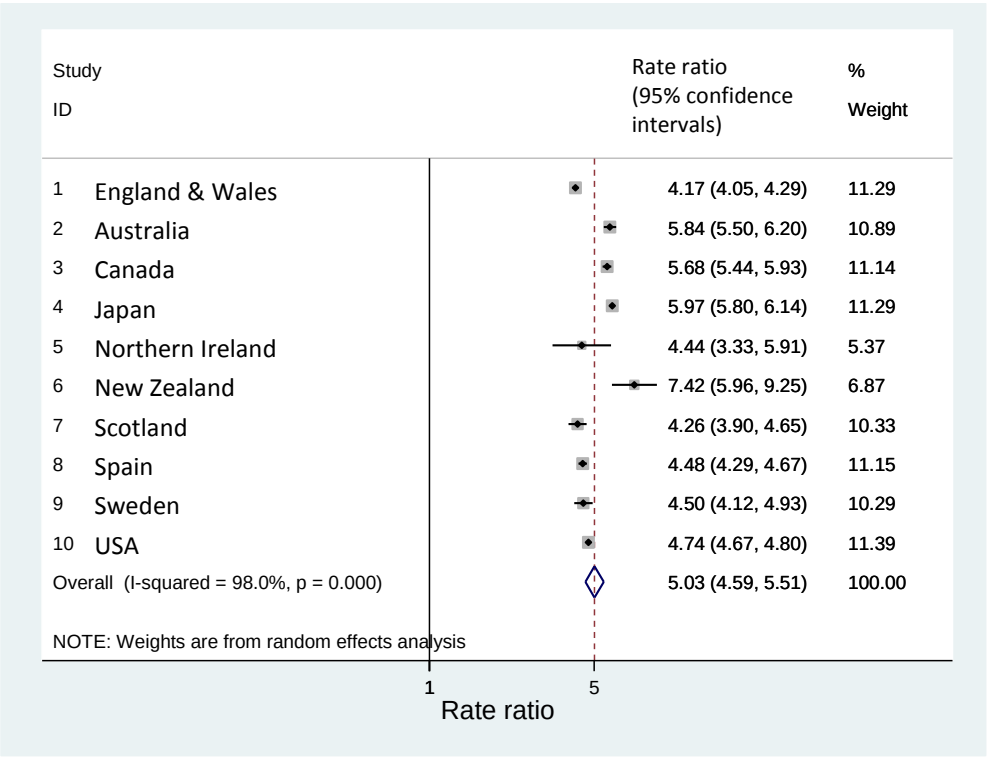
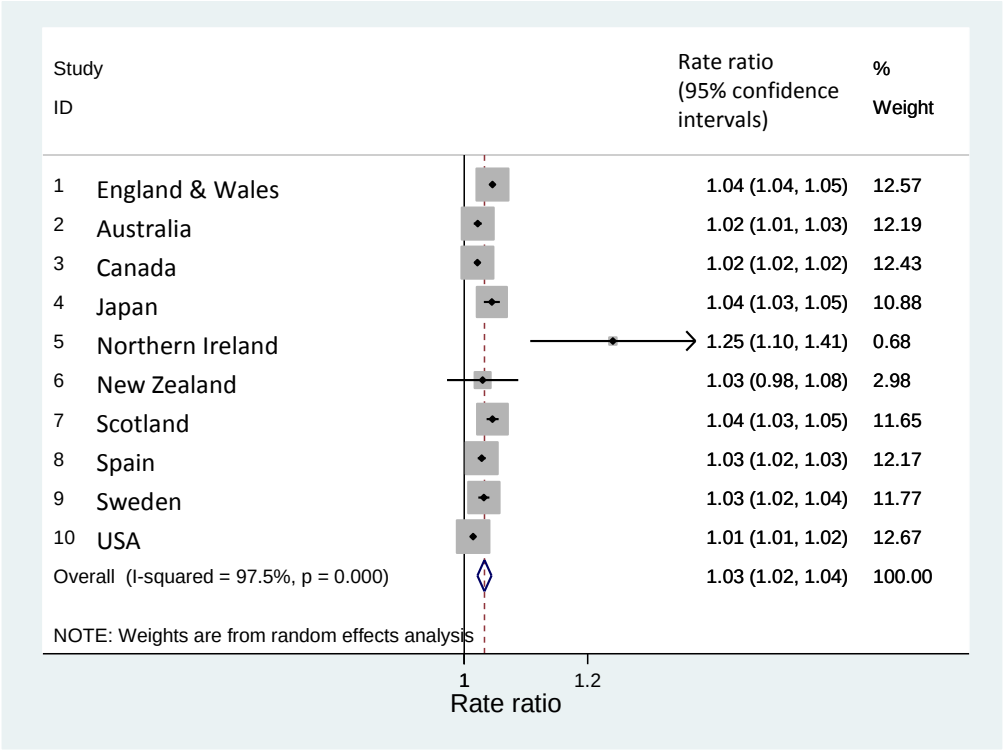


Figure 2-23: Meta-analysis of mortality rate ratios for >85 years vs 65-74 years, for J84 code over time, for underlying cause of death data (random effects model)



Mortality rates broadly increased over time across countries. Adjusted annual increases in mortality varied from 1 to 4%, with the exception of Northern Ireland where there was limited data and a large rise. The rate of increase was highest for the rest of the United Kingdom and Japan (4%), and lowest for the United States (1%). Meta-analysis of mortality rate ratios over time showed a 3% annual increase (1.03, 95% CI 1.02-1.04, p<0.001) (Figure 2-24).

Figure 2-24: Meta-analysis of mortality rate ratios for annual increase in mortality from J84 over time, for underlying cause of death data (random effects model)



Using J84.1/J84.9 combined coding, crude and age-standardised mortality rates were very similar to when using the J84 code. Age-standardised mortality varied from 5.25 per 100,000 (Spain, 2011) to 9.76 per 100,000 (England and Wales, 2012) (Figure 2-25). Rate ratios over time were essentially equivalent to J84 figures, and meta-analysis showed an overall 3% increase over time (rate ratio, 1.03, 95% CI 1.01-1.04, p <0.001) (Figure 2-26).

Figure 2-25: Age-standardised mortality rates for J84.1/J84.9 for selected countries by year, using underlying cause of death data

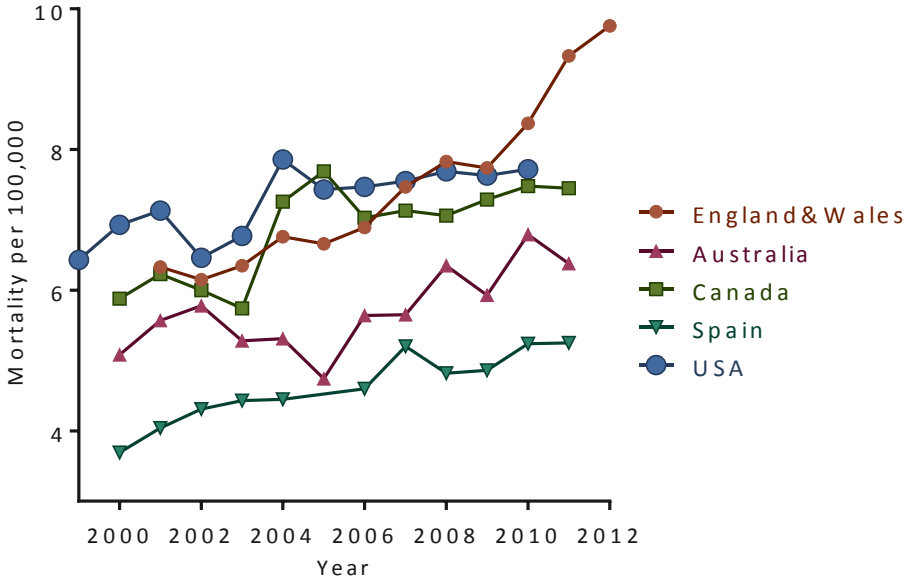
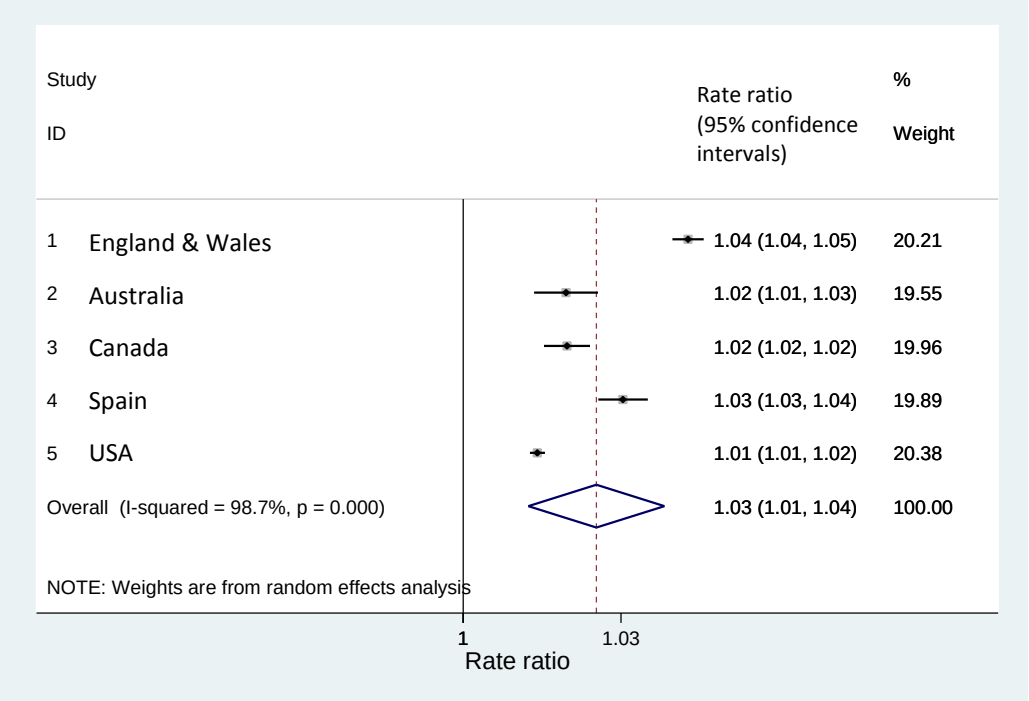


Figure 2-26: Meta-analysis of mortality rate ratios for annual increase in mortality from J84.1/J84.9 over time, for underlying cause of death data (random effects model)



Using the more specific J84.1 coding, crude and age-standardised mortality rates were slightly lower, but in similar proportions across countries. The highest rates were in England and Wales (8.28 per 100,000, in 2012) and the lowest in Spain (4.64 per 100,000, in 2011) (Figure 2-27). Rate ratios for increasing age versus younger age were higher than when using the broader codes. Rate ratios increased over time: the highest annual increase was for England and Wales (annual increase, 1.03, 95% CI 1.-027-1.034, p <0.001), and the lowest was for the United States (annual increase, 1.01, 95% CI 1.011-1.014, p <0.001). Meta-analysis of rate ratios over time showed a 2% increase overall (rate ratio 1.02, 95% CI 1.01-1.03, p <0.001) (Figure 2-28).

To enhance specificity for IPF, a further analysis was conducted excluding deaths under 65 years of age. However, this made no difference to summary rate ratios by meta-analysis for all three ICD-10 codes. A sensitivity analysis for J84 data excluding Japan and Northern Ireland (countries with only three years of data) also made no difference to the meta-analysis.

Figure 2-27: Age-standardised mortality rates from J84.1 for selected countries by year, using underlying cause of death data

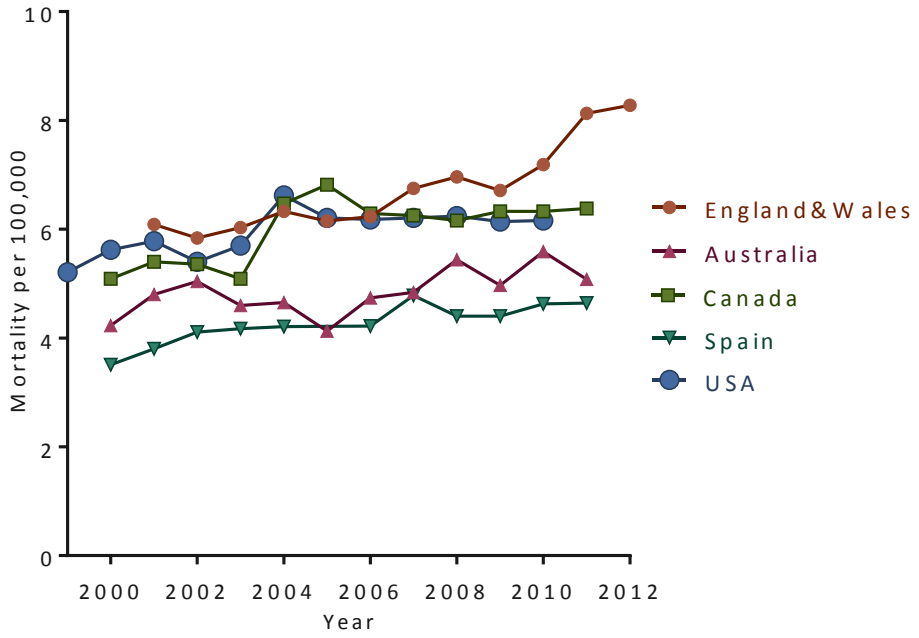
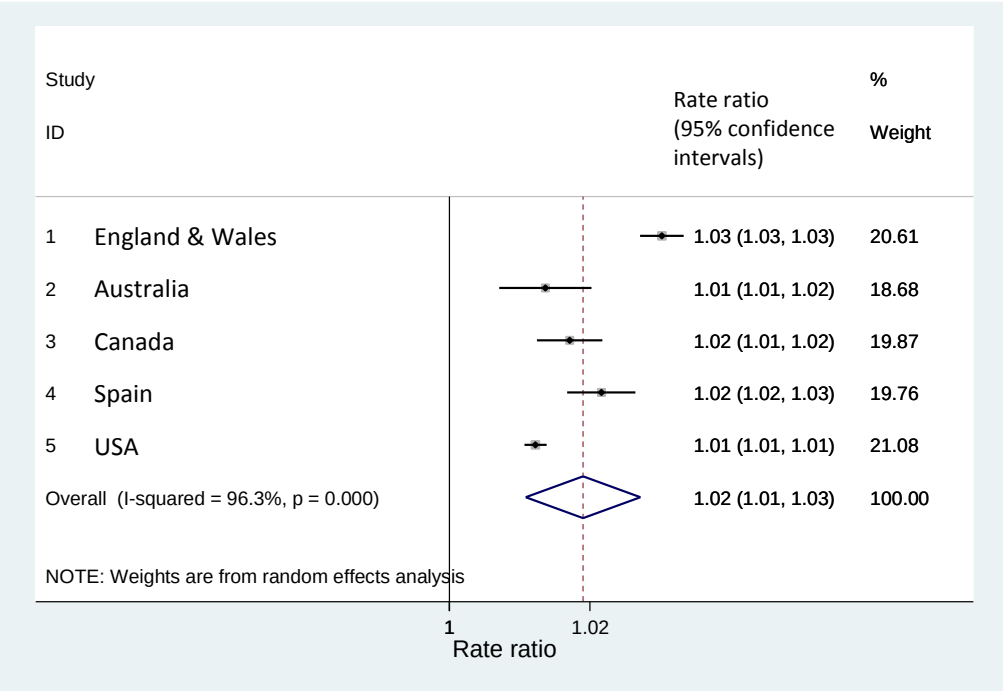


Figure 2-28: Meta-analysis of mortality rate ratios for annual increase in mortality from J84.1 over time, for underlying cause of death data (random effects model)



2.3.6 – Mortality using multiple cause of death data, by country

Multiple cause of death data were available for just three countries: England and Wales, Australia and the United States. There were considerably more deaths for each country (see Table 2-1). As all three countries provided data by sub-codes, analysis for this section was performed for J84.1 and J84.1/J84.9 groups. Numbers of deaths, crude mortality rates and age-standardised mortality rates are presented for each country, followed by summary data for all three.

2.3.6.1 – England and Wales

Using the broader J84.1/J84.9 code classification, in 2012 there were 7,487 deaths in England and Wales with IPF-clinical syndrome based on multiple cause of death data, compared to 4,610 deaths based on underlying cause of death alone (Table 2-22). The number of deaths increased year on year (Figure 2-29). Age-standardised mortality increased from 10.75 per 100,000 in 2001 to 15.92 per 100,000 in 2012. Using the more specific J84.1 code, numbers also increased annually, with an age-standardised mortality rate of 13.62 per 100,000 in 2012, up from 10.39 per 100,000 in 2001 (Table 2-23, Figure 2-30). The difference between numbers of deaths using each code classification was greater in later years.

Table 2-22: Mortality from idiopathic pulmonary fibrosis clinical syndrome in England and Wales (J84.1/J84.9 coding, for multiple cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	331.27	24449	7.38	7.65	1.00	
Male	319.38	41194	12.90	18.01	2.36	(2.32-2.40)*
Age group						
0-44	385.40	656	0.17	0.17	0.01	(0.01-0.01)
45-54	85.73	1252	1.46	1.46	0.05	(0.05-0.05)
55-64	75.03	5201	6.93	6.95	0.23	(0.22-0.24)
65-74	55.07	16322	29.64	30.09	1.00	
75-84	35.90	27389	76.30	80.91	2.68	(2.63-2.74)
85+	13.52	14823	109.63	129.92	4.27	(4.18-4.37) †
Year						
2001	51.61	3934	7.62	10.75	1.00	
2002	52.60	4206	8.00	10.56	0.98	(0.94-1.03)
2003	52.86	4393	8.31	10.88	1.02	(0.98-1.06)
2004	53.15	4687	8.82	11.48	1.08	(1.03-1.12)
2005	53.58	4795	8.95	11.57	1.08	(1.04-1.13)
2006	53.95	5082	9.42	12.09	1.13	(1.09-1.18)
2007	54.39	5551	10.21	13.12	1.22	(1.17-1.27)
2008	54.84	5934	10.82	13.78	1.28	(1.23-1.33)
2009	55.24	6103	11.05	13.94	1.30	(1.25-1.35)
2010	55.69	6549	11.76	14.65	1.36	(1.31-1.42)
2011	56.17	6922	12.32	15.22	1.41	(1.36-1.47)
2012	56.57	7487	13.24	15.92	1.49	(1.43-1.55) †

* p <0.001; † p for trend <0.001

Figure 2-29: Mortality from J84.1/J84.9 in England and Wales, 2001-2012 (multiple cause of death data)

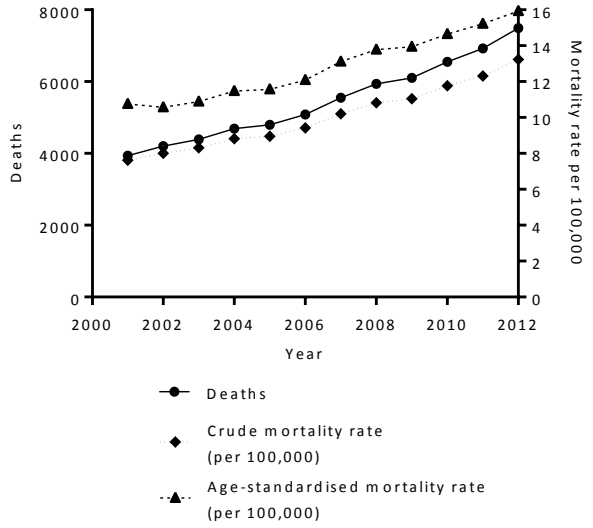
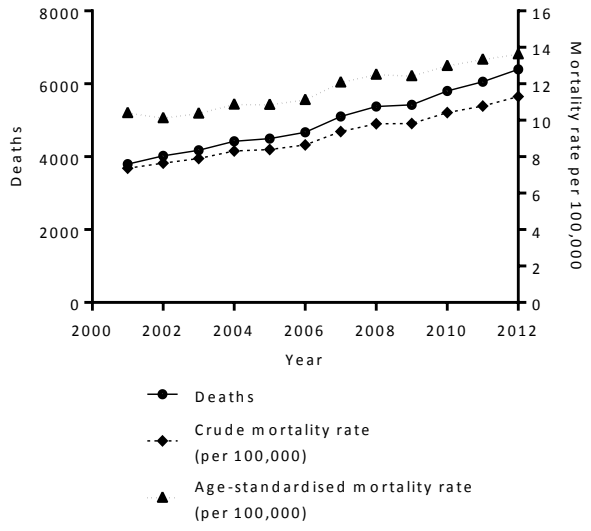


Table 2-23: Mortality from idiopathic pulmonary fibrosis clinical syndrome in England and Wales (J84.1 coding, for multiple cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	331.27	22240	6.71	6.96	1.00	
Male	319.38	37494	11.74	16.47	2.37	(2.34-2.41)*
Age group						
0-44	385.40	462	0.12	0.12	0.00	(0.00-0.00)
45-54	85.73	1050	1.22	1.23	0.04	(0.04-0.05)
55-64	75.03	4575	6.10	6.13	0.22	(0.22-0.23)
65-74	55.07	14792	26.86	27.33	1.00	
75-84	35.90	25186	70.16	74.55	2.72	(2.67-2.78)
85+	13.52	13669	101.10	120.03	4.36	(4.26-4.46) †
Year						
2001	51.61	3798	7.36	10.39	1.00	
2002	52.60	4023	7.65	10.11	0.97	(0.93-1.02)
2003	52.86	4175	7.90	10.37	1.00	(0.96-1.05)
2004	53.15	4420	8.32	10.86	1.05	(1.01-1.10)
2005	53.58	4496	8.39	10.85	1.05	(1.01-1.10)
2006	53.95	4669	8.65	11.12	1.08	(1.03-1.12)
2007	54.39	5104	9.38	12.07	1.16	(1.11-1.21)
2008	54.84	5377	9.80	12.50	1.20	(1.15-1.25)
2009	55.24	5422	9.82	12.42	1.19	(1.14-1.24)
2010	55.69	5801	10.42	12.98	1.25	(1.20-1.30)
2011	56.17	6055	10.78	13.33	1.28	(1.23-1.33)
2012	56.57	6394	11.30	13.62	1.32	(1.26-1.37) †

* p <0.001; † p for trend <0.001

Figure 2-30: Mortality from J84.1 in England and Wales, 2001-2012 (multiple cause of death data)



2.3.6.2 – Australia

Multiple cause of death data from Australia yielded almost twice as many deaths with IPF-clinical syndrome compared to underlying cause of death data. The number of deaths increased steadily for both J84.1/J84.9 and J84.1 codes, with age-standardised rates in 2011 of 11.69 per 100,000 and 9.46 per 100,000 respectively (Table 2-24, Table 2-25). Rates seemed to plateau in later years for J84.1 coding (Figure 2-31, Figure 2-32).

2.3.6.3 – United States

Over 200,000 deaths were available from the United States with IPF-clinical syndrome listed as a multiple cause of death. Numbers of deaths increased slowly, however age-standardised mortality appeared to peak in 2003 for both J84.1/J84.9 and J84.1 code classifications (Table 2-26, Table 2-27, Figure 2-33 and Figure 2-34). For the more specific J84.1 code, there was a slight decrease in age-standardised rates over later years. Age-standardised rates in 2010 were 11.73 per 100,000 for J84.1/J84.9 coding, and 9.37 per 100,000 for J84.1 coding.

Looking at individual states in the USA from year 2000, crude mortality rates ranged from 3.18 per 100,000 (Nevada) to 9.75 per 100,000 (Vermont) in 2010, for J84.1, however age-standardisation was not possible in most cases. For the largest five states - California, Texas, Florida, New York and Illinois – with full age-specific data, the highest rates were in Texas (age-standardised rates 12.20 per 100,000 for J84.1/J84.9; 10.69 per 100,000 for J84.1) and the lowest in New York (7.93 per 100,000 for J84.1/J84.9; 6.42 per 100,000 for J84.1) (Table 2-28, Table 2-29). Crude rates increased over time, but age-standardised rates remained stable. For J84.1/J84.9 coding, 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, with an overall rate ratio by meta-analysis of 1.00 (95% CI 1.00-1.01; p=0.219). For J84.1 coding, there was 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).

Table 2-24: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Australia (J84.1/J84.9 coding, for multiple cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	123.86	7098	5.73	7.25	1.00	
Male	122.36	10403	8.50	14.76	2.02	(1.96-2.08)*
Age group						
0-44	154.17	177	0.11	0.12	0.01	(0.00-0.01)
45-54	33.77	348	1.03	1.04	0.05	(0.04-0.05)
55-64	26.18	1225	4.68	4.69	0.22	(0.21-0.23)
65-74	17.17	3634	21.17	21.35	1.00	
75-84	11.11	7417	66.74	69.71	3.27	(3.15-3.41)
85+	3.82	4700	122.98	137.50	6.52	(6.24-6.81) †
Year						
2000	19.03	1102	5.79	9.67	1.00	
2001	19.27	1151	5.97	9.86	1.01	(0.93.1.09)
2002	19.50	1295	6.64	10.78	1.10	(1.02-1.19)
2003	19.72	1382	7.01	11.28	1.15	(1.06-1.24)
2004	19.93	1402	7.03	11.05	1.13	(1.05-1.23)
2005	20.18	1440	7.14	11.22	1.13	(1.04-1.22)
2006	20.45	1445	7.07	10.89	1.10	(1.02-1.19)
2007	20.83	1459	7.01	10.63	1.08	(1.00-1.17)
2008	21.25	1680	7.91	12.08	1.21	(1.12-1.31)
2009	21.69	1579	7.28	10.92	1.11	(1.02-1.19)
2010	22.03	1778	8.07	11.99	1.21	(1.12-1.30)
2011	22.34	1788	8.00	11.69	1.18	(1.09-1.27) †

* p <0.001; † p for trend <0.001

Figure 2-31: Mortality from J84.1/J84.9 in Australia, 2000-2011 (multiple cause of death data)

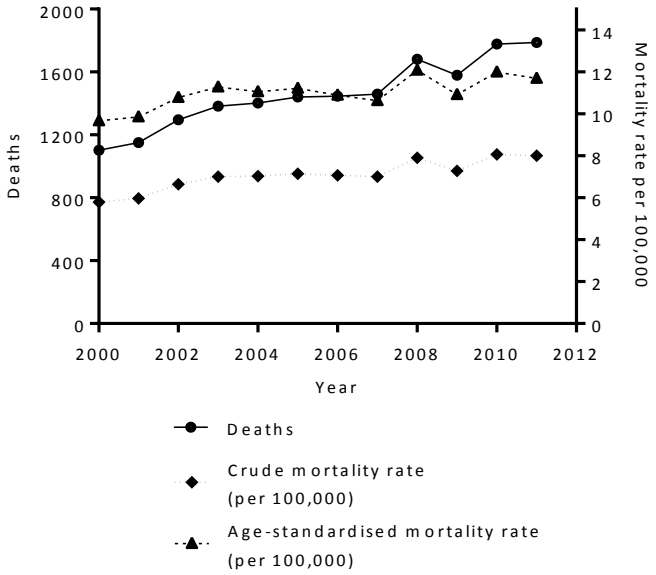


Table 2-25: Mortality from idiopathic pulmonary fibrosis clinical syndrome in Australia (J84.1 coding, for multiple cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	123.86	6032	4.87	6.18	1.00	
Male	122.36	8797	7.19	12.56	2.03	(1.96-2.09)*
Age group						
0-44	154.17	101	0.07	0.07	0.00	(0.00-0.00)
45-54	33.77	253	0.75	0.75	0.04	(0.04-0.05)
55-64	26.18	996	3.80	3.83	0.21	(0.20-0.23)
65-74	17.17	3052	17.78	17.98	1.00	
75-84	11.11	6338	57.03	59.66	3.33	(3.19-3.48)
85+	3.82	4089	106.99	119.43	6.76	(6.45-7.09) †
Year						
2000	19.03	941	4.95	8.28	1.00	
2001	19.27	1005	5.21	8.64	1.03	(0.94-1.13)
2002	19.50	1131	5.80	9.44	1.13	(1.03-1.23)
2003	19.72	1179	5.98	9.62	1.14	(1.05-1.25)
2004	19.93	1207	6.06	9.55	1.14	(1.05-1.24)
2005	20.18	1253	6.21	9.81	1.15	(1.06-1.25)
2006	20.45	1233	6.03	9.32	1.10	(1.01-1.20)
2007	20.83	1250	6.00	9.13	1.08	(0.99-1.18)
2008	21.25	1417	6.67	10.26	1.19	(1.10-1.30)
2009	21.69	1308	6.03	9.10	1.07	(0.98-1.16)
2010	22.03	1457	6.61	9.85	1.16	(1.07-1.26)
2011	22.34	1448	6.48	9.46	1.11	(1.03-1.21) ‡

* p <0.001; † p for trend <0.001; ‡ p for trend 0.016

Figure 2-32: Mortality from J84.1 in Australia, 2000-2011 (multiple cause of death data)

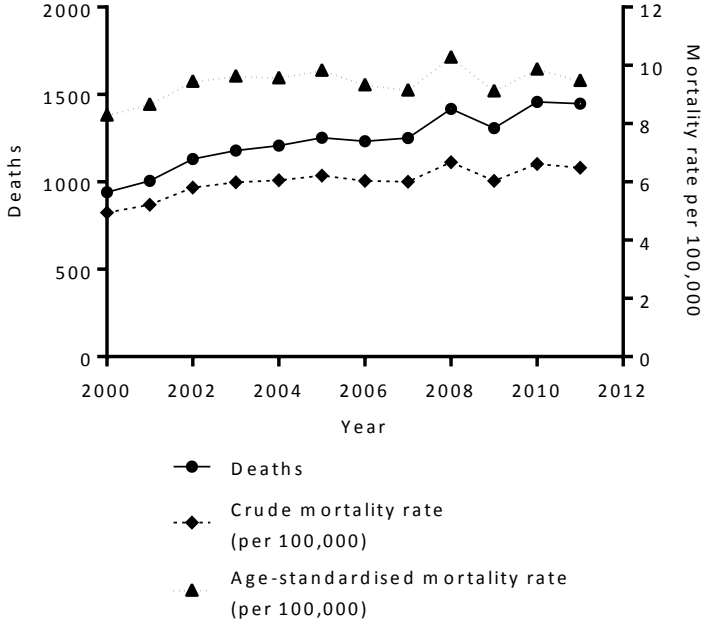


Table 2-26: Mortality from idiopathic pulmonary fibrosis clinical syndrome in the USA (J84.1/J84.9 coding, for multiple cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	1796.48	126086	7.02	8.77	1.00	
Male	1734.22	136509	7.87	14.22	1.60	(1.59-1.61)*
Age group						
0-44	2228.67	6004	0.27	0.27	0.01	(0.01-0.01)
45-54	500.14	10093	2.02	2.02	0.08	(0.08-0.08)
55-64	358.92	24547	6.84	6.92	0.27	(0.27-0.28)
65-74	231.99	57028	24.58	25.15	1.00	
75-84	154.25	98801	64.05	67.38	2.67	(2.64-2.70)
85+	56.74	66122	116.53	127.31	5.10	(5.04-5.16)†
Year						
1999	279.04	18555	6.65	10.67	1.00	
2000	281.42	19592	6.96	11.18	1.04	(1.02-1.06)
2001	284.97	20259	7.11	11.28	1.06	(1.04-1.08)
2002	287.63	21131	7.35	11.60	1.09	(1.07-1.11)
2003	290.11	21870	7.54	11.86	1.11	(1.09-1.13)
2004	292.81	21805	7.45	11.62	1.09	(1.07-1.11)
2005	295.52	22076	7.47	11.57	1.08	(1.06-1.10)
2006	298.38	22328	7.48	11.51	1.07	(1.05-1.09)
2007	301.23	22852	7.59	11.56	1.08	(1.06-1.10)
2008	304.09	23717	7.80	11.77	1.09	(1.07-1.12)
2009	306.77	23944	7.81	11.62	1.08	(1.06-1.10)
2010	308.75	24466	7.92	11.73	1.09	(1.07-1.11)†

* p <0.001; † p for trend <0.001

Figure 2-33: Mortality from J84.1/J84.9 in the USA, 1999-2010 (multiple cause of death data)

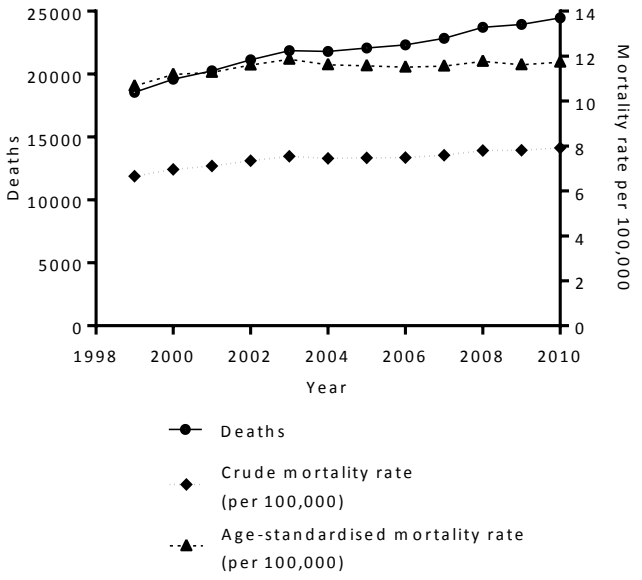


Table 2-27: Mortality from idiopathic pulmonary fibrosis clinical syndrome in the USA (J84.1 coding, for multiple cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	1796.48	102167	5.69	7.13	1.00	
Male	1734.22	112627	6.49	11.83	1.64	(1.63-1.66)*
Age group						
0-44	2228.67	3497	0.16	0.16	0.01	(0.01-0.01)
45-54	500.14	7493	1.50	1.51	0.07	(0.07-0.07)
55-64	358.92	19224	5.36	5.45	0.26	(0.26-0.27)
65-74	231.99	46788	20.17	20.68	1.00	
75-84	154.25	82354	53.39	56.27	2.72	(2.69-2.75)
85+	56.74	55438	97.70	107.00	5.24	(5.17-5.30) †
Year						
1999	279.04	15472	5.54	8.95	1.00	
2000	281.42	16302	5.79	9.37	1.04	(1.02-1.06)
2001	284.97	16759	5.88	9.40	1.05	(1.03-1.07)
2002	287.63	17505	6.09	9.67	1.08	(1.06-1.11)
2003	290.11	18112	6.24	9.88	1.10	(1.08-1.12)
2004	292.81	18063	6.17	9.69	1.08	(1.06-1.10)
2005	295.52	18220	6.17	9.61	1.07	(1.05-1.09)
2006	298.38	18273	6.12	9.49	1.05	(1.03-1.08)
2007	301.23	18537	6.15	9.46	1.05	(1.02-1.07)
2008	304.09	19110	6.28	9.55	1.06	(1.03-1.08)
2009	306.77	19059	6.21	9.34	1.03	(1.01-1.06)
2010	308.75	19382	6.28	9.37	1.03	(1.01-1.06) ‡

* p <0.001; † p for trend <0.001; ‡ p for trend 0.701

Figure 2-34: Mortality from J84.1 in the USA, 1999-2010 (multiple cause of death data)

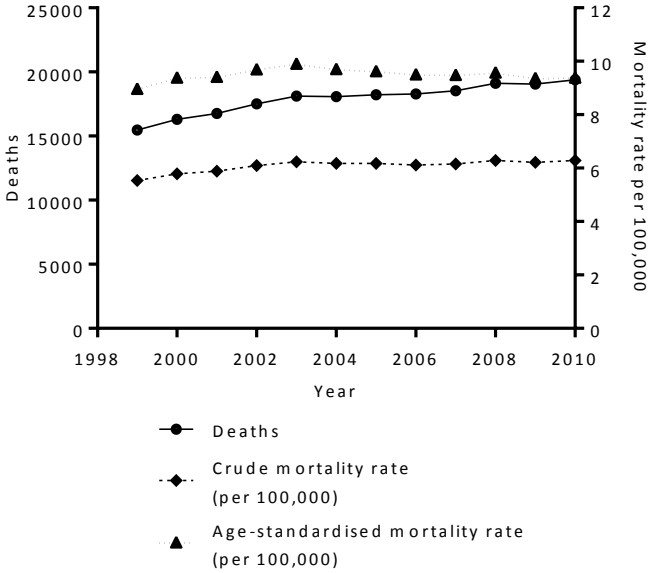


Table 2-28: Mortality from idiopathic pulmonary fibrosis clinical syndrome in the USA for five largest states (J84.1/J84.9 coding, for multiple cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	603.45	37577	6.23	8.04	1.00	
Male	585.56	40567	6.93	12.69	1.57	(1.55-1.59)*
Age group						
0-44	762.01	360	0.05	0.04	0.01	(0.00-0.01)
45-54	164.39	2773	1.69	1.64	0.07	(0.07-0.08)
55-64	117.28	7557	6.44	6.43	0.28	(0.27-0.28)
65-74	75.89	17358	22.87	23.22	1.00	
75-84	50.79	29954	58.98	61.55	2.65	(2.60-2.70)
85+	18.66	20142	107.96	115.06	5.07	(4.97-5.17) †
State						
California	392.97	25969	6.61	11.66	1.00	
Florida	193.81	16134	8.32	9.70	0.84	(0.82-0.85)
Illinois	138.90	9046	6.51	10.35	0.90	(0.87-0.92)
New York	210.81	11218	5.32	7.93	0.68	(0.66-0.69)
Texas	252.51	15777	6.25	12.20	1.06	(1.04-1.08)†
Year						
2000	102.10	6342	6.21	10.09	1.00	
2001	103.73	6434	6.20	9.97	0.99	(0.96-1.03)
2002	104.91	6580	6.27	10.28	1.00	(0.97-1.03)
2003	106.02	7001	6.60	10.67	1.04	(1.01-1.08)
2004	107.15	6935	6.47	10.36	1.02	(0.99-1.06)
2005	108.19	7031	6.50	10.27	1.01	(0.98-1.05)
2006	109.30	7066	6.46	10.10	1.00	(0.97-1.03)
2007	110.28	7304	6.62	10.28	1.01	(0.98-1.05)
2008	111.40	7599	6.82	10.63	1.03	(1.00-1.07)
2009	112.52	7895	7.02	10.71	1.04	(1.01-1.08)
2010	113.41	7957	7.02	10.68	1.04	(1.01-1.07) ‡

* p <0.001; † p for trend <0.001; ‡ p for trend 0.001

Table 2-29: Mortality from idiopathic pulmonary fibrosis clinical syndrome in the USA for five largest states (J84.1 coding, for multiple cause of death data)

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	603.45	30845	5.11	6.71	1.00	
Male	585.56	34024	5.81	10.82	1.61	(1.58-1.63)*
Age group						
0-44	762.01	327	0.04	0.03	0.01	(0.01-0.01)
45-54	164.39	2332	1.42	1.43	0.07	(0.07-0.08)
55-64	117.28	6013	5.13	5.25	0.27	(0.26-0.28)
65-74	75.89	14277	18.81	19.37	1.00	
75-84	50.79	25018	49.26	52.05	2.69	(2.63-2.75)
85+	18.66	16902	90.59	98.87	5.21	(5.09-5.32) †
State						
California	392.97	19928	5.07	9.00	1.00	
Florida	193.81	14156	7.30	8.53	0.96	(0.94-0.98)
Illinois	138.90	8005	5.76	9.18	1.03	(1.01-1.06)
New York	210.81	9043	4.29	6.42	0.71	(0.70-0.73)
Texas	252.51	13737	5.44	10.69	1.21	(1.18-1.23) †
Year						
2000	102.10	5427	5.32	8.75	1.00	
2001	103.73	5493	5.30	8.66	0.99	(0.95-1.03)
2002	104.91	5582	5.32	8.82	0.99	(0.95-1.03)
2003	106.02	5904	5.57	9.11	1.03	(0.99-1.07)
2004	107.15	5859	5.47	8.85	1.01	(0.97-1.05)
2005	108.19	5945	5.49	8.81	1.00	(0.97-1.04)
2006	109.30	5844	5.35	8.52	0.97	(0.93-1.00)
2007	110.28	6028	5.47	8.65	0.98	(0.94-1.02)
2008	111.40	6166	5.54	8.79	0.98	(0.94-1.01)
2009	112.52	6284	5.58	8.74	0.97	(0.94-1.01)
2010	113.41	6337	5.59	8.70	0.97	(0.93-1.00)‡

* p <0.001; † p for trend <0.001; ‡ p for trend 0.002

2.3.7 – Mortality using multiple cause of death data – all countries

Using the broader J84.1/J84.9 coding classification and multiple cause of death data, age-standardised mortality rates varied from 11.73 per 100,000 in the USA (2010) to 15.92 per 100,000 in England and Wales (2012). Rate ratios were similar to underlying cause of death data for England and Wales, but the rate of increase was less for Australia, with no increase over time in the USA (Figure 2-35). Using Poisson regression for data from all three countries (years where data were available for all three) there was a marginally reduced chance of having a diagnostic code of J84.1 or J84.9 in the USA (rate ratio 0.98, 95% CI 0.97-0.99, p <0.001) and a slightly reduced chance in Australia (rate ratio 0.90, 95% CI 0.88-0.91, p <0.001) (Table 2-30). The mutually adjusted rate ratio of annual change was 1.01 (95% CI 1.007-1.009, p for trend <0.001). Meta-analysis using the random effects model showed individual rates of 1.04 for England and 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% 0.99-1.04, p = 0.145) (Figure 2-36).

Figure 2-35: Age-standardised mortality rates for J84.1/J84.9 for selected countries by year, using multiple cause of death data

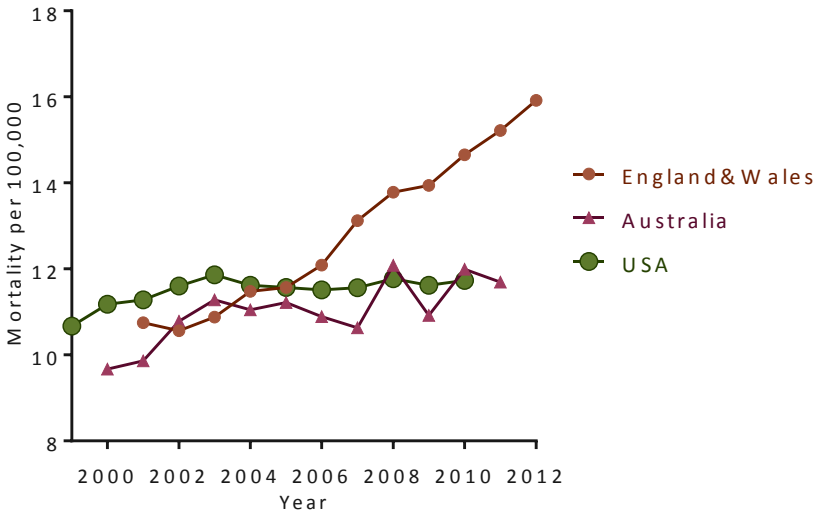
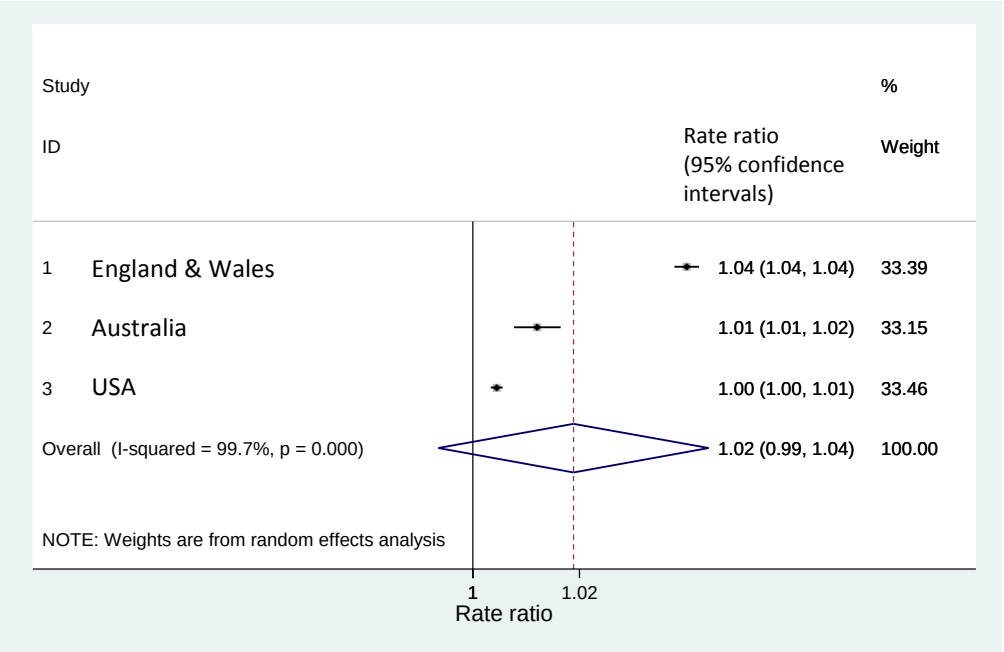


Table 2-30: Mortality from idiopathic pulmonary fibrosis clinical syndrome for J84.1/J84.9 coding, for England & Wales, Australia and USA, using multiple cause of death data, from 2001-2010

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

E&W: England & Wales. * p <0.001; † p for trend <0.001

Figure 2-36: Meta-analysis of mortality rate ratios for annual increase in mortality from J84.1/J84.9 for England and Wales, Australia and USA, using multiple cause of death data, from 2001-2010 (random effects model)



Using the more specific J84.1 coding, age-standardised mortality varied from 9.37 per 100,000 (USA, 2010) to 13.62 per 100,000 (England and Wales, 2012). Mortality rate ratios over time were similar to underlying cause of death data for England and Wales, but, as with the broader code, the rate of increase was less for Australia and there was no increase for the USA (Figure 2-37). Using Poisson regression for combined data, there was less chance of having a code of J84.1 in the USA compared to England and 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 2-31). The mutually adjusted mortality rate ratio for annual change was 1.00 (95% CI 1.001-1.003, p for trend 0.004). Meta-analysis showed individual rates of 1.03 for England and Wales (95% CI 1.027-1.032, p <0.001), 1.01 for Australia (95% CI 1.00-1.01, p = 0.016, and 1.00 for the USA (95% CI 0.999-1.001, p = 0.701), with an overall rate of 1.01 (95% CI 0.99-1.03, p = 0.280) (Figure 2-38).

Figure 2-37: Age-standardised mortality rates for J84.1 for selected countries by year, using multiple cause of death data

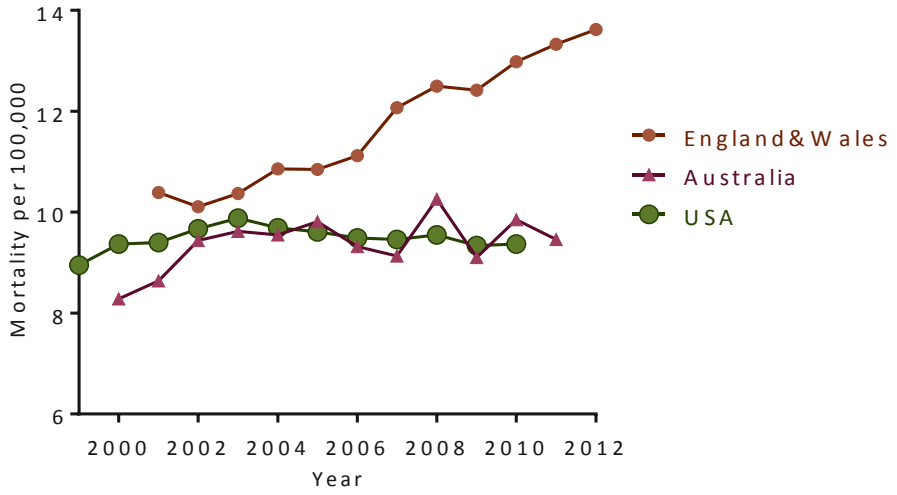
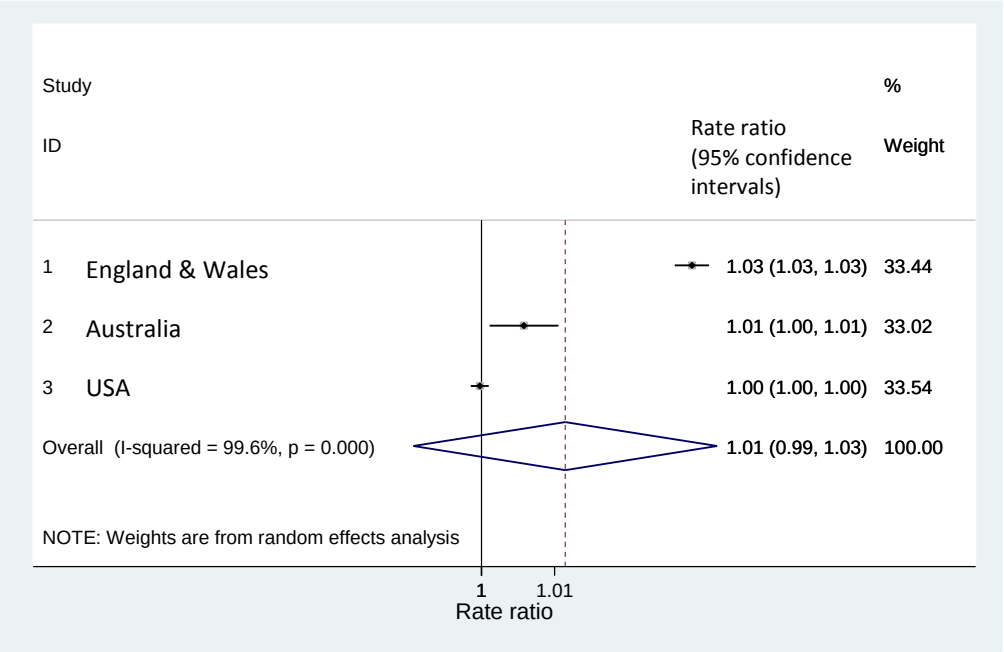


Table 2-31: Mortality from idiopathic pulmonary fibrosis clinical syndrome for J84.1 coding, for England & Wales, Australia and USA, using multiple cause of death data, from 2001-2010

	Population (millions)	Deaths	Crude mortality rate (per 100,000)	Age-standardised mortality rate (per 100,000)	Mutually adjusted mortality rate ratio (95% confidence interval)	
Sex						
Female	1887.95	109664	5.81	6.73	1.00	
Male	1825.06	133081	7.29	13.53	1.78	(1.77-1.79)*
Age group						
0-44	2308.71	3304	0.14	0.11	0.01	(0.01-0.01)
45-54	524.15	7311	1.39	1.13	0.07	(0.06-0.07))
55-64	394.75	20991	5.32	5.10	0.25	(0.25-0.25)
65-74	254.38	53786	21.14	22.00	1.00	
75-84	168.54	95554	56.69	63.08	2.76	(2.73-2.79)
85+	62.47	61799	98.92	114.40	5.13	(5.08-5.19)†
Country						
E&W	537.91	47285	8.79	11.37	1.00	
Australia	204.85	12440	6.07	9.47	0.83	(0.81-0.85)*
USA	2970.25	183020	6.16	9.55	0.87	(0.86-0.88)*

E&W: England & Wales. * p <0.001; † p for trend <0.001

Figure 2-38: Meta-analysis of mortality rate ratios for annual increase in mortality from J84.1 for England and Wales, Australia and USA, using multiple cause of death data, from 2001-2010 (random effects model)



Repeating the analyses for each country using multiple cause of death data but excluding those aged under 65 years made no difference to summary rate ratios for either code.

2.3.8 – Validity of death certification – UK data

In the UK cohort study, there were 124 deaths among 211 patients with IPF at the time of assessment. Of these, 83 individuals (67%) had IPF-clinical syndrome coded as an underlying cause of death, and 102 (82%) had it anywhere on the death certificate (multiple cause data). For 8 of these patients, the less specific code J84.9 was used. There was considerable variability in text used on death certificates, including idiopathic pulmonary fibrosis, idiopathic fibrosing alveolitis, pulmonary fibrosis, usual interstitial pneumonia, and interstitial lung disease. Both the latter two were coded as J84.9, when in reality J84.1 would have been more appropriate. There was one case listed as non-specific interstitial pneumonia and coded as J84.9.

Of the 41 patients with an alternative underlying cause of death, the majority had ischaemic heart disease or heart failure (16 patients) and lung cancer (8 patients). Three patients had chronic obstructive pulmonary disease chosen as the underlying cause of death, when in text form it appeared to be given equal status to IPF.

2.4 – Discussion

2.4.1 – Summary of findings

This study has demonstrated worldwide variation in mortality from idiopathic pulmonary fibrosis clinical syndrome. Crude mortality rates varied from 3 - 9 per 100,000, being lowest in New Zealand, Sweden and Spain, and highest in the United Kingdom and Japan. In most countries studied, there was an increase in age-standardised mortality rates over time, although this was more pronounced in some (such as the United Kingdom) than others. The rate of increase was lowest in the United States, where rates were lower than in the United Kingdom, and using multiple cause mortality data there was no apparent increase over the time period studied.

All countries confirmed the previously described association of IPF-CS with male sex and increasing age (32). 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 patients with confirmed IPF revealed that IPF-CS was listed as the underlying cause of death in two-thirds of cases, and anywhere on the death certificate in 80%, suggesting mortality data may underestimate incidence by 20-30%.

2.4.2 – Strengths of the current study

A key strength of this study is the inclusion of international data from many countries, some of which have not been previously studied, which allows comparison between regions. A further strength is the focus on data from the first decade of the twenty-first century, which has only previously been studied in England and Wales (24). This has allowed consistent use of more contemporary ICD-10 codes.

The comparison between alternative coding methods is valuable and reflects the challenges in identifying ‘true’ IPF in routinely collected data. The

similarity between J84.1/J84.9 combined codes (reflecting a broader definition of IPF) and the J84 umbrella code in countries such as the United States and England and Wales suggests that use of the J84 code alone in countries with less specific data is likely to provide a reasonable reflection of the broader J84.1/J84.9 definition of IPF.

The validation study from the United Kingdom, although relatively small, is the most recent attempt to assess the reported cause of death of patients with IPF, following previous studies from the 1990s from the United Kingdom (29) and the United States (16), and continues to show that death certification underestimates disease burden.

The use of meta-analysis to combine national disease mortality rates gives a global composite estimate that can be considered a synthesis of the best available data into global summary statistics, accepting that the high heterogeneity statistics are an inevitable consequence of comparisons between different populations and cultures.

2.4.3 – Limitations of the current study

The key limitation of this study relates to the variability in cause of death data and its reliability. Although the validation analysis shows that more patients with IPF have the disease listed on their death certificate than in earlier studies (16, 29), a significant proportion of patients with IPF will die from another cause, particularly cardiovascular disease or lung cancer. Even if IPF is listed as a contributing factor, multiple cause of death data are not widely published (available for only three countries in this study). When IPF is the underlying cause of death, it may be misclassified or misdiagnosed (for example, as heart failure), depending on the extent of diagnostic work-up prior to death, and also due to coding irregularities. The validation analysis yields useful evidence that some cases of confirmed IPF - participating in an IPF research study - are sometimes coded as ‘unspecified’ interstitial lung disease (ICD-10 code J84.9).

ICD-10 code J84.1 is the most specific code for IPF, and this is supported by this code being less common in younger patients, with higher rate ratios for increasing age – consistent with IPF being a disease of older people (15, 184). However, using this code on its own may miss unspecified cases that are actually IPF, thereby underestimating mortality. Using broader codes (for example, J84.1/J84.9 combined, or the approximate equivalent of J84 alone) is less accurate, but likely closer approximates true numbers. It is therefore likely that the combination of data used in this study for IPF-CS gives a reasonable estimation of true IPF mortality.

A further limitation is that the results relate only to the ten countries providing adequate data, and these may not therefore be generalizable to developing countries, where there may be different environment and risk factors for disease. Similarly, the validation study was only completed in one cohort from one country (England), and so may not be representative of other countries. This cohort was also from a research study, and therefore participants and clinical care may potentially be different from the general IPF population.

2.4.4 – Relation to previous work

There has only been one previous comparison of international mortality rates in IPF, by Hubbard and colleagues 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 (30). The authors found an increase in mortality from CFA over time for England and Wales, Scotland, Canada and Australia, but no increase for Germany or New Zealand, and a fall for the United States. There was considerable variation in mortality rates across countries.

Mannino and colleagues looked at multiple cause mortality data from the USA for a similar period, and noted a slight increase in mortality from IPF over time, although with much lower rates than in the United Kingdom (31). The authors speculated that part of this might be due to coding practice in the

United States, noting that post-inflammatory fibrosis (ICD-9 code 515) featured more prominently than IPF (ICD-9 code 516.3) under the sub-headings for 'fibrosis', in contrast to the United Kingdom, where CFA featured more prominently under the heading for 'alveolitis'. Olson and colleagues updated this work by looking at US mortality rates from 1992-2003 (17), 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 therefore increased diagnosis, and a stricter classification system that saw IPF more explicitly linked with the usual interstitial pneumonia pattern of disease, which has a poorer prognosis (13). The current study suggests that whereas deaths from IPF-CS continue to increase in the United States, 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 and Wales, where rates are much higher and increasing.

2.4.5 – Interpretation of findings

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, increased use of diagnostic imaging, a desire among specialists to 'categorize' 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 by 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 explanation: does this reflect physician behaviour or a different spectrum of disease (with a possible genetic component)? Previous

literature has suggested a lower incidence of IPF in East Asia (185, 186), although this likely relates to sampling of insurance databases featuring mainly severe disease. Assessment of data from other countries in East Asia would be useful to explore these patterns further.

There are three reasons why mortality from IPF-CS in the United States may not be increasing as much as elsewhere in the World. Firstly, the true incidence of IPF may be less in the United States, and secondly, it may be underdiagnosed. The third reason may relate to incorrect coding: issues surrounding poor coding noted by Mannino (31) are supported by Coultas and Hughes' death certificate study 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%) (16) – less that similar work by Johnston and colleagues in the United Kingdom (29), where the rates were 38% and 56% respectively. It is likely that coding of IPF has improved in the United States over time, but it may still be suboptimal. Fell and colleagues showed that the combination of increasing age and suggestive radiology could reasonably predict IPF in unclear cases without the need for surgical lung biopsy (184), but it may be that there is reluctance to code the diagnosis without biopsy evidence. On the other hand, Fernandez-Perez and colleagues (22) 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 United States would be useful to explore the reliability of coding further.

2.4.6 – Clinical Implications

If mortality rates from IPF-CS continue to increase as expected, the year 2014 would have been expected to potentially feature anywhere from 28,000 to 65,000 deaths from IPF across Europe – based on the lowest and highest mortality rates for underlying cause of death data from this study, summary estimates for yearly increase, and a European population of approximately 740 million. This could equate to 42,000 to 95,000 clinical cases, loosely

assuming the two-thirds percentage of cases dying from IPF in the UK cohort analysis to be representative of the wider population. For the United States, using similar methodology, 2014 would have been expected to see 13,000 to 17,000 deaths and 19,000-25,000 cases. Using the strictest code (J84.1), assuming rates continue to increase, there would be a doubling of deaths from IPF-CS in 36 years.

Although there is variation between countries in mortality from IPF-CS, rates are reasonably consistent, with less variation than was evident in previous work (30), suggesting that we may be approaching the true level. As new pharmaceutical options for treating IPF come to 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 practice. Increasing openness, detail and accuracy with death certification is likely to improve the usefulness 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. The most recent international diagnostic guidance from the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society and Latin American Thoracic Association from 2011 should help standardise and encourage specific diagnosis (15), and a follow-up to the current study in several years would be useful to assess the impact.

2.4.7 – Summary of chapter

This chapter has compared mortality from IPF clinical syndrome across several countries, demonstrating that it continues to increase with time in most countries studied, with some geographical variation. The impact of different codes used to classify IPF, and the likelihood that death certification will almost certainly underestimate true mortality, has been discussed. The clinical implications of this work are that more cases of IPF should be

expected worldwide, although improved coding accuracy would give weight to this claim.

This work was published in the Annals of the American Thoracic Society in 2014 (178). It was conducted as part of an overall aim to assess global incidence and mortality from IPF, and this theme is explored further in the next chapter.

Chapter 3 : Systematic review of incidence and mortality of idiopathic pulmonary fibrosis

This chapter systematically reviews the literature to assess incidence and mortality of idiopathic pulmonary fibrosis worldwide, with a view to deriving summary statistics. The merits of various data sources are considered, as well as potential reasons for differences.

This work was published in the European Respiratory Journal in 2015 (187).

3.1 – Introduction

3.1.1 – Background

Several studies have assessed the incidence of idiopathic pulmonary fibrosis in different countries worldwide, and there is evidence that it may be increasing (24, 25, 186). However, these studies use a variety of methodologies in terms of case ascertainment and classification systems, and this has prevented valid comparison between studies.

A small number of published reviews have examined incidence and prevalence data from certain countries (32, 188-191), but to date there has been no comprehensive systematic review of international incidence and mortality data in IPF.

3.1.2 – Methodology in incidence and mortality studies

Early studies of incidence of IPF tended to involve clinicians either recording the number of cases in their local area (using a variety of methods to find cases) (21, 192) or asking colleagues to contribute cases to a registry system (85). Mortality studies tended to use data from death certificates (30), as outlined in Chapter 2. Latterly, incidence studies have made use of larger routinely collected healthcare datasets (24, 25). All of these formats have strengths and weaknesses, and lie on a balance between confidence in data accuracy and generalisability to the wider population. These issues will be discussed further later in this chapter.

3.1.3 – Rationale for the study

IPF has long been considered a rare disease (193) but recent work from the United Kingdom has shown it to be more widespread than previously thought (24). The development of new targeted treatments and accompanying enthusiasm for research in the field has emphasised the need for accurate data on the global impact of the disease. Eliciting regional variation in

incidence and mortality may also shed light on possible aetiological factors that may explain such variation.

3.1.4 – Aims and Objectives

This chapter aims to systematically review all population-based studies of incidence and mortality of IPF worldwide, in an attempt to define the global burden of disease. Meta-analysis to derive summary statistics will be attempted if data are suitably homogeneous, although it is expected that variable methodologies might make descriptive analysis more appropriate. As part of the planning for this work, a search of national mortality statistics was considered, which ultimately led to the work described in the preceding chapter. The summary results of that work are incorporated into the mortality section of this chapter for completeness.

3.2 – Methods

3.2.1 – Study protocol, inclusions and exclusions

This review was registered on the PROSPERO international prospective register of systematic reviews on 6 February 2014 (registration number CRD42014007452), with a pre-specified protocol.

All original population-based studies and abstracts assessing incidence or mortality of IPF were to be included, with no restrictions on language that might exclude certain areas of the world. Prevalence studies were to be excluded: it was considered that incidence was a better marker than prevalence for a progressive disease like IPF. Clinical case studies were also to be excluded due to the lack of a baseline denominator population to allow accurate calculation of incidence statistics. Studies examining interstitial lung disease other than IPF (for example, in association with connective-tissue disease) were to be excluded, however those looking broadly at ILD with possible sub-classification were deemed potentially useful and were to be retained.

3.2.2 – Data sources and searches

Searches were performed using Medline (1946 to present) and Embase (1974 to latest) using OvidSP, with the latest search in June 2014. Search terms were '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'. These terms were reviewed and approved by two senior clinicians with expertise in respiratory medicine. The full search strategy was reviewed by a medical librarian and is detailed in Appendix B.

This search process was supplemented by using combinations of the search terms in the Google search engine, and screening abstract lists from the American Thoracic Society, British Thoracic Society and European Respiratory

Society annual conferences for relevant content. Finally, reference lists of selected articles and any identified review articles were screened for possible studies. As described, a planned review of websites of national statistics agencies for routine mortality data was completed separately and is described in full in Chapter 2.

3.2.3 – Study selection

All stages of study selection and elimination were performed independently by an experienced colleague, to ensure dual agreement on studies selected for inclusion. Professor Richard Hubbard co-screened the list of titles, Dr Tricia McKeever co-reviewed the selected abstracts, and Dr Andrew Fogarty co-reviewed the chosen papers and additional sources. All discrepancies in study selection were resolved 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 meaning or relevance.

3.2.4 – Data extraction and quality assessment

Data extraction used a pre-designed form that was piloted on four different studies independently by two reviewers. The form was then used on all remaining studies by the author and independently by Dr Tricia McKeever, with joint review and resolution of any differences reached by consensus discussion.

Data extracted included region and time period of study, source of data, exact condition studied, case definitions used, age of cases, exclusion criteria and incidence and mortality figures as provided. The data extraction form used is available in Appendix B. An assessment of methodological quality was made using a scoring system developed by consensus based on previous tools (194-196) (Table 3-1).

Table 3-1: Study methodological quality scoring for systematic review

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% *or* Has the dataset been fully sampled? *or* Has case registration been near complete?	☐	Total score:	☐

3.3 – Results

This section will outline the results of the search process, with numbers of studies and descriptions of their characteristics. It will then group the selected studies into four key categories: large pre-existing databases, local record systems, questionnaire surveys of physicians, and routine mortality statistics, describing each in detail with tables to allow easy comparison. Finally, the selected studies will be reviewed as a group to draw overall trends from the data and calculate summary statistics.

3.3.1 – Results of search process

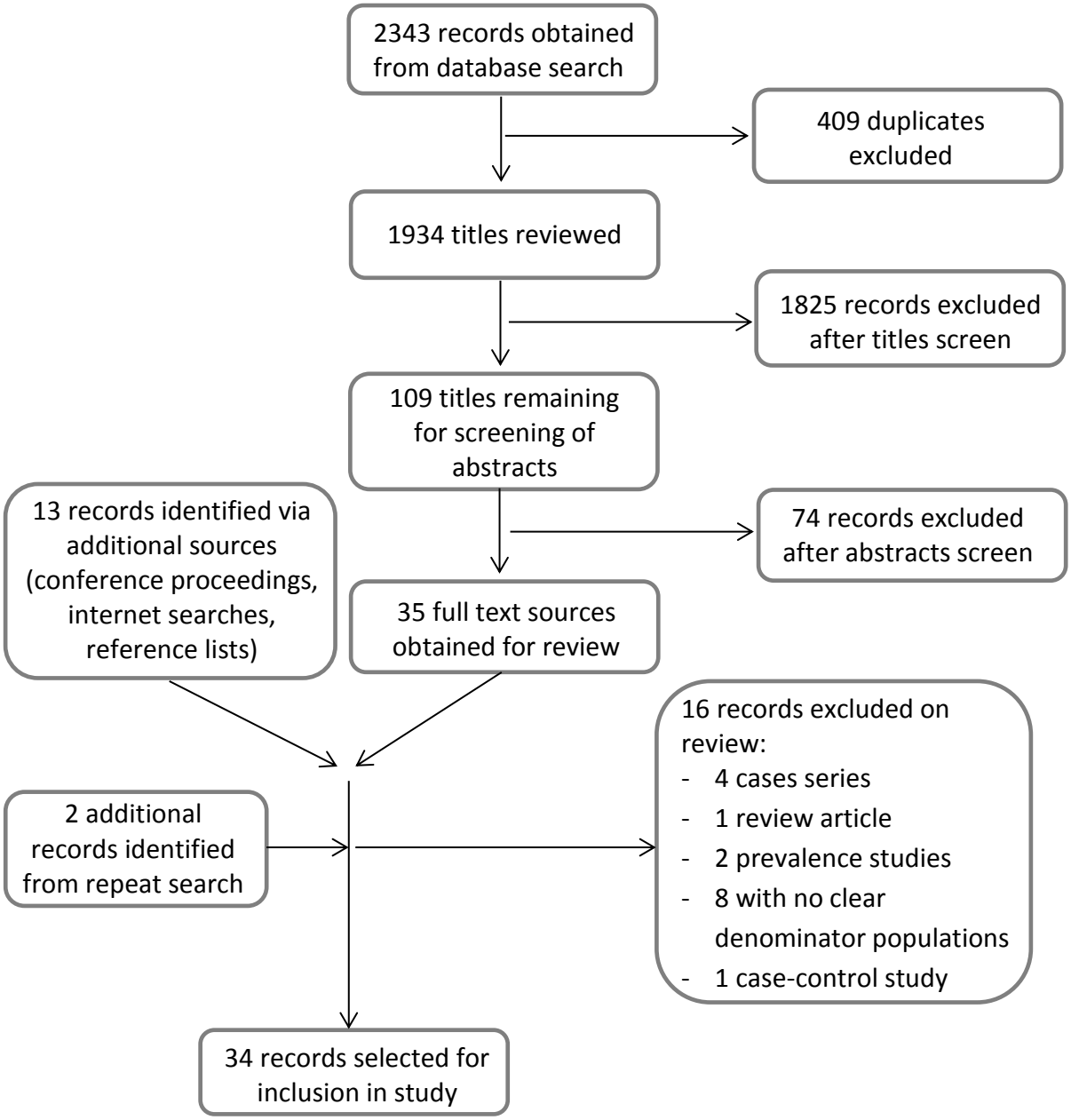
The search process is shown in a flow diagram (Figure 3-1). 1,984 titles were screened, with selection of 109 abstracts. The full texts of 35 of these were obtained for review. 13 records were added from additional sources (five from conference proceedings, seven from direct internet searching or reference lists of citations or review articles, and one published by the author and colleagues based on the mortality study in Chapter 2). From this total of 48 studies, 32 were selected for inclusion in the analysis. Two further studies were added after a repeat search. One study in abstract form (197) was replaced with the full version (198) after this was published during the review process.

3.3.2 – Summary of identified studies

The selected studies covered 21 countries, with data spanning 1968 to 2013. Eight studies reported mortality from IPF (17, 24, 30, 31, 178, 199-201) and 28 reported incidence (21-26, 85, 86, 185, 186, 192, 198, 200, 202-216). The majority 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.

There was variation in the quality scores, although overall quality was high: eight studies scored full marks, and 29 (85%) out of the 34 studies scored on at least half of the available criteria. There was no clear association between quality score and incidence of IPF: although some lower quality studies reported low incidence, there were other higher quality studies with similarly low incidence, and lower quality studies reporting higher incidence.

Figure 3-1: Flow diagram of search process for systematic review



3.3.3 – Review of studies

3.3.3.1 - Large databases

Pre-existing large databases were the most frequent data source (13 studies). Four studies from Europe used nationwide health databases, while four studies from North America and four from East Asia all used insurance claims databases. A final study from South America used Government health data. Details of large database studies are summarised in Table 3-2. Study quality varied, with some very high-quality sources but other lower quality studies providing less information on methodology and being less specific for IPF.

Gribbin *et al* examined the incidence of IPF in the United Kingdom from 1991-2003 using The Health Improvement Network (THIN), a large representative primary care database with around 1.5 million people for each year of the study (23). Cases were identified using Read codes for cryptogenic fibrosing alveolitis and idiopathic fibrosing alveolitis, with those aged under 40 years excluded. The crude incidence of IPF was 4.6 per 100,000 (95% confidence intervals (CI) 4.3-4.9) per year, with a higher rate in males than females (5.69 vs 3.44 per 100,000) and an increase over time – from 2.73 to 6.78 per 100,000 from the earliest to latest time periods of the study.

Navaratnam *et al* also used THIN to assess incidence of IPF in the UK, from 2000-2008, and identified 2,074 incident cases, equating to a crude incidence of 7.44 per 100,000 (95% CI 7.12-7.77) per year (24). Again, there was a higher incidence in males than females (9.46 vs 5.46 per 100,000) and an increase over time – from 5.77 to 8.04 per 100,000 from the earliest to latest years of the study. Both these studies offered large numbers of cases and identified these using appropriate search terms, although there was no scope to validate these using clinical data, and some non-IPF cases may have been included.

Table 3-2: Incidence of idiopathic pulmonary fibrosis in studies using large databases

Study (first author)	Year	Location	Years studied	Type of data source	Condition studied	Case definition	Incidence per 100,000/year †	Type of rate	Quality score	Comments
Europe										
Maher (202)	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 (24)	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 (203)	2008	Denmark	1995-2000	Nationwide health database	IPF *(and ILD)*	ICD-10 J84.1	7.27	Crude	9	Possible prevalent cases in earlier years. Reliant on accuracy of coding.
							4.17	Age-adjusted		
			2001-2005	Nationwide health database	IPF *(and ILD)*	ICD-10 J84.1	5.28	Crude		
							2.91	Age-adjusted		
Gribbin (23)	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 (204)	2014	USA	2001-2011	Medicare database – 5% random sample	IPF	ICD-9-CM 516.3, 515	93.7 (overall)	Crude, patients ≥65	6	Only patients aged ≥65. Medicare data may not be representative.
						ICD-9-CM 516.3	31.1-43.0 (broad) 15.9-31.1 (narrow)	Crude, patients ≥65		

Notes and abbreviations at foot of table (page 140)

(Continued)

Table 3-2: Incidence of idiopathic pulmonary fibrosis in studies using large databases (continued)

	Year	Location	Years studied	Type of data source	Condition studied	Case definition	Incidence per 100,000/year †	Type of rate	Quality score	Comments
Saad (206)	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 1 year.
Ehrlich (205)	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 to IPF, sample may not be representative.
Raghu (25)	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*(200)	2013	Brazil	1996-2010	Ministry of Health data	IPF	ICD-10 J84.1	0.48	Crude	6	Limited data available on methodology.
Asia										
Han*(207)	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 30 years. Estimated rates based on stable person-years over time, so potential underestimate. Sample may not be representative.

Notes and abbreviations at foot of table (page 140)
(Continued)

Table 3-2: Incidence of idiopathic pulmonary fibrosis in studies using large databases (continued)

	Year	Location	Years studied	Type of data source	Condition studied	Case definition	Incidence per 100,000/year †	Type of rate	Quality score	Comments
Lai (186)	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 (185)	2008	Japan	2005	Medical benefits database	IPF (and IIP)	2002 ATS guidelines (1)	1.22	Crude	4	Extrapolated from sample of cases. Sample may not be representative.
Munakata*(208)	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.

* Abstract only. † Average incidence for time period available; latest incidence stated where no average given, 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.
Probable cases from Saad study (206): 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.

A third study from the UK was completed by Maher *et al* using the Clinical Practice Research Datalink (CPRD), an alternative large primary care database (202). The authors investigated the incidence of IPF from 2000-2012 using broad and narrow criteria for IPF, although the data were only presented in abstract format and these criteria were undefined. The authors reported an incidence of 8.65 per 100,000 (95% CI 8.40-8.90) (broad criteria), with an increase over time. Although limited information was provided, the results of this study were consistent with the other two UK studies.

The final database study from Europe was by Kornum *et al*, who explored the incidence of all interstitial lung disease in Denmark using a comprehensive nationwide healthcare database covering all non-psychiatric hospital discharges, emergency department attendances and outpatient visits in the freely-accessible National Health Service (203). All new diagnoses of ILD from 1995 to 2005 were identified using ICD-10 criteria. The crude incidence of IPF was calculated as 7.27 per 100,000 (95% CI 6.97-7.57) for 1995-2000, and 5.28 per 100,000 (95% CI 5.01-5.56) for 2001-2005. Age-standardised incidence rates (adjusted to the 2000 World population) were 4.17 and 2.91 per 100,000 respectively. As with the UK studies, this study benefited from a detailed universal healthcare dataset, with limitations related to accuracy of coding. In contrast to the UK, the Danish data suggested a decrease in incidence of IPF over time, despite an increase in the incidence of ILD overall – the authors considered explanations for this, including prevalent cases being captured in the earlier time period, or a greater tendency to code alternative ILDs in the later time period.

The most comparable studies from North America both used insurance databases from the USA. Raghu *et al* used a large health care claims database covering around 3 million US residents across 20 states to investigate the incidence of IPF from 1996-2000 (25). Cases were selected using broad and narrow criteria: the broad definition required an ICD-9-CM diagnostic code of 516.3 during the study period and no other diagnostic codes for ILD, whereas the narrow definition required in addition that patients had undergone a

diagnostic test consistent with ILD on or before their first diagnostic code. The authors identified 295 incident 'broad' cases, and 120 incident 'narrow' cases, and extrapolated to the US population to estimate an incidence of 16.3 per 100,000 (broad criteria) and 6.8 per 100,000 (narrow criteria). This was a large database with clear diagnostic criteria, however as it included only health-plan members in specific regions of the United States, the authors acknowledged that it might not be fully representative of the wider population.

A later study by Raghu *et al* examined administrative claims from a 5% random sample of Medicare patients from 2001-2011 (204). In this study, there were three case definitions: an initial primary cohort comprising ICD-9-CM codes 516.3 and 515, without any other codes for ILD, and two subgroups equivalent to the broad and narrow criteria from the previous study. This large dataset yielded just over 12,000 patients in the primary cohort from across the United States, and reported a headline incidence of 93.7 per 100,000 person-years (95% CI 91.9-95.4). In the broad subgroup, the annual incidence ranged from 31.1-43.0 per 100,000, and in the narrow subgroup, the annual incidence ranged from 15.9-31.1 per 100,000. The likely reason for the significantly increased figure from this study was that the population comprised only patients aged 65 years and over, limiting comparison to other studies.

Two other US insurance datasets provided less precise estimates of IPF incidence. Ehrlich *et al* reported the age-adjusted incidence of 'pulmonary fibrosis' in diabetics and non-diabetics in northern California as 14 per 100,000 per year and 9 per 100,000 per year respectively, in a study looking primarily at pulmonary disease in diabetic patients (205). Saad *et al* examined the association between statin use and ILD (but not IPF specifically) in Quebec, Canada from 1990-2005, and reported incidence rates of 'probable' and 'definite' ILD of 81 per 100,000 and 35 per 100,000 respectively (206). The authors were able to provide an incidence of IPF specifically for 2006 of 36.6 per 100,000 per year (probable cases) (P Ernst, personal communication,

May 2014). Both these studies were limited by lack of precision for the diagnosis of IPF and potential bias in case mix.

Four studies from East Asia all used insurance and claims databases, and all reported lower incidence rates, ranging from 1.2-4.16 per 100,000 per year. The most detailed study, by Lai *et al,* explored the incidence in Taiwan using a large comprehensive population-based health insurance database linked to government death registration data (186). Crude annual incidence of IPF rose from 0.6 per 100,000 in 1998 to 1.4 per 100,000 in 2007, using the broad criteria proposed by Raghu (25). Using the narrow criteria, incidence rose from 0.5 to 1.2 per 100,000. The authors noted that mortality was higher and survival less than in other studies, suggesting a more severe cohort of disease and possible under-reporting of milder cases.

Han *et al* used similar criteria to examine healthcare claims data from South Korea, based on a cohort of around 1 million people who participated in a health evaluation between 1992 and 1995 (207). The study was reported as an abstract, with incidence rates calculated for various age categories for the time period 1995-2010. Using the limited data in the abstract, and loosely assuming stable populations for the time period, it was possible to calculate crude estimates for incidence in those aged over 30 years of 4.16 per 100,000 (broad criteria) and 1.84 per 100,000 (narrow criteria), acknowledging that the sample may not be representative and that this estimation process was not robust.

Ohno *et al* used a medical benefits database for patients with idiopathic interstitial pneumonia (IIP) from Japan to assess epidemiology of IPF (185). The authors identified over 4000 patients with IIP, and obtained clinical records for a 35% sample, which included 545 incident cases of IPF. Using extrapolation based on these details, an incidence of IPF of 1.22 could be estimated, although again it was noted that the database comprised mainly more severe cases. A brief abstract by Munakata *et al* reported the incidence of IIP (not IPF) in Hokkaido, Japan as 1.23 per 100,000, based on data from a financial support programme collected from 1989-1992, although the limited

data on methodology and representativeness of the sample in this older study limited its applicability (208).

Finally, Rufino *et al* examined the incidence of IPF in Brazil using data from the Ministry of Health from 1996-2011 (200). Cases were selected using ICD-10 code J84.1, with other types of ILD excluded. The incidence here was much lower than elsewhere, but did increase over time, from 0.26 per 100,000 in 1996 to 0.48 per 100,000 in 2010. This study, reported as an abstract, had fairly limited information on its methodology.

3.3.3.2 – Local records

Nine studies were classified as using local records to arrive at incidence statistics: seven from Europe and two from North America. In contrast to the large databases, these studies tended to probe deeper into clinical systems to verify cases, but centred on smaller geographical areas. Details of the studies are summarised in Table 3-3. As with the large database studies, lower quality studies often provided limited information, while other studies provided comprehensive information and were mainly limited by representativeness.

Agabiti *et al* explored the incidence of IPF in the Lazio region of Italy from 2005-2009, using data on adult patients admitted to local hospitals with an ICD-9-CM code of 516.3 (198). Data were obtained from three separate regional health systems linked by a unique identifier, and coding accuracy was assessed by review of a random sample of medical records from six hospitals in Rome. These records were chosen based on a wider range of ILD codes, and reviewed by specialists based on 2011 ATS/ERS guidelines (15). Incidence of IPF was estimated at 7.5 per 100,000 based on coding criteria (prior to case review) and a higher estimate of 9.3 per 100,000 after clinical case review. Although this study was limited to hospitalised patients, the detailed case review supported the reported figures and implied using codes alone would have underestimated true incidence.

Duchemann *et al* performed a similar study in the greater Paris region looking at all types of ILD, although the study was only available in abstract form at the time of this review (210). The authors collated data from various relevant hospital departments, primary care practitioners and a national health insurance database, and cases were reviewed centrally by an expert panel. Preliminary data reported 92 incident cases of ILD over 8 months, which could be extrapolated to an incidence of 11.7 per 100,000, although only prevalence data (rather than incidence) were available for IPF specifically.

Two recent single-centre European studies reported lower incidences of IPF. Hyldgaard *et al* investigated the incidence of ILD in central Denmark from 2003-2009, using the hospital registry of Aarhus University Hospital, one of three specialist ILD tertiary centres in the country, and lists of HRCT scans (209). All cases were re-evaluated according to current ATS/ERS criteria (15). The authors calculated an incidence of IPF of 1.3 per 100,000, commenting that the proportion of ILD cases classified as IPF was lower than expected, and suggesting that some patients classified as end-stage fibrosis may in fact have had IPF. Another similar study was by Szafranski, who explored the incidence of ILD in Radom, Poland (211). Cases were identified using ICD-10 criteria, and a crude incidence of 2.8 per 100,000 in patients aged over 14 was reported.

Table 3-3: Incidence of idiopathic pulmonary fibrosis in studies using local records

Study (first author)	Year	Location	Years studied	Type of data source	Condition studied	Case definition	Incidence per 100,000/year †	Type of rate	Quality score	Comments
Europe										
Agabiti (198)	2014	Lazio, Italy	2005-2009	Regional hospital and mortality systems	IPF	ICD-9-CM 516.3, ATS/ERS 2011 criteria (15)	7.5 (coding) 9.3 (after case review)	Crude	7	Hospitalised patients only. Case review of random sample of records.
Hyldgaard (209)	2014	Aarhus, Denmark	2003-2009	Hospital registry and lists of HRCT scans from the University Hospital	IPF (and ILD)	ICD-10 codes, ATS/ERS 2011 criteria	1.3	Crude	6	Single centre study. Cases reviewed by international criteria.
Duchemann* (210)	2013	Seine Saint Denis, France	2011	Hospitals and general practitioners in the 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.
Szafranski*(211)	2012	Radom, Poland	2000-2009	Hospital admissions database, single hospital	IPF (and ILD)	ICD-10 J84.1	2.8	Crude, in patients aged >14 years	7	Single centre, only age >14 years in denominator.
Von Plessen (26)	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 aged >16 years	6	Hospitalised patients only. Only age >16 years in denominator.

Notes and abbreviations at foot of table (page 147)
(Continued)

Table 3-3: Incidence of idiopathic pulmonary fibrosis in studies using local records (continued)

Study (first author)	Year	Location	Years studied	Type of data source	Condition studied	Case definition	Incidence per 100,000/year †	Type of rate	Quality score	Comments
Kolek (192)	1994	Czech Republic	1981-1990	Multiple hospital medical records review	CFA	n/a	1.28 (1990)	Crude	5	Unclear case definition.
Liebetrau (212)	1992	Thuringia, Germany	1986-1990	Patient population of tertiary hospital	PF	n/a	2.42 (1988)	Crude	3	Unclear case definition.
North America										
Fernandez-Perez (22)	2010	Minnesota, USA	1997-2005	Population-based medical records linkage system	IPF	ATS/ERS 2002 criteria (1)	17.4 (broad) 8.8 (narrow)	Age-adjusted, in patients aged >50 years	9	Low numbers, only patients aged >50 years
Coultas (21)	1994	New Mexico, USA	1988-1990	Population-based, multiple sources (eg medical records, autopsies)	IPF (and ILD)	ICD-9 516.3, 515	10.7 (male) 7.4 (female)	Crude	8	Small region

* Abstract only. † Average incidence for time period available; latest incidence stated where no average given and for Kolek (192) and Liebetrau (212) studes. 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; HRCT: high resolution computed tomography; ATS: American Thoracic Society. ERS: European Respiratory Society. ICD-*n*-*[CM]*: International Classification of Diseases, n^{th} Revision, *[Clinical Modification]*; n/a: not available.

Broad and narrow criteria for Fernandez-Perez study based on the 2002 ATS/ERS guidelines (1).

Three older European studies reported incidence of IPF using earlier case terminology. Von Plessen *et al* explored the incidence of cryptogenic fibrosing alveolitis (CFA) in Bergen, Norway from 1984-1998, using the records of the region's two hospitals, and calculated an incidence of 4.3 per 100,000 (hospitalised patients >16 years of age) (26). Kolek investigated cases of CFA from 24 hospitals in Moravia and Silesia, regions of the eastern Czech Republic from 1981-1990, and reported an incidence of 0.74-1.28 per 100,000 over the years (192). Finally, Liebetrau *et al* investigated the incidence of 'pulmonary fibrosis' in Thuringia, central Germany, from 1986-1990, based on cases from the region's tertiary hospital, calculating an incidence of 2.35-2.42 per 100,000 (212).

The two major North American studies were both from the USA. Coultas *et al* investigated the incidence of ILD in New Mexico in 1988-1990, with a thorough attempt to locate all cases using medical records, hospital discharge forms, autopsy and pathology reports, and death certificates (21). The authors calculated a crude incidence of IPF of 10.7 per 100,000 in males and 7.4 per 100,000 in females. In a later study, Fernandez-Perez *et al* explored the incidence of IPF in Olmsted County, Minnesota from 1997-2005 (22), again with efforts to verify all cases (using 2002 ATS/ERS criteria) (1). Age and sex adjusted incidence in residents aged 50 years and older was 17.4 per 100,000 (95% CI 12.4-22.4) (broad criteria) and 8.8 per 100,000 (95% CI 5.3-12.4) (narrow criteria). In contrast to most other studies, incidence decreased in later years (2003-2005) with rates of 11.0 per 100,000 (broad) and 6.0 per 100,000 (narrow). While case ascertainment was thorough, case numbers were low, with only 47 broad cases and 24 narrow cases for the whole study.

3.3.3.3 – Questionnaire surveys

Six studies estimated the incidence of IPF across a country by surveying pulmonary physicians. Details are summarised in Table 3-4. Quality scores were lower for most of these studies, primarily due to the nature of case-finding.

The highest incidence of IPF was calculated from the most recent study by Musellim *et al* from Turkey, where physicians from six regions of the country submitted cases of ILD electronically from 2007-2009 (213). Diagnosis was made by local specialists according to ATS/ERS 2002 criteria, and 408 incident cases of IPF were reported. A crude incidence of 4.69 per 100,000 per year was calculated based on the overall estimate for ILD.

Other studies had lower incidence estimates however. A similar study from Greece by Karakatsani *et al* reported an incidence of IPF of 0.93 per 100,000 (only 52 cases, from 2004) using non-electronic reporting (214). Tinelli *et al* used a registry to explore incidence of ILD in Italy (215), and although the authors did not provide incidence estimates for IPF, an estimate of 0.8 per 100,000 could be calculated based on the incidence of ILD in one province (Bolzano) and the percentage of cases of ILD that were classified as IPF. The authors of this study noted an increase in reporting after a switch to electronic registration.

Two studies from Spain yielded slightly higher results: Lopez-Campos *et al* explored the incidence of ILD in nine provinces in southern Spain from 1998-2000 using a multi-centre registry, questionnaires, and ICD-9 coding, and reported an incidence of IPF of 1.4 per 100,000 (216). Xaubet *et al* contacted centres with a special interest in ILD from 2000-2001 and received responses from 62%: those participating contributed 197 incident cases of IPF diagnosed using ATS/ERS criteria, giving an incidence of 2.9 per 100,000 (86).

Finally, an older study from Flanders, northern Belgium involved 20 respiratory centres in a prospective registration system between 1992 and 1996 (85). The authors reported a low incidence of IPF of 0.22 per 100,000.

Table 3-4: Incidence of idiopathic pulmonary fibrosis in studies using questionnaire surveys

Study (first author)	Year	Location	Years studied	Type of data source	Condition studied	Case definition	Incidence per 100,000/year †	Type of rate	Quality score	Comments
Musellim (213)	2013	Turkey	2007-2009	Questionnaire registration system	IPF (as %ILD)	ATS/ERS 2002 criteria (1)	4.69	Crude	5	Lack of response from certain centres
Karakatsani (214)	2009	Greece	2004	Pulmonology departments with interest in ILD	IPF (and ILD)	ATS/ERS 2002 criteria	0.93	Crude	5	60% response rate. Lower proportion IPF than other registries.
Tinelli (215)	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 (216)	2004	Southern Spain	1998-2000	Questionnaire registration system from 29 hospitals	IPF (and ILD)	ICD-9 516.3	1.4	Crude	7	Other IIP noted under IPF code.
Xaubet (86)	2004	Spain	2000-2001	Respiratory centres with interest in ILD	IPF (as %ILD)	ATS/ERS 2002 criteria	2.9	Crude	5	62% response rate.
Thomeer (85)	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.

† Average incidence for time period available; latest incidence stated where no average given. 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; ATS: American Thoracic Society. ERS: European Respiratory Society. ICD-*n*-*[CM]*: International Classification of Diseases, *n*th Revision, *[Clinical Modification]*.

3.3.3.4 – Routine mortality statistics

Eight studies used routine mortality statistics to assess mortality from IPF. Two compared mortality across countries, one looked specifically at the UK, three explored data from the USA, and two reported data from Brazil (see Table 3-5). All studies commented on change over time. Quality scores were high due to clearly defined populations and standardised methods.

One of the earliest studies of mortality from pulmonary fibrosis was by Hubbard *et al*, who obtained mortality statistics from seven countries, predominantly from the 1980s (30). 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 risk ratios over time in most countries, but no change in Germany or New Zealand, and a fall in the USA.

The second multi-country study was reported recently based on the work in Chapter 2 of this thesis (178). In summary, data were obtained from ten countries, using both broad (J84) and narrow (J84.1) ICD-10 codes for IPF-clinical syndrome. 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 the 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 the 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.

Table 3-5: Mortality from idiopathic pulmonary fibrosis in studies using routine mortality statistics

Study (first author)	Year	Location	Years studied	Type of data source	Condition studied	Case definition	Mortality per 100,000/year †	Type of rate	Quality score	Comments
Multi-centre										
Hutchinson (178)	2014	England & Wales	2001-2012	National statistics agencies	IPF	ICD-10 J84 (less specific)	9.84 (2012)	Age-adjusted	9	Possible coding misclassification, IPF may not be cause of death.
		Australia	2000-2011				6.49 (2011)			
		Canada	2000-2011				7.52 (2011)			
		Japan	2009-2011				10.26 (2011)			
		New Zealand	2006-2010				5.55 (2010)			
		Northern Ireland	2009-2011				13.36 (2011)			
		Scotland	2001-2012				10.71 (2012)			
		Spain	2000-2011				5.38 (2011)			
		Sweden	2000-2012				4.68 (2012)			
		USA	1999-2010				7.80 (2010)			
		England & Wales	2001-2012	National statistics agencies	IPF	ICD-10 J84.1 (more specific)	8.28 (2012)	Age-adjusted		
		Australia	2000-2011				5.08 (2011)			
		Canada	2000-2011				6.38 (2011)			
		Spain	2000-2011				4.64 (2011)			
		USA	1999-2010				6.16 (2010)			
Hubbard (30)	1996	England & Wales	1979-1992	National statistics agencies	IPF and PF	ICD-9 516.3, 515	Specific data not available	Crude	8	Data presented graphically only. Possible coding misclassification, IPF may not be cause of death.
		Scotland	1979-1991							
		Australia	1979-1991							
		Canada	1979-1991							
		USA	1979-1988							
		New Zealand	1980-1987							
		Germany	1987-1992							

Notes and abbreviations at foot of table (page 153)

(Continued)

Table 3-5: Mortality from idiopathic pulmonary fibrosis in studies using routine mortality statistics (continued)

Study (first author)	Year	Location	Years studied	Type of data source	Condition studied	Case definition	Mortality per 100,000/year †	Type of rate	Quality score	Comments
Europe										
Navaratnam (24)	2011	UK	1968-2008	UK ONS	IPF	ICD-8 517 ICD-9 516.3, 515 ICD-10 J84.1	5.10 (2008)	Age-adjusted	9	Possible coding misclassification, IPF may not be cause of death.
North America										
Pinheiro (199)	2008	USA	1999-2003	US NCHS	IPF‡	ICD-10 J84.1	7.57	Age-adjusted	9	
Olson (17)	2007	USA	1992-2003	US NCHS	IPF‡	ICD-9 516.3, 515 ICD-10 J84.1	5.08	Age-adjusted	9	Possible coding misclassification. Multiple cause of death data used - not comparable to other studies.
Mannino (31)	1996	USA	1979-1991	US NCHS	IPF and PF‡	ICD-9 516.3, 515	3.65 (1991)	Age-adjusted	9	
South America										
Rufino*(200)	2013	Brazil	1996-2010	Ministry of Health	IPF	ICD-10 J84.1	1.21 (2010)	Crude	7	
Fortuna (201)	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	Possible under-reporting. Limited information on reliability of data.

* Abstract only. † Average mortality, or latest mortality (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; ILD: interstitial lung disease; ONS: Office of National Statistics; NCHS: National Center for Health Statistics; ICD-*n*-*[CM]*: International Classification of Diseases, *n*th Revision, *[Clinical Modification]*.

Navaratnam *et al* explored mortality in the UK from 1968-2008 using data from the Office of National Statistics, with age-standardisation to the 2008 population (24). Over 56,000 deaths from IPF-clinical syndrome were identified from England and Wales, with an overall age-standardised mortality rate of 2.54 per 100,000, but 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 was calculated at 5%.

Three studies looked at multiple cause mortality in the USA using death certificate reports compiled by the National Center for Health Statistics. Mannino *et al* looked at data from 1979-1991 (31), and reported age-adjusted mortality of pulmonary fibrosis (ICD-9 codes 516.3 and 515) as increasing from 3.2 per 100,000 in 1979 to 3.65 per 100,000 in 1991. The authors noted the vast majority of cases were coded as post-inflammatory fibrosis (515) rather than IPF (516.3) and speculated that this might be due to coding practices.

Olson *et al* examined similar data from 1992-2003 (17), using the ICD-10 code J84.1 in addition, and calculated an overall adjusted mortality of 5.08 per 100,000. This study was age-standardised to the 2000 US population, as opposed to the 1980 population used in the Mannino study. Finally, Pinheiro *et al* investigated occupational risks for IPF mortality using the same US data from 1999-2003 (199), and reported age-adjusted mortality of 7.57 per 100,000 (9.89 per 100,000 for males, 6.07 per 100,000 for females).

The two Brazilian studies reported lower levels of mortality from IPF. Rufino *et al's* incidence study also provided mortality statistics, with an increase from 0.65 per 100,000 in 1996 to 1.21 per 100,000 in 2010 (200). Fortuna *et al* looked specifically at the southern Brazilian state of Rio Grande do Sul from 1970-2000 using ICD-coded mortality statistics from the Regional Center for Health Information (201), and reported just 777 cases where IPF was the underlying cause of death, giving a mortality of 0.22 per 100,000 in the 1970s, 0.3 per 100,000 in the 1980s, and 0.48 per 100,000 in the 1990s. It was noted that mortality increased notably after a change in coding practice in 1996.

3.3.4 – Trends

3.3.4.1 – 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 (24, 202), with a strong increase over time. Lower rates were noted in Scandinavia (26, 203, 209) and southern Europe (86, 214-216), although some of these studies were likely subject to under-reporting, and a more recent study from Italy with thorough case ascertainment had a higher incidence (198).

In the USA, mortality statistics were lower and estimates using narrow criteria suggested an incidence of 5-8 per 100,000 (17, 22, 25, 199). Both incidence and mortality studies from South America suggested a low incidence (0.4-1.2 per 100,000) (200, 201). Insurance claims-based incidence studies from East Asia also showed a low incidence (1.2-3.8 per 100,000) (185, 186, 207, 208), although routine mortality statistics from Japan suggested a higher incidence (adjusted mortality rate of 10.26 per 100,000 for broad coding) (178). Adjusted mortality statistics from Oceania ranged from 5.08-6.49 per 100,000 (178).

3.3.4.2 – 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 (30, 31, 192, 212), while later studies using similar data showed far higher rates (17, 24). Increasing incidence rates were particularly evident in UK datasets (23, 24), but were also noted in South America (200, 201), East Asia (186) and Europe (192). However, mortality data from the USA appeared to plateau in some studies, and a decline was noted in studies from the USA (22, 30) and Denmark (203).

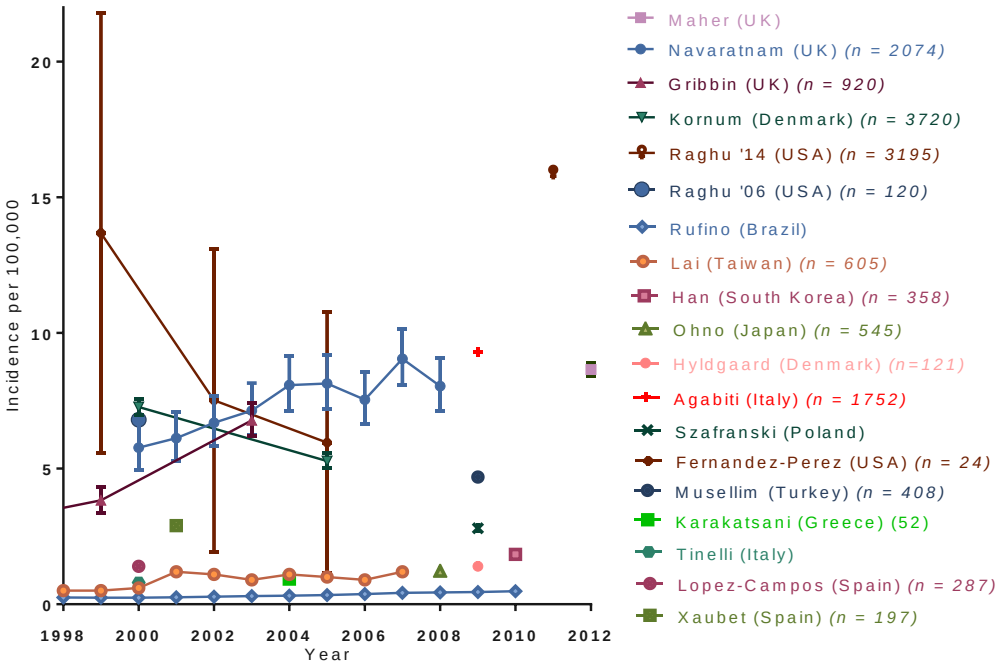
3.3.5 – Summary statistics

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 statistics of >98%, suggesting extremely high heterogeneity (values >75% considered 'high') (217), and this was also the case when roughly estimated confidence intervals were created from available raw data from other incidence studies.

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

Figure 3-2 attempts to display incidence figures over time in different studies.

Figure 3-2: Incidence of idiopathic pulmonary fibrosis over time according to various studies



Included studies use variable case definitions. Where broad and narrow criteria are reported, narrow criteria have been plotted. Where incidence is reported as a range over several years, the latest years have been plotted. 95% confidence intervals plotted where provided. For Agabiti (2014) study, most definitive estimate plotted.

3.4 – Discussion

3.4.1 – Summary of findings

This review has summarised 34 studies of IPF incidence and mortality, grouping together different study designs from around the World. Calculating summary statistics was challenging due to varying study methodologies, case definitions and time periods, however incidence ranged from 0.2 per 100,000 per year to 93.7 per 100,000 per year, with a tighter range of 3-9 per 100,000 per 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.

3.4.2 – Strengths and limitations of different study designs

Different study designs had different strengths and weaknesses. Large database studies and routine mortality statistics had the benefit of large numbers of patients, but at the expense of clinical verification of diagnoses. This therefore allowed for potential misclassification, particularly with changing case definitions over time, and there is some evidence from validation studies suggesting that routinely-coded data may over-estimate the incidence of IPF (218). A further potential limitation of databases is whether they represent the underlying population, for example, an insurance claims dataset might only include employed patients or those able to afford private insurance cover.

Mortality studies rated highly on quality scoring, in part due to the clearly defined populations. These studies also allowed comparison across countries, although only those providing an appropriate level of coding detail. However, a major limitation of routine mortality statistics was that IPF might not be the underlying cause of death – or might not be selected as the underlying cause – and therefore would not be captured. Alternatively it could be misdiagnosed in life, for example as heart failure. Many countries only report

the most common respiratory causes of death, such as pneumonia or chronic obstructive pulmonary disease, and full ICD-10 codes are used infrequently, hence the broad codes used to identify cases in some 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 and therefore might not be generalizable to the broader population, however where possible, diagnoses were verified by review of clinical records including imaging, in some cases with external expert review against international diagnostic criteria. While potentially more accurate, this time-consuming approach limits the size of the population under review. One of the most detailed assessments by Fernandez-Perez *et al* identified only 24 cases of narrowly defined IPF over 8 years (22). Quality assessment of these studies varied considerably due to limited information on methods and verification of cases in some studies.

The low incidence of IPF in questionnaire surveys undoubtedly reflects underreporting of cases from participating centres. The highest level was reported most recently in Turkey in 2013 (213) – this may reflect increased effectiveness of electronic case registration in the internet age, and widespread awareness of international guidelines and the increased profile of interstitial lung disease in the respiratory community may have enhanced participation. A further limitation of these studies was the lack of response from certain centres, which may mean the sample is less representative. However, despite criticism of these studies, some questionnaires have provided greater detail on subdivisions of idiopathic interstitial pneumonia (for example, non-specific interstitial pneumonia and cryptogenic organising pneumonia) than has been possible using ICD-10 coding, and this therefore gives some idea of the proportion of cases of IPF that might be over-diagnosed using routine coding studies.

3.4.3 – Strengths and weaknesses of the current review

One of the main strengths of this review is the systematic approach to searching the literature. Other studies summarising the epidemiology of IPF have not taken this approach, which has meant certain studies have not been identified. In particular, this is the first review to include conference abstracts, which may be the sole means of reporting a national incidence study. The comprehensive nature of the review, protocol pre-registration, duplicate search strategy and careful quality scoring all ensured the process was thorough and rigorous. Although meta-analysis was not possible, a composite estimate was obtained which is among the strongest available in the field of IPF epidemiology thus far.

A limitation of this review is the unavoidable heterogeneity of included studies, and the fact that decisions taken to deal with this might not be replicated by others. However strong the search strategy, all conclusions depend on the quality of included studies, although overall quality scoring was reasonably high. A second limitation is that although there were no language restrictions on the search strategy, it used only English search terms, which may have missed some studies from other regions – however non-English language studies were still obtained, as well as studies from countries with less use of English (for example, Brazil). The omission of non-population-based studies (without a clear denominator population) meant exclusion of some clinical studies from diverse areas of the world with no other data – such as the Middle East, where Iran (219) and Saudi Arabia (220) both contributed studies – however any incidence statistics derived from these studies would require too many assumptions to be reliable. Overall, it was felt that the extent of the search strategy struck the correct balance between adequate scope and consistency of retrieved data.

3.4.4 – Interpretation of findings

Although a summary rate of 3-9 per 100,000 was calculated, there was still variation between countries in this review, and there are several explanations why this may be, foremost being variation in disease incidence or variation in disease reporting. The lower incidence in South America may be due to under-diagnosis or under-reporting on death certificates, as both studies here used routine data, and IPF may have less of a focus here in healthcare terms than other conditions. The lower life expectancy in countries such as Brazil compared to countries such as the UK also means that fewer older patients will have time to develop IPF, and this may mean future studies will yield more cases as the population ages.

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 in Japan from the multi-centre death certificate study outlined in Chapter 2 (178) may support this argument. However, the coding used here was broad, and sub-classification suggested the majority of cases were recorded as 'unspecified interstitial lung disease' rather than 'IPF', which might imply a different spectrum of interstitial lung disease in East Asia. On the other hand, a recent study reporting variation in the reporting of adverse drug reactions as ILD in Japan compared to elsewhere suggests that this might relate to coding practice (221), and it may be that similar cases would be diagnosed differently in different regions.

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 in COPD, and more widespread use of international guidelines, should help to address this.

In most studies, the incidence of IPF appears to be increasing over time, although two good quality studies from Denmark (203) and the USA (22) 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' ILD in the latter time period suggesting diagnostic transfer. It is possible that some of the increase in IPF in studies reflects increased capture of patients with other types of ILD by imprecise coding algorithms; however the increasing incidence seen in the UK studies seems unlikely to be purely due to coding, and more needs to be done to assess the reasons behind international variation in incidence.

3.4.5 – Clinical implications

Overall, available data is fairly consistent with regards the incidence and mortality of IPF worldwide. Most variation is likely the 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.

Despite this variation, the cumulative evidence from current data from western countries suggests the incidence of IPF is comparable to that of several malignancies, including stomach, liver, testicular and cervical cancers (222, 223). This contrasts with public awareness of the disease being far lower (224, 225). Extrapolated data from Chapter 2 suggests that broadly-defined IPF will result in around 5,000 deaths per year in England and Wales, which is around 1% of the total deaths (226). The apparent increase in incidence seen in most countries means that the burden of IPF on healthcare systems in likely to rise, and accurate epidemiological studies are crucial to map this demand.

3.4.6 – Proposals for future epidemiological studies

Further studies should ideally be designed to allow appropriate comparisons between studies. The ideal study would sample a large representative dataset, but with an attempt to validate clinical diagnoses by review of an appropriate number of records. Agabiti *et al's* study from Italy followed this approach in a region of 4.7 million people (198), with sampling from six hospitals and a review of additional less-specific codes, and in fact yielded more cases with this detailed approach than were identified using the initial database search. This contrasts with validation work by Esposito *et al* from the United States where follow-up clinical review reduced the number of cases (218).

The following recommendations for future work may help researchers maximise the value of their studies – accepting the limitations they may have in achieving these targets.

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 October 2015 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 by 2018.
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 (15).
3) In countries where insurance datasets are used, broad and narrow criteria proposed by Raghu (25) 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. These studies will however have clear limitations over other methods.
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.

It would be assumed that with greater acceptance of international guidelines, more widespread use of imaging technology and greater education of clinicians, there may be less uncertainty regarding the diagnosis of interstitial lung disease, which in turn should result in more reliable disease estimates. Any underlying variation may then yield useful insights into the cause or causes of this disease.

3.4.6 – Summary of chapter

This chapter has reported a comprehensive systematic review of worldwide incidence and mortality from IPF, proposing a conservative estimate of 3-9 per 100,000 per year for Europe and North America, with a lower incidence in East Asia and South America that could be due to case ascertainment. The strengths and limitations of various research studies were examined, including issues with accuracy of clinical coding and the representativeness of study populations, and proposals were made to help standardise future studies.

The clinical implications of this work support the mortality data presented in Chapter 2, in that IPF is present in countries worldwide, incidence appears to be increasing, and although there is some variation, rates are fairly consistent across countries. Current data suggests incidence is similar to that of conditions such as stomach, liver, testicular and cervical cancers.

This work was published in the European Respiratory Journal with an accompanying editorial in 2015 (187).

Chapter 4 : The association between recent major surgery and the onset of idiopathic pulmonary fibrosis

This chapter explores the theory that recent major surgery may be a risk factor for the development of idiopathic pulmonary fibrosis, using a large primary care database from the United Kingdom.

4.1 – Introduction

4.1.1 – Background

As discussed in Chapter 1, the cause of idiopathic pulmonary fibrosis (IPF) is not known. There have been a number of theories relating to inhalational exposures (often occupational) (33, 227) and there is likely to be a genetic contribution (74, 228), but in many people no obvious cause is identified.

The pathophysiology of IPF can be summarised as repetitive alveolar injury and repair (229). It is known that surgical procedures such as lung biopsy can cause worsening of known IPF (82, 142), presumably by accelerating this process and causing acute exacerbations, and there are also reports of acute exacerbations developing in people with 'sub-clinical' disease that only gets diagnosed post-operatively (230, 231). However, there is no data on whether such surgery is a risk factor for the onset of the disease in susceptible people without disease.

4.1.2 – Rationale for the study

Anecdotal evidence from clinicians has suggested that some people present with IPF following major surgery, with coronary artery bypass grafting and joint replacement being particularly noted. Two reasons why this might be the case include sub-clinical disease being undetected prior to surgery but made manifest as a result of the procedure, and new-onset disease developing as a direct result of the surgery.

The possibility that IPF may be caused by surgery warrants further investigation, as this may shed light on the aetiological triggers for the disease. The hypothesis for this chapter is that there is a higher likelihood of people with IPF having had major surgery in the preceding five years than people without IPF.

4.1.3 – Aims and Objectives

This chapter aims to explore the association between diagnosis of IPF and recent major surgery using primary care data from the United Kingdom. The objectives are to see if any such association exists, and if so, to identify any factors that may explain or contribute to the link.

4.2 – Methods

This was a case-control study using a large longitudinal clinical database. This chapter will describe the dataset, how cases were identified and excluded, and the statistical methods used.

4.2.1 – Source of data

This study used The Health Improvement Network (THIN), an anonymised database of primary care medical records from the United Kingdom. THIN is a partnership between IMS Health (previously Cegedim Strategic Data) and In Practice Systems (INPS), the provider of 'Vision' software used by a proportion of general practices in the UK, and was established in 2002 with the aim of collating anonymous patient data for use in research (232). Data are collected routinely from participating practices, with a full upload of retrospective data added when the practice joins the programme alongside the continual collection of new data.

Data are available in four main files: a 'patient' file with information on demographics, a 'medical' file with details of medical events and consultations, a 'therapy' file with data on prescriptions, and an 'additional health data' file with information about prevention, lifestyle and diagnostics. Records of diagnoses are classified using the Read code system, a widely-used and extensively-detailed coding system employed in UK primary care, and prescriptions are classified using a drug dictionary with codes based on the chapters and subheadings of the British National Formulary prior to its recent re-organisation.

The version of THIN used for this study was from May 2014. As of January 2014, the database contained records from 587 practices with a total of over 12 million patients, 3.6 million of whom were registered at the time (233) – thereby representing around 6% of the UK population. An advantage of using THIN for this research, apart from the large sample size, is the ability to follow a patient's entire clinical pathway and capture all consultations and records,

as a result of the gatekeeper role taken by UK general practitioners. THIN has been shown to be broadly representative of the wider population (234), and has been used previously to study the epidemiology of IPF (23, 24).

Use of THIN for the current study was approved by the THIN Scientific Review Committee (reference number 14-047) in July 2014. A case-control dataset for use in this study was created from the master THIN database by Dr Jack Gibson, Assistant Professor in Epidemiology at the University of Nottingham.

4.2.2 – Case selection

Cases were identified from THIN based on the following five Read codes: H563.00 (idiopathic fibrosing alveolitis), H563.11 (Hamman-Rich syndrome), H563.12 (cryptogenic fibrosing alveolitis); H563100 (diffuse pulmonary fibrosis), and H563z00 (idiopathic fibrosing alveolitis NOS). These codes were used to define the population of patients with IPF-clinical syndrome (IPF-CS) in the 2011 incidence study using THIN by Navaratnam *et al* (24), where it was acknowledged that this classification might include some patients with other idiopathic interstitial pneumonias that were labelled as IPF.

Incident cases of IPF were identified by selecting the first recorded diagnosis of IPF-CS for each patient that occurred at least one year after the start of their electronic record: this date was labelled as the diagnosis date, and ensured that those without adequate records prior to this (and therefore uncertainty as to whether this might be the first or subsequent record of a new diagnosis) were excluded. In the rare situation where a diagnosis was listed after a date of death (for example, due to a post-mortem finding) the date of diagnosis was specified as the date of death.

Any patient without a specified month or day in their date of diagnosis was excluded, and those with a month but no day were pragmatically assigned to the first of the month. Any patient with a date of diagnosis prior to the year 2000 was excluded, as higher coding reliability was expected after this date.

4.2.3 – Control selection

Controls were identified as a 4:1 incidence density sample, matched on age, sex, and GP practice. Each case would therefore have at least one and up to four possible controls. The incidence density sample process selected non-cases at the time of diagnosis, and allowed that a control patient could act as a control for more than one case, and a case that had yet to be diagnosed could act as a control for an earlier case. Controls were assigned the diagnosis date of their matched case.

4.2.4 – Exclusions

All patients with a record for a condition associated with interstitial lung disease other than IPF were excluded, to enhance specificity of the cohort. The full list of Read codes of excluded conditions is listed in Appendix C: in summary these included rheumatoid arthritis, other rheumatological and connective tissue disease, occupational interstitial lung disease such as asbestosis, sarcoidosis, hypersensitivity pneumonitis, and other rare causes of ILD. The list of exclusions was based on that used by Navaratnam *et al* (24) previously, with review for additional codes using the SearchRC Read code search tool developed by Dr Jack Gibson at the University of Nottingham (235).

In addition, all patients with a prescription record for amiodarone, methotrexate or nitrofurantoin were excluded. These drugs are common and established causes of pulmonary fibrosis (10). For simplicity, it was decided not to quantify duration or cumulative dosing of drug use with an arbitrary cut-off period, but to exclude *any* use in the records. Read codes for selection of drugs are listed in Appendix C.

To further enhance specificity of the cohort for IPF, any patient who was diagnosed at age 40 or under was excluded. Patient ages were calculated

using a variable specifying the year of birth with random allocation of month and day when these were not available. Finally, any cases without a matched control were excluded, as were any controls without a case.

4.2.5 – Exposures

Read codes for coronary artery bypass grafting (CABG), hip replacement and knee replacement were selected using the SearchRC Read code search tool described above, with manual review to ensure appropriate selection (see Appendix C). These procedures are common and major surgery, and were proposed by Professor Richard Hubbard based on prior experience in the interstitial lung disease clinic seeing people diagnosed with IPF following these procedures. All records with a code for these operations were identified in THIN. As these were events that would have taken place in hospital, any record that did not appear to refer to the index event were excluded: these included those with a 'source code' suggesting referral to hospital (for example, to contemplate the procedure or due to a complication) rather than a discharge summary, and those with an 'episode code' suggesting continuation rather than a first or new event. Where these codes were not specified the records were retained.

Records were categorized into the three main categories: CABG, hip and knee. Any record with a missing date was excluded, and those with imprecise dates were assumed: those with a missing day were assigned to the 1st of the month, and those with a missing day and month were assigned to January 1st. If there were multiple records for one of the operations, then the first of these only was retained, and any operation subsequent to the diagnosis date was excluded. Finally, only operations within five years of the diagnosis date were considered, as it was felt unlikely that operations before this time would be relevant.

4.2.6 – Confounders

As cases and controls were already matched in terms of age, sex and practice, it was not required to treat these as confounders. A further confounder considered was smoking status, which might reflect risk of IPF and lung function.

Smoking data was obtained using the codes listed in Appendix C: these codes have been used previously to analyse THIN data by researchers in the Division of Epidemiology and Public Health at the University of Nottingham. In view of the complexity of scoring smoking status based on multiple encounters over time and potential temporary quit attempts, any patient with a record for 'current' smoking in the five years prior to diagnosis of IPF was labelled a current smoker, any patient with a record for being an ex-smoker in this period but no record of being a current smoker was labelled an ex-smoker, any patient with a record of being a never smoker with no record of smoking was labelled as such, and any patient without a record for the previous three was labelled as unclear of not specified.

4.2.7 – Statistical analysis

Statistical analysis was performed using Stata, version 14.0 (StataCorp, College Station, Texas, USA). In view of the incidence density sampling process, conditional logistic regression was used to assess differences between cases and controls. Measures of association were odds ratios, although these would estimate rate ratios as a result of the sampling method being based on person-time of exposure.

4.3 – Results

This section will outline the number of cases and controls, basic demographics, the number with an operation within five years prior to their IPF diagnosis, and the results of conditional logistic regression.

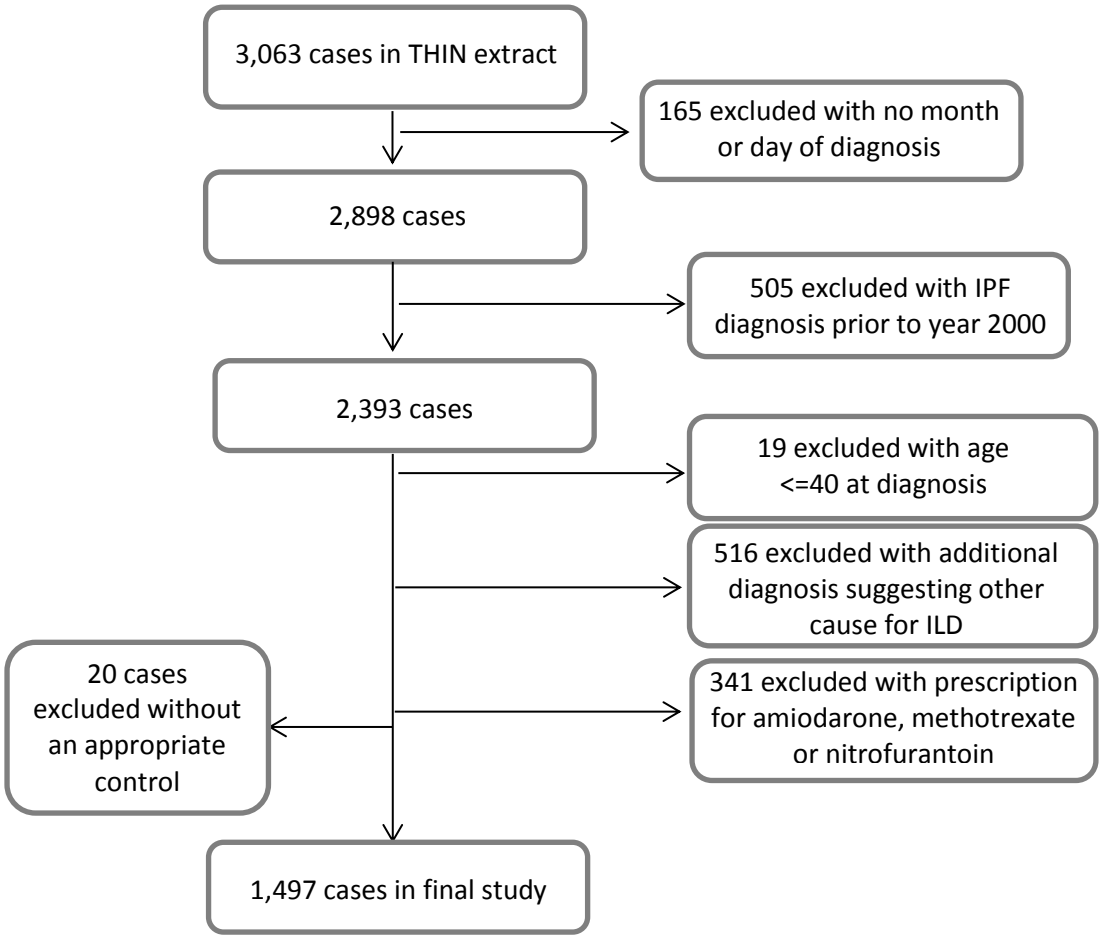
4.3.1 – Cases

The initial database included 3,063 cases. After exclusions, there were 1,497 cases remaining. Case selection is shown as a flow diagram in Figure 4-1. The majority of exclusions were due to diagnoses prior to the year 2000 and additional codes suggesting alternative causes of ILD (other medical conditions or medications).

4.3.2 – Controls

After exclusions, there were 4,411 controls in the dataset. Almost 80% of cases had three or more controls; less than 5% of cases had only a single control.

Figure 4-1: Flow diagram of selection of cases from THIN database



4.3.3 – Demographics of cohort

68% of patients were male, and 83% were aged 65 or over. Almost 20% had a record for current smoking, whereas there was no clear record for 30%. Cases were more likely to be smokers than controls. Further demographics for both cases and controls are shown in Table 4-1.

Table 4-1: Demographics of cases and controls from THIN database

	Cases (n=1,497)	**Controls *(n=4,411)***
	Number (%)	Number (%)
Sex		
Male	995 (66.47)	3,049 (69.12)
Female	502 (33.53)	1,362 (30.88)
Age group (years)		
<45	11 (0.73)	32 (0.73)
45-54	51 (3.41)	155 (3.51)
55-64	174 (11.62)	546 (12.38)
65-74	466 (31.13)	1,380 (31.29)
75-84	588 (39.28)	1,711 (38.79)
>84	207 (13.83)	569 (12.90)
Smoking status		
'Current'	313 (20.91)	801 (18.16)
'Ex'	500 (33.40)	998 (22.63)
'Never'	314 (20.98)	1,194 (27.07)
Unclear or not specified	370 (24.72)	1,418 (32.15)

THIN: The Health Improvement Network
Smoking status reflects any reference within five years prior to diagnosis.

4.3.3 – Presence of surgery during five years before diagnosis

191 patients had one of the major surgical procedures in the five years prior to their diagnosis, with four of these having two procedures. For cases, the proportion with a procedure within the previous five years was 3.1%; for controls this was 3.3%.

In terms of individual procedures, coronary artery bypass grafting was more common for cases (0.9%) than controls (0.6%), whereas for joint replacements, there were a higher proportion of controls undergoing procedures than cases: 1.0% of cases had undergone hip replacement compared to 1.3% of controls, and 1.3% of cases had undergone knee replacement compared to 1.5% of controls.

Using conditional logistic regression, there was no significant increased risk for cases compared to controls (see Table 4-2).

Table 4-2: Proportion of cases and controls undergoing major surgery within 5 years prior to diagnosis of IPF, with odds ratios by conditional logistic regression

Variables	Cases (%)	Controls (%)	Unadjusted OR (95% CI)	p value	Adjusted OR* (95% CI)	p value
Coronary artery bypass grafting within 5 years prior to diagnosis						
No	1,483 (99.4)	4,386 (99.4)	1.00		1.00	
Yes	14 (0.9)	25 (0.6)	1.50 (0.77-2.93)	0.230	1.67 (0.74-3.79)	0.217
Hip replacement within 5 years prior to diagnosis						
No	1,482 (99.0)	4,355 (98.7)	1.00		1.00	
Yes	15 (1.0)	56 (1.3)	0.76 (0.42-1.36)	0.350	0.69 (0.34-1.40)	0.307
Knee replacement within 5 years prior to diagnosis						
No	1,477 (98.7)	4,346 (98.5)	1.00		1.00	
Yes	20 (1.3)	65 (1.5)	0.94 (0.56-1.56)	0.808	0.83 (0.44-1.53)	0.544

* Adjusted for smoking status

4.4 – Discussion

4.4.1 – Summary of findings

This study has shown no association between recent major surgery – coronary artery bypass grafting, hip replacement or knee replacement – and the diagnosis of IPF. Slightly more cases than controls underwent coronary artery bypass grafting in the five years prior to diagnosis, but this was not statistically significant.

4.4.2 – Strengths

The key strength of this study was the use of the THIN database: a large, representative collection of primary care records that allowed identification of a considerable number of cases of IPF and appropriately matched controls. As all residents in the UK must be registered with a general practitioner, anyone undergoing major surgery should expect this information to be communicated between secondary and primary care, and therefore it was possible to compare the presence of an operation with some reliability. It was also possible to refine the definition of cases by excluding a wide variety of terms that might suggest alternative diagnoses.

4.4.3 – Limitations

There are a number of limitations to this study however. Despite the strengths of the THIN dataset, it is not linked directly to secondary care data sources, and therefore estimated operation dates may be imprecise and in some cases were arbitrarily allocated within a specific year. The frequency of repeated references to the same operation was a concern, and although only the first record was selected to ensure follow-ups were not counted, it was not certain how closely this related to the actual operation date, and a linked dataset would be more appropriate to tackle this issue. A consequence of retaining only the first record was that additional surgery, for example a

second hip replacement on the other side or a revision knee replacement, would not be captured, and clearly this could have some impact. It was also not possible to capture specific details about operations such as their duration, which could impact on the occurrence of IPF, in the event that there was a 'dose-dependent' relationship linked to the 'severity' of the surgery.

Although the THIN dataset is fairly comprehensive, it is unlikely to capture all environmental and occupational data that might influence the risk of IPF. While there are Read codes for a considerable number of professions, whether these will be elicited and recorded in a consultation is unclear. As a primary care database, THIN is also unlikely to yield comprehensive data on lung function or imaging findings. Although excluding older diagnoses and additional codes suggesting alternative diagnoses will have increased the specificity of cases, this process reduced the number of cases available, and consequently the power of the study to detect a true effect (potential type II error). There is also the concern that cases of IPF were incorrectly labelled, although the codes used have been supported previously (24). While use of three common drugs that cause pulmonary fibrosis was excluded, other rarer medications may have been in use (including over-the-counter remedies) and these would not have been considered.

From a methodological point of view, the use of incidence density sampling of controls may have resulted in controls developing IPF and becoming cases later in the study, and a prevalent controls design may have been more appropriate. A further concern is the time period under study: it may be that cases with IPF have subclinical disease (for example, asymptomatic interstitial lung abnormalities) for a prolonged period of time prior to formal diagnosis, and a five year period where major surgery might influence onset might be insufficient. However, a longer period would raise the question about whether the surgery could truly be responsible, and there is no clear consensus on how long people have IPF prior to 'diagnosis' and whether this differs between people. Finally, the choice of cardiac surgical operations may have resulted in some confounding: the higher incidence of cardiovascular

disease in people with IPF may mean that this surgery is more likely in these people that others, and the data on joint replacements may therefore be more reliable.

4.4.4 – Interpretation of findings

This data suggests that recent major surgery is not a major risk factor for a new diagnosis of IPF. One possible explanation for the apparent increase in presentations to the respiratory clinic following surgical intervention is enhanced identification of subclinical undiagnosed disease, either during detailed pre-operative assessment or while recovering in the post-operative period. The latter explanation could also see disease made manifest as a result of surgical stresses, as has been shown with acute exacerbations after surgical lung biopsy (142) and following lobectomy for lung cancer (231). These possibilities would be expected to lead to a more timely diagnosis, but no overall change in the rate of diagnosis, and are likely to be at least partially responsible for the timing of some referrals.

Another possibility is that the patient population being diagnosed with IPF – predominantly males in their 60s and 70s, but getting older – is similar to the population undergoing coronary artery bypass grafting and joint replacement. These operations are likely to be offered to patients with poorly-controlled angina and advanced osteoarthritis respectively, both of which are more common in older patients.

A final possibility is that inadequate power prevented detection of an association, particularly for coronary artery bypass grafting where there was the suggestion of an increased rate. Loosening inclusion criteria (making cases more ‘pulmonary fibrosis’ than IPF) might allow re-assessment with an increased number cases, however any increase would be even more likely to be the result of increased detection rather than causation, given the alternative ‘known’ cause for the fibrosis.

4.4.5 – Comparison to the literature

There is no research in the literature currently addressing the question of whether IPF may be caused by surgical procedures. There is a clear suggestion that surgery can worsen pre-existing IPF (including previously undiagnosed disease), mainly as a result of increased exacerbations, and this adds weight to the suggestion that increased detection as a result of surgery is the most likely explanation behind any apparent association.

4.4.6 – Summary of chapter

This chapter has explored the possible association between major surgery and the development of IPF, using a large primary care database from the United Kingdom. In almost 1500 cases with over 4000 matched controls, there was no significant increased incidence of coronary artery bypass grafting, hip replacement or joint replacement in the five year prior to diagnosis in cases compared to controls. This suggests that major surgery is unlikely to cause IPF, although several limitations inherent in this type of study design and the THIN dataset are acknowledged.

While IPF is unlikely to be caused by major surgery, it is possible that surgery may make the disease worse and in some cases precipitate a formal diagnosis. The role of surgery in people with IPF is explored further in the rest of this thesis: Chapters 5 and 6 examine the risks of surgical lung biopsy for diagnosis of ILD, and Chapter 7 considers the impact of major surgery in people with known IPF with a focus on post-operative mortality.

Chapter 5 : Risk of surgical lung biopsy for diagnosing interstitial lung disease in the United States

This chapter examines the use of surgical lung biopsy to diagnose interstitial lung disease, using data from the United States. The frequency of the procedure and associated risks are considered, as well as the implications of these risks for clinicians and patients.

This work was published in the American Journal of Respiratory and Critical Care Medicine in 2016 (236).

5.1 – Introduction

5.1.1 – Background

When a patient presents with characteristic clinical features, a confident diagnosis of idiopathic pulmonary fibrosis (IPF) can be made after demonstrating typical appearances on high resolution computed tomography (HRCT) of the lungs and ensuring alternative causes of interstitial lung disease (ILD) have been excluded (15). However, if imaging is atypical or there is diagnostic concern, then a surgical lung biopsy may be required to confirm the diagnosis.

Achieving histological confirmation of a specific diagnosis via lung biopsy may be crucial to ensure appropriate management and prognostication, as this varies greatly between the various types of ILD. Unfortunately, patients with suspected ILD often have impaired pulmonary function, and as a result the risks of thoracic surgery are an important consideration.

5.1.2 – Rationale for the study

Several detailed case series have explored the morbidity and mortality following surgical lung biopsy for interstitial lung disease, with 30-day mortality varying from 0-24% (104, 131) (see Table 1-8, Section 1.4.4.3). However, it is clear that case series have several limitations: often these involve careful case selection and enthusiastic local expertise, both of which may result in a more optimistic appraisal of the surgical risks. These data are therefore difficult to generalise to the wider population, and there is a need for more representative data to guide clinicians.

5.1.3 – Aims and Objectives

This chapter aims to assess the use of surgical lung biopsy for the diagnosis of interstitial lung disease using a large national secondary care dataset from the United States. The objectives are to estimate how frequently the procedure is

performed, its associated risks (with a focus on post-operative mortality), and the patient factors that impact on this risk.

5.2 – Methods

This was an observational study using a large clinical database. This section outlines the source of the data, selection of the cases to be analysed, descriptions of relevant variables, and the statistical methods used.

5.2.1 – Source of data

The source of data used for this study was the Nationwide Inpatient Sample (NIS), part of the Healthcare Cost and Utilization Project (HCUP), which is sponsored by the Agency for Healthcare Research and Quality (AHRQ) (237). The database comprises anonymised yearly samples of discharges from community hospitals from the United States, where community hospitals are defined (according to the American Hospital Association) as 'all non-Federal, short-term, general and other specialty hospitals, excluding hospital units of institutions'. This definition includes public hospitals and academic medical centres.

The NIS is the largest all-payer publically available inpatient care database available in the US. It is drawn from all states that make their data available to HCUP – this varies from year to year, with a trend for increasing numbers contributing over time. In 2011 this was 46 states, comprising 97% of the US population. Until it was re-designed in 2012, each yearly dataset reported *all* discharges from a sample of 20% of hospitals in the overall 'hospital universe'. In 2011, this provided data from just over 1,000 hospitals and around 8,000,000 hospital stays per year. Subsequent to 2012, the database was rebranded the *National* Inpatient Sample, with 20% of discharges reported from *all* contributing hospitals.

Each yearly dataset uses a complex sampling procedure to ensure adequate representation of hospitals. The hospital universe is divided into strata using five characteristics: bed size, teaching status, urban/rural location, US region, and ownership/control. The dataset then uses a stratified probability sample

depending on the number of hospitals in each stratum. To enable calculation of national estimates from the sample, discharge weights are provided for each hospital.

Each record in the NIS represents a discharge from hospital and reports on the inpatient stay, with details of diagnoses and procedures coded based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Details are available on age and sex of the patients, their admission and discharge dates (and consequently length of stay), and their disposition (for example, discharge home, transfer to another facility, or died). To preserve confidentiality, there are no unique patient identifiers, and therefore record linkage is not possible.

Data from 2000-2011 were used for this study. 2011 was the latest year available at the time of requesting data. Years prior to 1998 comprised a different sampling and weighting process, and earlier years had fewer states contributing to the project. The year 2000 saw the addition of four new states including one of the largest, Texas, and represented a sensible compromise start year, balancing the additional numbers from older data with potential for outdated clinical practice.

The large sample size of the NIS makes it useful for rare conditions and uncommon procedures, hence its suitability for the current study. Several studies have used the NIS previously for other conditions (238-241). No specific ethical approval is required to use the datasets, but users must sign a data-use agreement and complete an online training module. Further information on the database is available from HCUP online (237).

5.2.2 – Case selection

All records with a diagnostic code for interstitial lung disease were identified using the following ICD-9-CM codes: 515 (post-inflammatory pulmonary fibrosis), 516.3 (idiopathic fibrosing alveolitis), 517.2 (lung involvement in systemic sclerosis), 714.81 (rheumatoid lung), 517.8 (lung involvement in

diseases classified elsewhere), 495 (extrinsic allergic alveolitis), 500-505 (pneumoconioses, including asbestosis) and 135 (sarcoidosis). Disease synonyms for these codes are listed in Table 1-4, Chapter 1.

Records featuring a surgical lung biopsy were then identified using the following ICD-9-CM procedural codes: 33.28 (open biopsy of lung), 32.29 (other local excision or destruction of lesion or tissue of lung), 33.20 (thoracoscopic lung biopsy) and 32.20 (thoracoscopic excision of lesion or tissue of lung). The latter two thoracoscopic codes were introduced in October 2007: prior to this, code 33.28 was used for all lung 'biopsies', and code 32.29 for all 'excisions'. The 'biopsy' codes (33.28 and 33.20) were considered more reliable and potentially more accurate than the 'excision' codes, and therefore a sensitivity analysis was planned using these alone. The decision to code an operation as either a biopsy or excision would be determined by clinical coders based on documentation by the operating surgeon.

5.2.3 – Exclusion criteria

All records with a code specifying a lung resection (segmental resection, lobectomy or pneumonectomy) that implied a therapeutic rather than diagnostic procedure were excluded. Also excluded were records with a diagnostic code for lung cancer, to ensure that diagnostic procedures to investigate malignancy were not included. Relevant codes are listed in Appendix D. Finally, any records without an indicator of patient sex were excluded.

5.2.4 – Outcome variables

An estimate of the number of procedures performed nationwide was derived using weighted data. Both unweighted and weighted data were used to assess the demographics of patients undergoing lung biopsies: the

unweighted data being easier to understand but without an appreciation of the sampling process, and the weighted data more technically accurate but necessarily given as a range with 95% confidence intervals.

The primary outcome measure was in-hospital mortality. This was derived from the NIS variable 'DIED', which indicated whether the patient died in hospital. The nature of the database meant that it was not possible to estimate 30-day or 90-day mortality figures.

Additional outcomes were length of stay and the number (and nature) of complications post-operatively. Complications were derived from additional diagnostic codes and therefore only assessed for elective procedures to exclude problems occurring prior to unplanned inpatient surgery. Complications assessed were limited to those clearly reflecting acute post-operative problems: some codes were unambiguous, such as post-operative stroke, whereas others may have represented chronic problems, such as atrial fibrillation, and these were therefore not assessed. Complications studied are listed in Appendix D.

5.2.5 – Exposure and confounding variables

Key demographics were the sex and age of the patient. Age was categorised into six groups: less than 45 years, 45-54 years, 55-64 years, 65-74 years, 75-84 years, and older than 84 years. The year of the biopsy was recorded, and records were grouped into four time periods, 2000-2002, 2003-2005, 2006-2008 and 2009-2011. Records were also grouped by US geographical (census) region: Northeast, Midwest, South and West, based on the state coded in the discharge record.

Admissions were coded as elective or non-elective, with a key focus on elective (scheduled) procedures, which would be most useful to clinicians planning a biopsy in the outpatient setting. Non-elective (urgent or emergency) cases were assessed separately. This information was derived from the NIS variable 'ELECTIVE', which was in turn derived from an

'admission type' variable ('ATYPE'). Elective admissions were those with admission type code 3 ('elective') and non-elective admissions were those with admission type codes 1 (emergency) or 2 (urgent). If the admission type was missing or invalid, then the elective/non-elective code was also missing or invalid. For data from California, there was no 'admission type' variable; records were allocated as 'elective' or 'non-elective' based on whether an admission was 'scheduled' or 'unscheduled' respectively.

Co-morbidities were assessed using the updated Charlson score proposed by Quan *et al* (242), a modified version of the widely used Charlson co-morbidity index (243). The updated score takes account of advances in disease management since the original score was published almost 30 years ago, giving extra weight to conditions such as dementia and heart failure, and less weight to conditions such as myocardial infarction and peptic ulcer disease that are more treatable with less impact on mortality. An outline of the updated Charlson score, and comparison with the original score, is shown in Table 5-1.

Table 5-1: Composition of the updated Charlson score, with comparison to the original score

Co-morbidity	Updated Charlson score weighting	Original Charlson score weighting
Myocardial infarction	*0*	*1*
Peripheral vascular disease	*0*	*1*
Cerebrovascular disease	*0*	*1*
Peptic ulcer disease	*0*	*1*
Diabetes without chronic complications	*0*	*1*
Chronic pulmonary disease	1	1
Rheumatological disease	1	1
Renal disease	1	2
Diabetes with chronic complications	1	2
Congestive cardiac failure	2	1
Dementia	2	1
Mild liver disease *	2	1
Hemiplegia or paraplegia	2	2
Any malignancy † (including leukaemia and lymphoma)	2	2
Moderate or severe liver disease *	4	3
AIDS/HIV	4	6
Metastatic solid tumour †	6	6

*Patients can score for either 'mild liver disease' or 'moderate to severe liver disease'
†Patients can score for either 'any malignancy' or 'metastatic solid tumour'

Modified from Quan H *et al*. Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data from 6 Countries. Am J Epidemiol 2011; 173: 676-682, by permission of Oxford University Press. Oxford University Press controls this copyright on behalf of The John Hopkins Bloomberg School of Public Health. See original article for justification of weightings.

For explanation of what conditions are included under each co-morbidity category, see Quan H *et al*. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care* 2005; 43: 1130-1139.

Co-morbidities were scored based on additional diagnoses coded in the discharge record, with allocation based on published guidance (244). For example, the presence of one of the ICD-9-CM codes 196-199 meant a positive score for the category of metastatic cancer. In the rare circumstance where there was disagreement between the codes used or not used for a certain category, the views of two additional clinicians (Professor Richard Hubbard and Dr Andrew Fogarty) were taken into account, and slight modifications were made as outlined in Table 5-2. An updated Charlson score for each patient (record) was calculated based on the presence of positive indicators for each of the constituent diagnoses.

Table 5-2: Modifications to matching process of ICD-9-CM codes and co-morbidity categories

Co-morbidity	Modifications to matching process
Chronic pulmonary disease	Cor pulmonale (415.0, 416.8, 416.9) included. Bronchitis – not specified acute or chronic (490) excluded.
Rheumatological disease	Polyarteritis nodosa (446.0) and Granulomatosis with polyangiitis (Wegener's) (446.4) included.
Dementia	Alzheimer's disease (331.0), Frontotemporal dementia (331.1), Dementia with Lewy bodies (331.82) included.
Liver disease	Viral hepatitis *with hepatic coma* (070.22, 070.23, 070.44, 070.6) classified as 'moderate-to-severe' liver disease rather than 'mild' liver disease.
Malignancy	Malignant carcinoid (209.0) included.

For full explanation of what conditions are included under each co-morbidity category, see Quan H *et al*. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care* 2005; 43: 1130-1139.

Operations were classified as either video-assisted thoracoscopic surgery ('VATS') or open surgery ('open') for the later years (Oct 2007 onwards) where this information was available. As the specific ILD diagnosis in the discharge record might not be the final pathological diagnosis, this was presumed to be the working or provisional diagnosis. In most cases this was a direct reflection of the ILD code specified in the record, for example, the subdivisions of code 495 (extrinsic allergic alveolitis) were labelled as hypersensitivity pneumonitis, the current preferred term. ICD-9-CM code 516.3 was most specific for idiopathic pulmonary fibrosis (IPF), but in October 2011 (the end of the study) this code was subdivided to include other idiopathic interstitial pneumonia, and therefore these records were labelled as 'idiopathic pulmonary fibrosis clinical syndrome' (IPF-CS) (24). Any record with a code for sarcoidosis alongside a code for 'lung involvement in diseases classified elsewhere' was coded as sarcoidosis. Records with isolated codes 517.2, 714.81 and 517.8 were grouped together as connective tissue disease related ILD (CTD-ILD). For clarity, records with multiple ILD diagnosis (except for sarcoidosis, as mentioned above) were not given a provisional diagnosis and not included in analyses involving this variable.

5.2.6 – Statistical analysis

Statistical analysis was performed using Stata, version 13.1 (StataCorp, College Station, Texas, USA). To account for the complex stratified sample design, estimates were calculated using the specialized survey commands, taking account of year and strata, and using weights to create national estimates (245). Logistic regression was used to identify risk factors for in-hospital mortality, adjusting for sex, age, co-morbidity, geographical (census) region, year group, type of operation (VATS or open), and provisional diagnosis. For the multivariable logistic regression, type of operation was excluded as a result of the lower numbers providing data.

5.3 – Results

This section will describe the selection process for the records included in the study, followed by basic demographics such as the age and sex distribution of records. Demographics will be presented for records involving both elective and non-elective procedures, as well as for the 'biopsy' and 'excision' cohorts (records featuring one or the other of these two categories of procedure codes). The in-hospital mortality and other outcomes will then be described, according to whether the procedure was elective or non-elective, and with additional details for the 'biopsy' codes specifically. A combination of unweighted and weighted data will be presented: unweighted data reflecting the 'raw' data from the NIS, and weighted data a more 'accurate' estimate accounting for the sampling process.

5.3.1 – Cohort selection

A flow diagram of cohort selection is shown in Figure 5-1. There were 871,401 discharge records in the NIS with a diagnostic code for interstitial lung disease between 2000 and 2011, and 34,530 of these had a procedure code for surgical lung biopsy. Just over half of these used an 'excision' code, with just under half using a 'biopsy' code – a small minority used both codes. The number of records of interstitial lung disease with a code for surgical lung biopsy each year is shown in Table 5-3, alongside total available records, contributing states and hospitals included in the NIS.

353 records were excluded due to the presence of codes for lung resection, 2,104 additional records were excluded due to codes for lung cancer, and 51 were further excluded due to no indicator of the sex of the patient. This resulted in 32,022 records included in the final study.

Figure 5-1: Flow diagram of selection process for records with a surgical lung biopsy for interstitial lung disease in USA

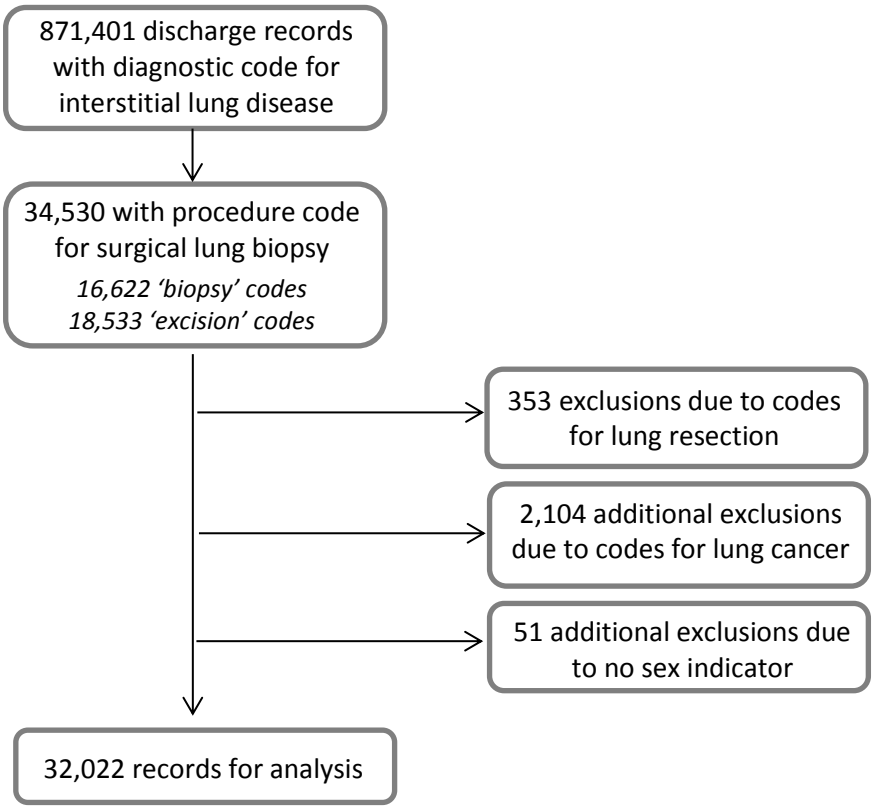


Table 5-3: Details of records available for each year sample from NIS

Year	Total records	Total states	Total hospitals	Records with ILD	Records with ILD & SLB
2000	7,450,992	28	994	57,186	2,499
2001	7,452,727	33	986	57,539	2,844
2002	7,853,982	35	995	65,534	3,105
2003	7,977,728	37	994	69,247	2,975
2004	8,004,571	37	1,004	68,317	2,843
2005	7,995,048	37	1,054	74,218	2,968
2006	8,074,825	38	1,045	77,565	3,011
2007	8,043,415	40	1,044	76,356	2,870
2008	8,158,381	42	1,056	78,144	2,853
2009	7,810,762	44	1,050	79,581	2,883
2010	7,800,441	45	1,051	79,276	2,742
2011	8,023,590	46	1,049	88,438	2,937
Total	*94,646,462*	*n/a*	*n/a*	*871,401*	*34,530*

NIS: Nationwide Inpatient Sample
ILD: interstitial lung disease; SLB: surgical lung biopsy

5.3.2 – Demographics of cohort

Basic demographics of the cohort (sex, age, and level of co-morbidity) are shown in Table 5-4 (unweighted data) and Table 5-5 (weighted data). 66.3% of admissions were for elective procedures, 32.2% were for non-elective procedures, and for 1.5% the urgency of the operation was not clear. 48% of total records were male, with 61% below age 65. The non-elective group had a slightly higher proportion of older patients (75+) and those with increasing co-morbidity (updated Charlson score 1 or higher).

Details of demographics for the 'biopsy' cohort are presented in Table 5-6 (unweighted data) and Table 5-7 (weighted data); details for the 'excision' cohort are presented in Table 5-8 (unweighted data) and Table 5-9 (weighted data). Demographics were similar, although a higher proportion of the 'biopsy' cohort was non-elective admissions.

In terms of geographical distribution, biopsies were less commonly performed in the West census region (see Table 5-10). The most commonly coded provisional diagnosis (excluding cases with more than one type of ILD coded) was post-inflammatory fibrosis (PIF, ICD-9-CM 515, 80% of cohort) followed by idiopathic pulmonary fibrosis clinical syndrome (IPF-CS, ICD-9-CM 516.3, 9.3% of cohort) and sarcoidosis (5.4% of cohort). 8.3% of records had codes for more than one type of ILD (excluded from the multivariable analysis).

Table 5-4: Demographics of NIS cohort (unweighted data)

	Total admissions ***(n=32,022)***	**Elective admissions** ***(n=21,227)***	**Non-elective admissions** ***(n=10,310)***
	Number (%)	Number (%)	Number (%)
Sex			
Male	15,351 (47.94)	9,942 (46.84)	5,163 (50.08)
Female	16,671 (52.06)	11,285 (53.16)	5,147 (49.92)
Age group (years)			
<45	5,192 (16.21)	3,153 (14.85)	1,958 (18.99)
45-54	6,264 (19.56)	4,229 (19.92)	1,944 (18.86)
55-64	8,093 (25.27)	5,643(26.58)	2,331 (22.61)
65-74	8,147 (25.44)	5,623 (26.58)	2,406 (23.34)
75-84	4,037 (12.61)	2,431 (11.45)	1,535 (14.89)
>84	289 (0.90)	148 (0.70)	136 (1.32)
Level of co-morbidity (Updated Charlson score)			
0	13,908 (43.43)	10,627 (50.06)	3,030 (29.39)
1	10,844 (33.86)	7,158 (33.72)	3,558 (34.51)
2	3,304 (10.32)	1,728 (8.14)	1,523 (14.77)
3 or greater	3,966 (12.39)	1,714 (8.07)	2,199 (21.33)

NIS: Nationwide Inpatient Sample

Higher Updated Charlson score = greater co-morbidity.

Table 5-5: Demographics of NIS cohort (weighted data)

		Total admissions		Elective admissions		Non-elective admissions	
		Number (95% CI)	Percent (95% CI)	Number (95% CI)	Percent (95% CI)	Number (95% CI)	Percent (95% CI)
Total cohort		151,857 (147,283-156,430)	-	79,068 (76,533-81,602)	-	72,789 (70,424-75,154)	-
Sex	Male	72,789 (70,423-75,154)	47.9 (47.4-48.5)	47,147 (45,283-49,010)	46.8 (46.1-47.5)	24,497 (23,540-25,454)	50.1 (49.1-51.1)
	Female	79,068 (76,533-81,602)	52.1 (51.5-52.6)	53,552 (51,481-55,622)	53.2 (52.5-53.9)	24,388 (23,406-25,370)	49.9 (48.9-50.9)
Age group (years)	<45	24,638 (23,649-25,628)	16.2 (15.8-16.7)	14,985 (14,226-15,745)	14.9 (14.4-15.4)	9,267 (8,746-9,787)	19.0 (18.1-19.8)
	45-54	29,711 (28,587-30,835)	19.6 (19.1-20.0)	20,073 (19,161-20,985)	19.9 (19.4-20.5)	9,218 (8,702-9,734)	18.9 (18.1-19.7)
	55-64	38,288 (36,899-39,676)	25.2 (24.7-25.7)	26,680 (25,539-27,822)	26.5 (25.9-27.1)	11,045 (10,490-11,600)	22.6 (21.8-23.4)
	65-74	38,657 (37,245-40,070)	25.5 (25.0-26.0	26,702 (25,537-27,867)	26.5 (25.9-27.1)	11,408 (10,840-11,976)	23.3 (22.5-24.2)
	75-84	19,183 (18,339-20,028)	12.6 (12.2-13.0)	11,547 (10,919-12,175)	11.5 (11.0-11.9)	7,300 (6,875-7,726)	14.9 (14.2-15.7)
	>84	1,378 (1,213-1,544)	0.9 (0.8-1.0)	711 (594-828)	0.7 (0.6-0.8)	647 (537-757)	1.3 (1.1-1.6)
Level of co-morbidity (Updated Charlson score)	0	65,903 (63,660-68,146)	43.4 (42.8-44.0)	50,389 (48,395-52,384)	50.0 (49.3-50.8)	14,330 (13,613-15,047)	29.3 (28.3-30.3)
	1	51,430 (49,701-53,159)	33.9 (33.3-34.4)	33,949 (32,573-35,384)	33.7 (33.0-34.4)	16,885 (16,161-17,608)	34.5 (33.6-35.5)
	2	15,706 (14,983-16,430)	10.3 (10.0-10.7)	8,222 (7,720-8,724)	8.2 (7.8-8.6)	7,238 (6,812-7,664)	14.8 (14.1-15.5)
	3 or greater	18,817 (17,952-19,682)	12.4 (12.0-12.8)	8,139 (7,561-8,717)	8.1 (7.6-8.6)	10,432 (9,880-10,985)	21.3 (20.5-22.2)

NIS: Nationwide Inpatient Sample. 95% CI: 95% confidence intervals. Higher Updated Charlson score = greater co-morbidity. Numbers rounded to nearest integer.

Table 5-6: Demographics of NIS 'biopsy' cohort (unweighted data)

	Total admissions ***(n=15,265)***	**Elective admissions** ***(n=9,049)***	**Non-elective admissions** ***(n=5,903)***
	Number (%)	Number (%)	Number (%)
Sex			
Male	7,302 (47.83)	4,291 (47.42)	2,858 (48.42)
Female	7,963 (52.17)	4,758 (52.58)	3,045 (51.58)
Age group (years)			
<45	2,473 (16.20)	1,376 (15.21)	1,041 (17.64)
45-54	2,858 (18.72)	1,723 (19.04)	1,077 (18.24)
55-64	3,858 (25.27)	2,421 (26.75)	1,365 (23.12)
65-74	3,902 (25.56)	2,394 (26.46)	1,434 (24.29)
75-84	2,053 (13.45)	1,085 (11.99)	920 (15.59)
>84	121 (0.79)	50 (0.55)	66 (1.11)
Level of co-morbidity (Updated Charlson score)			
0	6,489 (42.51)	4,547 (50.25)	1,784 (30.22)
1	4,924 (32.26)	3,039 (33.58)	1,805 (30.58)
2	1,776 (11.63)	782 (8.64)	955 (16.18)
3 or greater	2,076 (13.60)	681 (7.53)	1,359 (23.02)

NIS: Nationwide Inpatient Sample.
Excludes those with any code for 'excision' procedure.
Higher Updated Charlson score = greater co-morbidity.
'Biopsy' codes: ICD-9-CM procedure codes for 'open biopsy of lung' (33.28) or 'thoracoscopic lung biopsy' (33.20; introduced October 2007).
'Excision' codes: ICD-9-CM procedure codes for 'other local excision or destruction of tissue of lung' (32.29) or 'thoracoscopic excision of lesion or tissue of lung' (32.20; introduced October 2007).

Table 5-7: Demographics of NIS 'biopsy' cohort (weighted data)

		Total admissions		Elective admissions		Non-elective admissions	
		Number (95% CI)	Percent (95% CI)	Number (95% CI)	Percent (95% CI)	Number (95% CI)	Percent (95% CI)
Total cohort		74,703 (72,287-77,119)	-	44,510 (42,726-46,295)	-	28,685 (27,571-29,798)	-
Sex	Male	35,793 (34,476-37,110)	47.9 (47.1-48.7)	21,145 (20,162-22,128)	47.5 (46.4-48.6)	13,917 (13,272-14,561)	48.5 (47.3-49.8)
	Female	38,910 (37,513-40,307)	52.1 (51.3-52.9)	23,365 (22,320-24,411)	52.5 (51.4-53.6)	14,768 (14,090-15,446)	51.5 (50.2-52.7)
Age group (years)	<45	12,135 (11,537-12,733)	16.2 (15.6-16.9)	6,781 (6,353-7,210)	15.2 (14.5-16.0)	5,086 (4,726-5,445)	17.7 (16.7-18.8)
	45-54	14,007 (13,365-14,649)	18.8 (18.1-19.4)	8,510 (8,027-8,994)	19.1 (18.3-19.9)	5,222 (4,861-5,583)	18.2 (17.2-19.2)
	55-64	18,871 (18,069-19,674)	25.3 (24.6-25.9)	11,882 (11,261-12,502)	26.7 (25.8-27.6)	6,632 (6,232-7,033)	23.1 (22.1-24.2)
	65-74	19,028 (18,191-19,864)	25.5 (24.8-26.2)	11,724 (11,084-12,364)	26.3 (25.4-27.3)	6,948 (6,530-7,366)	24.2 (23.1-25.4)
	75-84	10,082 (9,539-10,625)	13.5 (12.9-14.1)	5,371 (4,987-5,754)	12.1 (11.4-12.8)	4,479 (4,157-4,801)	15.6 (14.7-16.6)
	>84	581 (476-686)	0.8 (0.6-0.9)	242 (175-309)	0.5 (0.4-0.7)	318 (240-395)	1.1 (0.9-1.4)
Level of co-morbidity (Updated Charlson score)	0	31,544 (30,323-32,765)	42.2 (41.4-43.1)	22,196 (21,171-23,222)	49.9 (48.8-50.9)	8,583 (8,094-9,073)	29.9 (28.7-31.2)
	1	24,269 (23,304-25,235)	32.5 (31.8-33.2)	15,052 (14,309-15,795)	33.8 (32.9-34.8)	8,838 (8,368-9,309)	30.8 (29.7-32.0)
	2	8,680 (8,210-9,150)	11.6 (11.1-12.1)	3,809 (3,511-4,108)	8.6 (8.0-9.2)	4,681 (4,356-5,006)	16.3 (15.4-17.3)
	3 or greater	10,209 (9,682-10,736)	13.7 (13.1-14.3)	3,453 (3,168-3,737)	7.8 (7.2-8.4)	6,582 (6,176-6,988)	22.9 (21.9-24.1)

Higher Updated Charlson score = greater co-morbidity. 95% CI: 95% confidence intervals. Numbers rounded to nearest integer. Further notes – see below Table 5-6

Table 5-8: Demographics of NIS 'excision' cohort (unweighted data)

	Total admissions ***(n=16,216)***	**Elective admissions** ***(n=11,799)***	**Non-elective admissions** ***(n=4,253)***
	Number (%)	Number (%)	Number (%)
Sex			
Male	7,780 (47.98)	5,464 (46.31)	2,227 (52.36)
Female	8,436 (52.02)	6,335 (53.69)	2,026 (47.64)
Age group (years)			
<45	2,631 (16.22)	1,726 (14.63)	880 (20.69)
45-54	3,295 (20.32)	2,426 (20.56)	838 (19.70)
55-64	4,087 (25.20)	3,112 (26.38)	931 (21.89)
65-74	4,122 (25.42)	3,141 (26.62)	939 (22.08)
75-84	1,914 (11.80)	1,296 (10.98)	596 (14.01)
>84	167 (1.03)	98 (0.83)	69 (1.62)
Level of co-morbidity (Updated Charlson score)			
0	7,230 (44.59)	5,925 (50.22)	1,214 (28.54)
1	5,704 (35.18)	3,968 (33.63)	1,690 (39.74)
2	1,469 (9.06)	922 (7.81)	535 (12.58)
3 or greater	1,813 (11.18)	984 (8.34)	814 (19.14)

NIS: Nationwide Inpatient Sample.
Excludes those with any code for 'biopsy' procedure.
Higher Updated Charlson score = greater co-morbidity.
'Biopsy' codes: ICD-9-CM procedure codes for 'open biopsy of lung' (33.28) or 'thoracoscopic lung biopsy' (33.20; introduced October 2007).
'Excision' codes: ICD-9-CM procedure codes for 'other local excision or destruction of tissue of lung' (32.29) or 'thoracoscopic excision of lesion or tissue of lung' (32.20; introduced October 2007).

Table 5-9: Demographics of NIS 'excision' cohort (weighted data)

		Total admissions		Elective admissions		Non-elective admissions	
		Number (95% CI)	Percent (95% CI)	Number (95% CI)	Percent (95% CI)	Number (95% CI)	Percent (95% CI)
Total cohort		79,697 (76,443-82,952)	-	57,965 (55,215-60,715)	-	20,931 (19,939-21,923)	-
Sex	Male	38,264 (36,586-39,942)	48.0 (47.2-48.8)	26,883 (25,501-28,265)	46.4 (45.5-47.3)	10,950 (10,355-11,546)	52.3 (50.8-53.9)
	Female	41,433 (39,631-43,236)	52.0 (51.2-52.8)	31,082 (29,528-32,636)	53.6 (52.7-54.5)	9,981 (9,392-10,569)	47.7 (46.1-49.2)
Age group (years)	<45	12,919 (12,225-13,614)	16.2 (15.6-16.8)	8,444 (7,882-9,005)	14.6 (13.9-15.3)	4,356 (4,019-4,693)	20.8 (19.6-22.1)
	45-54	16,215 (15,384-17,046)	20.3 (19.7-21.0)	11,934 (11,229-12,639)	20.6 (19.8-21.4)	4,127 (3,796-4,458)	19.7 (18.5-21.0)
	55-64	20,116 (19,131-21,102)	25.2 (24.6-25.9)	15,316 (14,467-16,165)	26.4 (25.7-27.2)	4,581 (4,243-4,919)	21.9 (20.7-23.1)
	65-74	20,215 (19,205-21,224)	25.4 (24.7-26.1)	15,394 (14,519-16,270)	26.6 (25.8-27.4)	4,619 (4,280-4,958)	22.1 (20.8-23.4)
	75-84	9,431 (8,851-10,011)	11.8 (11.3-12.4)	6,409 (5,942-6,875)	11.1 (10.5-11.7)	2,914 (2,660-3,169)	13.9 (12.9-15.0)
	>84	802 (676-928)	1.0 (0.9-1.2)	469 (372-566)	0.8 (0.7-1.0)	333 (255-411)	1.6 (1.3-2.0)
Level of co-morbidity (Updated Charlson score)	0	35,237 (33,626-36,849)	44.2 (43.3-45.1)	28,916 (27,435-30,397)	49.9 (48.9-50.9)	5,893 (5,467-6,320)	28.2 (26.7-29.6)
	1	28,181 (26,948-29,414)	35.4 (34.5-36.2)	19,611 (18,596-20,626)	33.8 (32.9-34.8)	8,344 (7,859-8,828)	39.9 (38.3-41.4)
	2	7,309 (6,807-7,810)	9.2 (8.7-9.7)	4,526 (4,148-4,904)	7.8 (7.3-8.3)	2,716 (2,460-2,973)	13.0 (12.0-14.1)
	3 or greater	8,970 (8,344-9,596)	11.3 (10.7-11.8)	4,912 (4,433-5,391)	8.5 (7.9-9.1)	3,977 (3,640-4,314)	19.0 (17.7-20.3)

Higher Updated Charlson score = greater co-morbidity. 95% CI: 95% confidence intervals. Numbers rounded to nearest integer. Further notes – see below Table 5-8

Table 5-10: Estimated total number of lung biopsies per region, 2000-2011 (weighted data)

Region (person-years)	Total admissions		Elective admissions		Non-elective admissions	
	Number of records (95% CI)	Biopsies per 100,000 population per year (95% CI)	Number of records (95% CI)	Biopsies per 100,000 population per year (95% CI)	Number of records (95% CI)	Biopsies per 100,000 population per year (95% CI)
Midwest (791,106,362)	38,504 (36,310-40,699)	4.87 (4.82-4.92)	26,824 (25,042-28,606)	3.39 (3.35-3.43)	11,506 (10,693-12,319)	1.45 (1.43-1.48)
Northeast (656,063,179)	32,835 (30,286-35,384)	5.00 (4.95-5.06)	22,108 (20,020-24,197)	3.37 (3.33-3.41)	10,702 (9,948-11,456)	1.63 (1.60-1.66)
South (1,198,517,748)	54,197 (51,614-56,780)	4.52 (4.48-4.56)	35,345 (33,329-37,361)	2.95 (2.92-2.98)	18,803 (17,688-19,917)	1.57 (1.55-1.59)
West (820,412,146)	26,321 (24,603-28,039)	3.21 (3.17-3.25)	16,421 (15,037-17,805)	2.00 (1.97-2.03)	7,874 (7,285-8,463)	0.96 (0.94-0.98)

95% CI: 95% Confidence Intervals.

Person-years: Cumulative annual population estimates, US Census Bureau, Population Division, accessed Oct 2015 from http://www.census.gov/popest/data/historical/index.html.

5.3.3 – Number of biopsies over time

Using weighted data, there were around 12,000 surgical lung biopsies performed for ILD each year in the United States (see Table 5-11). Numbers were relatively stable over time (see Figure 5-2) although the use of 'biopsy' codes decreased, and 'excision' codes became more prevalent (see Table 5-12, Table 5-13). The estimated number of biopsies for a suspected diagnosis of IPF-CS dropped noticeably around 2003 (Figure 5-3).

Table 5-11: Estimated number of biopsies performed in USA nationwide (weighted data)

Year of biopsy	Total admissions Number (95% CI)	Elective admissions Number (95% CI)	Non-elective admissions Number (95% CI)
2000	10,889 (9,859-11,919)	6,292 (5,523-7,061)	3,568 (3,114-4,021)
2001	12,843 (11,537-14,148)	7,868 (6,870-8,867)	3,916 (3,424-4,407)
2002	13,324 (11,962-14,686)	9,151 (8,048-10,254)	4,163 (3,682-4,644)
2003	12,750 (11,522-13,979)	8,397 (7,394-9,400)	4,335 (3,879-4,792)
2004	12,433 (11,202-13,663)	8,450 (7,489-9,411)	3,973 (3,536-4,409)
2005	13,259 (11,914-14,603)	8,872 (7,801-9,934)	4,370 (3,846-4,894)
2006	13,367 (11,984-14,750)	8,898 (7,778-10,017)	4,455 (3,980-4,930)
2007	12,877 (11,352-14,402)	8,739 (7,450-10,028)	4,104 (3,636-4,571)
2008	12,404 (11,141-13,668)	8,526 (7,519-9,533)	3,860 (3,358-4,362)
2009	12,932 (11,564-14,300)	8,495 (7,432-9,558)	4,433 (3,842-5,023)
2010	12,278 (10,908-13,648)	8,380 (7,237-9,523)	3,893 (3,412-4,374)
2011	12,502 (11,108-13,896)	8,631 (7,483-9,779)	3,817 (3,371-4,262)
Total	*151,857 (147,283-156,430)*	*100,698 (97,024-104,373)*	*48,885 (47,207-50,563)*

95% CI: 95% confidence intervals. Numbers rounded to nearest integer.

Figure 5-2: Estimated number of surgical lung biopsies performed in USA nationwide for ILD

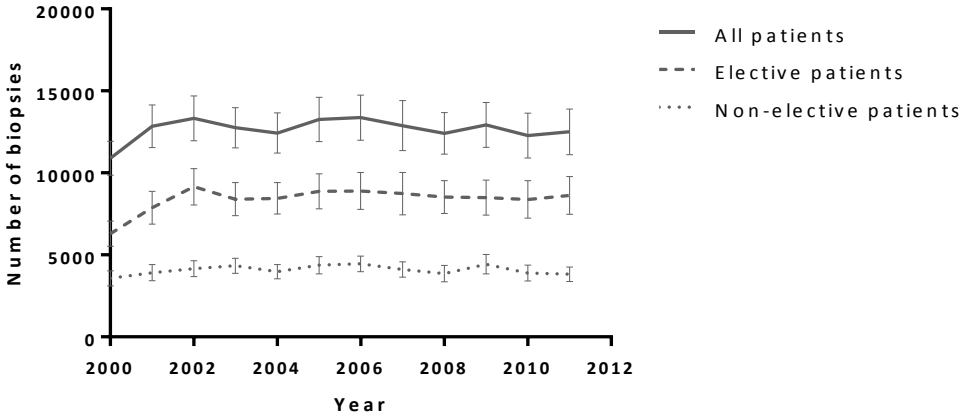


Table 5-12: Estimated number of biopsies performed in USA nationwide ('biopsy' codes only, weighted data)

Year of biopsy	Total admissions Number (95% CI)	Elective admissions Number (95% CI)	Non-elective admissions Number (95% CI)
2000	5,992 (5,347-6,636)	3,105 (2,655-3,556)	2,253 (1,942-2,565)
2001	7,269 (6,480-8,057)	3,987 (3,412-4,563)	2,560 (2,205-2,914)
2002	7,221 (6,488-7,953)	4,517 (3,955-5,080)	2,694 (2,358-3,029)
2003	7,255 (6,483-8,028)	4,371 (3,763-4,979)	2,870 (2562-3,179)
2004	6,747 (6,005-7,490)	4,211 (3,658-4,765)	2,530 (2,222-2,839)
2005	7,220 (6,412-8,028)	4,464 (3,860-5,069)	2,747 (2,376-3,117)
2006	7,050 (6,263-7,836)	4,315 (3,710-4,919)	2,721 (2,377-3,064)
2007	6,306 (5,602-7,009)	3,811 (3,307-4,315)	2,475 (2,132-2,818)
2008	4,376 (3,846-4,906)	2,600 (2,227-2,974)	1,771 (1,504-2,038)
2009	4,661 (4,094-5,228)	2,687 (2,297-3,076)	1,970 (1,675-2,264)
2010	4,208 (3,678-4,738)	2,386 (2,027-2,745)	1,822 (1,518-2,125)
2011	3,855 (3,359-4,350)	2,277 (1,926-2,628)	1,541 (1,303-1,780)
Total	74,703 (72,287-77,119)	44,510 (42,726-46,295)	28,685 (27,571-29,798)

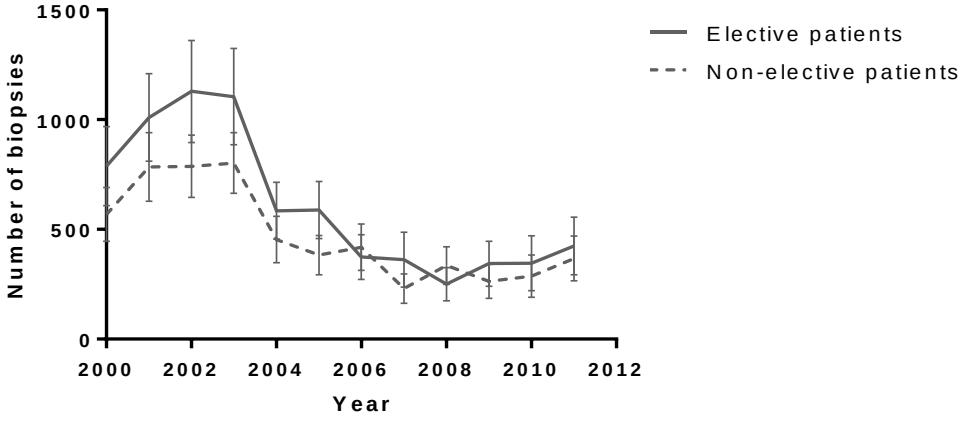
95% CI: 95% confidence intervals. Numbers rounded to nearest integer.
Excludes those with any code for 'excision' procedure.
'Biopsy' codes: ICD-9-CM procedure codes for 'open biopsy of lung' (33.28) or 'thoracoscopic lung biopsy' (33.20; introduced October 2007).
'Excision' codes: ICD-9-CM procedure codes for 'other local excision or destruction of tissue of lung' (32.29) or 'thoracoscopic excision of lesion or tissue of lung' (32.20; introduced October 2007).

Table 5-13: Estimated number of biopsies performed in USA nationwide ('excision' codes only, weighted data)

Year of biopsy	Total admissions	Elective admissions	Non-elective admissions
	Number (95% CI)	Number (95% CI)	Number (95% CI)
2000	4,676 (4,109-5,243)	3,061 (2,611-3,511)	1,238 (1,011-1,465)
2001	5,279 (4,549-6,009)	3,680 (3,097-4,263)	1,279 (1,042-1,516)
2002	5,805 (4,903-6,708)	4,420 (3,664-5,176)	1,385 (1,148-1,623)
2003	5,193 (4,474-5,912)	3,796 (3,197-4,395)	1,393 (1,142-1,644)
2004	5,492(4,704-6,281)	4,092 (3,447-4,737)	1,396(1,168-1,623)
2005	5,782 (4,906-6,658)	4,243 (3,515-4,970)	1,531(1,254-1,807)
2006	6,110 (5,213-7,007)	4,427 (3,673-5,181)	1,683 (1,435-1,931)
2007	6,374 (5,233-7,514)	4,792 (3,766-5,819)	1,566 (1,335-1,797)
2008	7,874 (6,912-8,837)	5,805 (5,004-6,605)	2,056 (1,717-2,396)
2009	8,158 (7,107-9,209)	5,738 (4,871-6,605)	2,420 (2,022-2,818)
2010	7,932 (6,787-9,077)	5,909 (4,906-6,912)	2,018 (1,700-2,336)
2011	8,479 (7,348-9,609)	6,226 (5,262-7,189)	2,235 (1,916-2,554)
Total	79,697 (76,443-82,952)	57,965 (55,215-60,715)	20,931 (19,939-21,923)

95% CI: 95% confidence intervals. Numbers rounded to nearest integer.
Excludes those with any code for 'biopsy' procedure.
'Biopsy' codes: ICD-9-CM procedure codes for 'open biopsy of lung' (33.28) or 'thoracoscopic lung biopsy' (33.20; introduced October 2007).
'Excision' codes: ICD-9-CM procedure codes for 'other local excision or destruction of tissue of lung' (32.29) or 'thoracoscopic excision of lesion or tissue of lung' (32.20; introduced October 2007).

Figure 5-3: Estimated number of surgical lung biopsies performed in USA nationwide for a suspected diagnosis of idiopathic pulmonary fibrosis clinical syndrome



5.3.4 – Mortality

There were 2,051 deaths prior to hospital discharge in the unweighted cohort. Using weighted data, there were estimated to be 9,700 deaths nationally (95% confidence interval (CI) 9,209-10,192) following surgical lung biopsy for ILD from 2000-2011, giving an overall in-hospital mortality of 6.4% (95% CI 6.1%-6.7%).

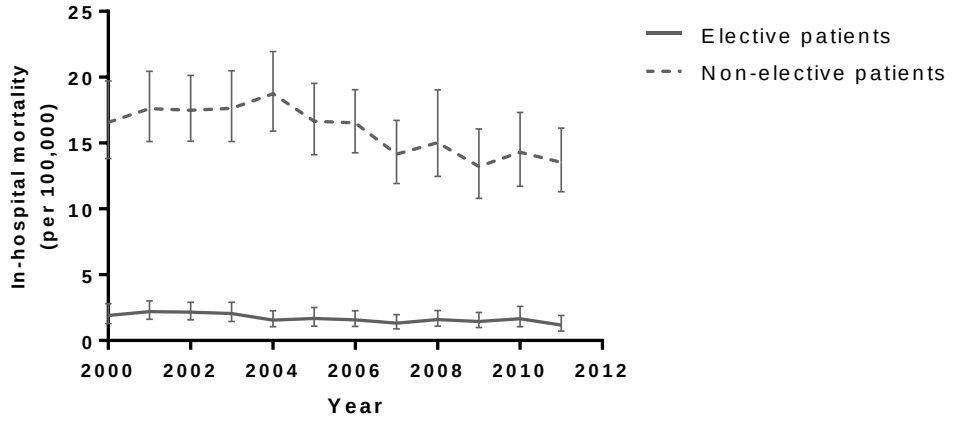
There were estimated to be 1,695 deaths nationally following elective operations (95% CI 1,506-1,883), giving an in-hospital mortality of 1.7% (95% CI 1.5%-1.9%), and 7,796 deaths nationally following non-elective operations (95% CI 7,361-8,230), giving an in-hospital mortality of 16.0% (95% CI 15.2%-18.8%). In-hospital mortality reduced over time (see Table 5-14, Figure 5-4).

Table 5-14: In-hospital mortality following surgical lung biopsy for interstitial lung disease in USA, by year (weighted data)

Year of biopsy	**Total admissions** Deaths (% mortality)	**Elective admissions** Deaths (% mortality)	**Non-elective admissions** Deaths (% mortality)
2000	822 (7.6)	120 (1.2)	591 (16.6)
2001	962 (7.5)	173 (2.2)	690 (17.6)
2002	923 (6.9)	196 (2.1)	727 (17.5)
2003	934 (7.3)	173 (2.1)	761 (17.6)
2004	875 (7.0)	131 (1.6)	745 (18.8)
2005	876 (6.6)	148 (1.7)	727 (16.6)
2006	876 (6.6)	139 (1.6)	736 (16.5)
2007	696 (5.4)	116 (1.3)	580 (14.1)
2008	715 (5.8)	135 (1.6)	580 (15.0)
2009	709 (5.5)	123 (1.5)	586 (13.2)
2010	696 (5.7)	139 (1.7)	557 (14.3)
2011	617 (4.9)	101 (1.2)	516 (13.5)
Total	*9700 (6.4)*	1695 (1.7)	7796 (16.0)

Deaths estimates rounded to nearest integer. Totals calculated using raw data rather than sum of rounded values.

Figure 5-4: In-hospital mortality following surgical lung biopsy for interstitial lung disease in USA



5.3.5 – Length of stay

The median length of stay in this cohort was 5 days, with a range of 0-308 days. 96% of records represented stays of 30 days or less. Excluding those remaining in hospital more than 30 days, in-hospital mortality was 5.4% (1.5% for elective patients, 14.2% for non-elective patients). The median length of stay was less for elective operations than non-elective ones (3 days vs 12 days).

5.3.6 – Post-operative complications

Post-operative complications were estimated to occur in 30% of elective records. The most common were post-operative pneumothorax (8.7%), pulmonary collapse (6.4%), pneumonia (5.8%), pleural effusion (3.2%), respiratory failure (3.1%), other respiratory complications (encompassing ventilator-associated pneumonia, chemical pneumonitis and transfusion-related acute lung injury) (2.0%), ventilator dependence (1.8%), acute kidney injury (1.7%), bleeding complications (accidental puncture, laceration, bleeding, haemorrhage or haematoma complicating the procedure) (1.7%), and surgical emphysema (1.1%).

5.3.7 – Risk factors for early mortality

Using logistic regression, the following risk factors were identified to be associated with increased in-hospital mortality: male sex, increasing age, higher level of co-morbidity, undergoing open rather than thoracoscopic surgery, and having a provisional diagnosis of IPF-CS or CTD-ILD. After adjusting for sex, age, co-morbidity, census region, type of operation and provisional diagnosis, these associations remained significant. There was some variation between regions but no clear trends for either elective or non-elective procedures. Results of multivariable logistic regression for all admissions, elective admissions, and non-elective admissions are shown in Table 5-15, Table 5-16, and Table 5-17 respectively.

Repeating the analysis for 'biopsy' codes only made a small difference to the overall results: mortality increased to 9.4% overall, 2.6% in elective patients, and 20.0% in non-elective patients. Most of the associations were strengthened slightly (see Table 5-18, Table 5-19, and Table 5-20).

To aid risk stratification for the individual patient, risk tables were constructed to demonstrate in-hospital mortality after surgical lung biopsy for ILD according to the key demographic factors of sex, age, and co-morbidity (see Table 5-21 for elective patients, Table 5-22 for non-elective patients). For each sex, a risk of in-hospital mortality was estimated using weighted data for each of three age categories depending on whether the patient had a lower or higher level of co-morbidity (updated Charlson score of 0-1 vs 2 or greater). This showed that a male aged under 55 years with no or minor co-morbidity could be expected to have an in-hospital mortality of 0.4% (95% CI 0.19-0.67) after elective lung biopsy, whereas a male aged over 74 years with several co-morbidities could potentially expect an in-hospital mortality of 10.1% (95% CI 7.33-13.87) after elective biopsy. Predicted mortality was considerably higher for non-elective patients, at over 30% for the oldest age categories with a higher level of co-morbidity.

Table 5-15: Multivariable analysis – associations with in-hospital death after surgical lung biopsy – all procedures (weighted data)

Variables	Cases	Deaths (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Sex						
Female	79,068	4,398 (5.6)	1.00		1.00	
Male	72,789	5,302 (7.3)	1.33 (1.22-1.46)	<0.001	1.28 (1.16-1.41)	<0.001
Age group (years)						
<45	24,638	818 (3.3)	1.00	<0.001 (p for trend)	1.00	<0.001 (p for trend)
45-54	29,711	996 (3.4)	1.01 (0.82-1.24)		0.95 (0.77-1.18)	
55-64	38,288	2,036 (5.3)	1.64 (1.36-1.96)		1.44 (1.19-1.74)	
65-74	38,657	3,207 (8.3)	2.63 (2.21-3.14)		2.25 (1.88-2.71)	
75-84	19,183	2,410 (12.6)	4.19 (3.49-5.02)		3.16 (2.60-3.83)	
>84	1,378	232 (16.9)	5.90 (4.17-8.36)		4.62 (3.15-6.77)	
Updated Charlson score						
0	65,903	2,210 (3.4)	1.00	<0.001 (p for trend)	1.00	<0.001 (p for trend)
1	51,430	2,475 (4.8)	1.46 (1.28-1.66)		1.50 (1.31-1.71)	
2	15,706	2,022 (12.9)	4.26 (3.71-4.89)		3.83 (3.31-4.43)	
≥3	18,817	2,994 (15.9)	5.46 (4.79-6.21)		4.95 (4.31-5.68)	
Geographical region						
South	54,197	3,553 (6.6)	1.00		1.00	
Northeast	32,835	1,921 (5.9)	0.89 (0.77-1.02)	0.093	0.78 (0.67-0.92)	0.002
Midwest	38,504	2,214 (5.8)	0.87 (0.76-0.99)	0.036	0.86 (0.75-0.98)	0.025
West	26,321	2,012 (7.6)	1.18 (1.03-1.35)	0.015	1.06 (0.92-1.23)	0.409
Year group						
'00-'02	37,056	2,707 (7.3)	1.00	<0.001 (p for trend)	1.00	<0.001 (p for trend)
'03-'05	38,441	2,685 (7.0)	0.95 (0.84-1.08)		0.97 (0.85-1.12)	
'06-'08	38,648	2,287 (5.9)	0.80 (0.70-0.91)		0.84 (0.72-0.97)	
'09-'11	37,712	2,021 (5.4)	0.72 (0.62-0.83)		0.71 (0.61-0.84)	
Type of operation (post-Oct '07 patients only)						
VATS	37,739	1,418 (3.8)	1.00		-	-
Open	15,732	1,562 (9.9)	2.82 (2.36-3.37)	<0.001	-	-
Provisional diagnosis (patients with single ILD diagnostic code only)						
PIF	115,832	6,339 (5.5)	1.00		1.00	
IPF-CS	13,387	2,056 (15.4)	3.13 (2.78-3.54)	<0.001	2.71 (2.38-3.09)	<0.001
CTD-ILD	2,208	238 (10.8)	2.08 (1.54-2.82)	<0.001	1.62 (1.18-2.22)	0.003
Sarcoid	7,848	199 (2.5)	0.45 (0.32-0.62)	<0.001	0.65 (0.47-0.91)	0.012
HP	1,532	44 (2.9)	0.52 (0.26-1.01)	0.053	0.48 (0.24-0.95)	0.036
Pneum	3,545	62 (1.7)	0.30 (0.17-0.53)	<0.001	0.19 (0.11-0.33)	<0.001

Multivariable analysis excludes type of operation due to lower numbers; type of operation remained significant if included.
Higher Updated Charlson score reflects greater degree of co-morbidity.
Estimated numbers of cases and deaths rounded to nearest integer.
VATS: video-assisted thoracoscopic surgery. OR: Odds Ratio; 95% CI: 95% confidence interval.
PIF: post-inflammatory fibrosis; IPF-CS: idiopathic pulmonary fibrosis clinical-syndrome; CTD-ILD: connective tissue disease related interstitial lung disease; HP: hypersensitivity pneumonitis; Pneum: pneumoconioses, including asbestosis.

Table 5-16: Multivariable analysis – associations with in-hospital death after surgical lung biopsy – elective procedures (weighted data)

Variables	Cases	Deaths (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Sex						
Female	53,552	733 (1.4)	1.00		1.00	
Male	47,147	962 (2.0)	1.50 (1.22-1.85)	<0.001	1.41 (1.14-1.76)	0.002
Age group (years)						
<45	14,985	95 (0.6)	1.00	<0.001	1.00	<0.001
45-54	20,073	148 (0.7)	1.16 (0.67-2.01)	(p for trend)	1.20 (0.68-2.12)	(p for trend)
55-64	26,680	393 (1.5)	2.33 (1.42-3.83)		2.00 (1.19-3.38)	
65-74	26,702	611 (2.3)	3.66 (2.28-5.88)		3.09 (1.87-5.09)	
75-84	11,547	418 (3.6)	5.86 (3.63-9.47)		4.46 (2.69-7.40)	
>84	711	29 (4.0)	6.56 (2.58-16.65)		5.25 (2.16-12.74)	
Updated Charlson score						
0	50,389	410 (0.8)	1.00	<0.001	1.00	<0.001
1	33,949	509 (1.5)	1.86 (1.41-2.45)	(p for trend)	1.83 (1.38-2.43)	(p for trend)
2	8,222	359 (4.4)	5.56 (4.09-7.56)		5.17 (3.75-7.14)	
≥3	8,139	417 (5.1)	6.58 (4.83-8.96)		5.95 (4.32-8.20)	
Geographical region						
South	35,345	716 (2.0)	1.00		1.00	
Northeast	22,108	234 (1.1)	0.52 (0.37-0.73)	<0.001	0.53 (0.37-0.76)	0.001
Midwest	26,824	492 (1.8)	0.91 (0.69-1.19)	0.477	0.94 (0.71-1.25)	0.668
West	16,421	252 (1.5)	0.75 (0.55-1.03)	0.076	0.75 (0.54-1.04)	0.083
Year group						
'00-'02	23,311	490 (2.1)	1.00	0.009	1.00	0.028
'03-'05	25,719	452 (1.8)	0.83 (0.62-1.12)	(p for trend)	0.83 (0.61-1.14)	(p for trend)
'06-'08	26,163	391 (1.5)	0.71 (0.53-0.95)		0.76 (0.56-1.05)	
'09-'11	25,505	362 (1.4)	0.67 (0.49-0.93)		0.67 (0.47-0.95)	
Type of operation (post-Oct '07 patients only)						
VATS	26,647	314 (1.2)	1.00		-	-
Open	9,511	218 (2.3)	1.96 (1.36-2.83)	<0.001	-	-
Provisional diagnosis (patients with single ILD diagnostic code only)						
PIF	79,853	1,143 (1.4)	1.00		1.00	
IPF-CS	7,303	374 (5.1)	3.71 (2.83-4.88)	<0.001	3.17 (2.36-4.26)	<0.001
CTD-ILD	1,111	67 (6.0)	4.39 (2.52-7.64)	<0.001	2.93 (1.65-5.22)	<0.001
Sarcoid	5,270	15 (0.3)	0.19 (0.06-0.59)	0.004	0.28 (0.09-0.89)	0.031
Other	3,148	14 (0.5)	0.32 (0.10-1.00)	0.050	0.19 (0.06-0.61)	0.005

Multivariable analysis excludes type of operation due to lower numbers; type of operation remained significant if included.
Higher Updated Charlson score reflects greater degree of co-morbidity.
Estimated numbers of cases and deaths rounded to nearest integer.
VATS: video-assisted thoracoscopic surgery. OR: Odds Ratio; 95% CI: 95% confidence interval.
PIF: post-inflammatory fibrosis; IPF-CS: idiopathic pulmonary fibrosis clinical-syndrome; CTD-ILD: connective tissue disease related interstitial lung disease; 'Other': hypersensitivity pneumonitis and pneumoconioses (including asbestosis) – grouped due to smaller numbers.

Table 5-17: Multivariable analysis – associations with in-hospital death after surgical lung biopsy – non-elective procedures (weighted data)

Variables	Cases	Deaths (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Sex						
Female	24,388	3,574 (14.7)	1.00		1.00	
Male	24,497	4,222 (17.3)	1.21 (1.09-1.35)	<0.001	1.17 (1.04-1.32)	0.008
Age group (years)						
<45	9,267	696 (7.5)	1.00	<0.001 (p for trend)	1.00	<0.001 (p for trend)
45-54	9,218	812 (8.8)	1.19 (0.95-1.50)		1.13 (0.89-1.43)	
55-64	11,045	1,606 (14.6)	2.10 (1.71-2.57)		1.86 (1.50-2.31)	
65-74	11,408	2,554 (22.4)	3.56 (2.92-4.33)		3.12 (2.53-3.84)	
75-84	7,300	1,932 (26.5)	4.44 (3.61-5.46)		3.62 (2.90-4.52)	
>84	647	196 (30.3)	5.34 (3.54-8.04)		4.49 (2.88-7.02)	
Updated Charlson score						
0	14,330	1,745 (12.2)	1.00	<0.001 (p for trend)	1.00	<0.001 (p for trend)
1	16,885	1,935 (11.5)	0.93 (0.80-1.09)		1.00 (0.85-1.17)	
2	7,238	1,596 (22.1)	2.04 (1.73-2.41)		1.81 (1.52-2.16)	
≥3	10,432	2,519(24.2)	2.30 (1.97-2.67)		2.06 (1.75-2.42)	
Geographical region						
South	18,803	2,838 (15.1)	1.00		1.00	
Northeast	10,702	1,686 (15.8)	1.05 (0.90-1.23)	0.523	0.88 (0.75-1.05)	0.153
Midwest	11,506	1,722 (15.0)	0.99 (0.84-1.16)	0.886	0.90 (0.76-1.06)	0.208
West	7,874	1,550 (19.7)	1.38 (1.18-1.61)	<0.001	1.21 (1.02-1.43)	0.033
Year group						
'00-'02	11,646	2,008 (17.3)	1.00	<0.001 (p for trend)	1.00	<0.001 (p for trend)
'03-'05	12,677	2,233 (17.7)	1.03 (0.88-1.20)		1.06 (0.90-1.25)	
'06-'08	12,419	1,896 (15.3)	0.87 (0.74-1.01)		0.90 (0.76-1.07)	
'09-'11	12,143	1,659 (13.7)	0.76 (0.64-0.90)		0.77 (0.64-0.92)	
Type of operation (post-Oct '07 patients only)						
VATS	11,043	1,104 (10.0)	1.00		-	-
Open	6,189	1,344 (21.7)	2.50 (2.04-3.06)	<0.001	-	-
Provisional diagnosis (patients with single ILD diagnostic code only)						
PIF	34,509	5,111 (14.8)	1.00		1.00	
IPF-CS	5,677	1,589 (28.0)	2.23 (1.93-2.58)	<0.001	2.05 (1.76-2.39)	<0.001
CTD-ILD	1,071	171 (16.0)	1.09 (0.76-1.57)	0.624	1.19 (0.82-1.73)	0.370
Sarcoid	2,436	184 (7.6)	0.47 (0.33-0.67)	<0.001	0.72 (0.51-1.04)	0.077
Other	1,854	91 (4.9)	0.30 (0.19-0.48)	<0.001	0.28 (0.17-0.46)	<0.001

Multivariable analysis excludes type of operation due to lower numbers; type of operation remained significant if included.
Higher Updated Charlson score reflects greater degree of co-morbidity.
Estimated numbers of cases and deaths rounded to nearest integer.
VATS: video-assisted thoracoscopic surgery. OR: Odds Ratio; 95% CI: 95% confidence interval.
PIF: post-inflammatory fibrosis; IPF-CS: idiopathic pulmonary fibrosis clinical-syndrome; CTD-ILD: connective tissue disease related interstitial lung disease; 'Other': hypersensitivity pneumonitis and pneumoconioses (including asbestosis) – grouped due to smaller numbers.

Table 5-18: Multivariable analysis – associations with in-hospital death after surgical lung biopsy – all procedures, 'biopsy' codes only (weighted data)

Variables	Cases	Deaths (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Sex						
Female	38,910	3,216 (8,3)	1.00		1.00	
Male	35,793	3,828 (10.7)	1.33 (1.20-1.48)	<0.001	1.24 (1.10-1.40)	<0.001
Age group (years)						
<45	12,135	593 (4.9)	1.00	<0.001	1.00	<0.001
45-54	14,007	693 (4.9)	1.01 (0.79-1.30)	(p for trend)	0.94 (0.72-1.21)	(p for trend)
55-64	18,871	1,515 (8.0)	1.70 (1.37-2.10)		1.46 (1.17-1.84)	
65-74	19,028	2,306 (12.1)	2.68 (2.18-3.30)		2.19 (1.75-2.74)	
75-84	10,082	1,757 (17.4)	4.11 (3.31-5.10)		3.03 (2.40-3.84)	
>84	581	180 (31.0)	8.74 (5.66-13.48)		6.81 (4.19-11.07)	
Updated Charlson score						
0	31,544	1,682 (5.3)	1.00	<0.001	1.00	<0.001
1	24,269	1,739 (7.2)	1.37 (1.18-1.60)	(p for trend)	1.42 (1.21-1.67)	(p for trend)
2	8,680	1,494 (17.3)	3.70 (3.14-4.36)		3.28 (2.75-3.90)	
≥3	10,209	2,128 (20.9)	4.68 (4.01-5.47)		4.19 (3.55-4.94)	
Geographical region						
South	26,665	2,600 (9.8)	1.00		1.00	
Northeast	13,825	1,302 (9.4)	0.96 (0.82-1.13)	0.625	0.92 (0.77-1.09)	0.316
Midwest	18,893	1,590 (8.4)	0.85 (0.73-0.99)	0.033	0.81 (0.69-0.95)	0.012
West	15,320	1,553 (10.1)	1.04 (0.90-1.21)	0.593	0.98 (0.83-1.16)	0.819
Year group						
'00-'02	21,295	2,159 (10.1)	1.00	0.043	1.00	0.139
'03-'05	21,974	2,110 (9.6)	0.94 (0.82-1.08)	(p for trend)	0.98 (0.85-1.12)	(p for trend)
'06-'08	18,290	1,591 (8.7)	0.84 (0.72-0.98)		0.88 (0.74-1.04)	
'09-'11	13,143	1,184 (9.0)	0.88 (0.74-1.04)		0.91 (0.75-1.09)	
Type of operation (post-Oct '07 patients only)						
VATS	10,952	597 (5.5)	1.00		-	-
Open	8,181	1,183 (14.5)	2.93 (2.32-3.69)	<0.001	-	-
Provisional diagnosis (patients with single ILD diagnostic code only)						
PIF	54,077	4,521 (8.4)	1.00		1.00	
IPF-CS	9,114	1,612 (17.7)	2.35 (2.05-2.71)	<0.001	2.16 (1.86-2.51)	<0.001
CTD-ILD	1,238	160 (13.0)	1.63 (1.12-2.37)	0.011	1.37 (0.93-2.03)	0.115
Sarcoid	3,815	103 (2.7)	0.30 (0.19-0.49)	<0.001	0.46 (0.29-0.75)	0.002
HP	958	33 (3.5)	0.40 (0.19-0.85)	0.017	0.39 (0.18-0.84)	0.017
Pneum	1,353	41 (3.1)	0.34 (0.18-0.68)	0.002	0.23 (0.11-0.45)	<0.001

'Biopsy' codes: ICD-9-CM procedure codes for 'open biopsy of lung' (33.28) or 'thoracoscopic lung biopsy' (33.20; introduced October 2007).
Multivariable analysis excludes type of operation due to lower numbers; type of operation remained significant if included.
Higher Updated Charlson score reflects greater degree of co-morbidity.
Estimated numbers of cases and deaths rounded to nearest integer.
VATS: video-assisted thoracoscopic surgery. OR: Odds Ratio; 95% CI: 95% confidence interval.
PIF: post-inflammatory fibrosis; IPF-CS: idiopathic pulmonary fibrosis clinical-syndrome; CTD-ILD: connective tissue disease related interstitial lung disease; HP: hypersensitivity pneumonitis; Pneum: pneumoconioses, including asbestosis.

Table 5-19: Multivariable analysis – associations with in-hospital death after surgical lung biopsy – elective procedures, 'biopsy' codes only (weighted data)

Variables	Cases	Deaths (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Sex						
Female	23,365	494 (2.1)	1.00		1.00	
Male	21,145	640 (3.0)	1.45 (1.12-1.86)	0.004	1.30 (1.00-1.70)	0.050
Age group (years)						
<45	6,781	48 (0.7)	1.00	<0.001 (p for trend)	1.00	<0.001 (p for trend)
45-54	8,510	100 (1.2)	1.67 (0.79-3.54)		1.90 (0.84-4.27)	
55-64	11,882	269 (2.3)	3.26 (1.65-6.43)		2.97 (1.40-6.31)	
65-74	11,724	373 (3.2)	4.63 (2.40-8.94)		4.14 (1.98-8.66)	
75-84	5,371	320 (6.0)	8.93 (4.64-17.18)		7.14 (3.44-14.82)	
>84	242	24 (10.0)	15.61 (5.10-47.76)		11.04 (3.66-33.37)	
Updated Charlson score						
0	22,196	267 (1.2)	1.00	<0.001 (p for trend)	1.00	<0.001 (p for trend)
1	15,052	333 (2.2)	1.86 (1.31-2.64)		1.78 (1.24-2.56)	
2	3,809	249 (6.5)	5.74 (3.92-8.42)		5.05 (3.37-7.58)	
≥3	3,453	285 (8.3)	7.40 (5.08-10.80)		6.08 (4.08-9.05)	
Geographical region						
South	15,920	512 (3.2)	1.00		1.00	
Northeast	7,999	140 (1.7)	0.54 (0.35-0.81)	0.003	0.63 (0.42-0.96)	0.030
Midwest	11,826	317 (2.7)	0.83 (0.60-1.14)	0.251	0.85 (0.60-1.19)	0.338
West	8,766	166 (1.9)	0.58 (0.40-0.85)	0.006	0.63 (0.42-0.95)	0.026
Year group						
'00-'02	12,150	367 (3.0)	1.00	0.110 (p for trend)	1.00	0.248 (p for trend)
'03-'05	13,589	341 (2.5)	0.83 (0.59-1.15)		0.84 (0.59-1.20)	
'06-'08	11,139	249 (2.2)	0.74 (0.51-1.05)		0.76 (0.52-1.12)	
'09-'11	7,633	177 (2.3)	0.77 (0.51-1.14)		0.79 (0.52-1.22)	
Type of operation (post-Oct '07 patients only)						
VATS	7,123	106 (1.5)	1.00		-	-
Open	4,023	159 (3.9)	2.72 (1.58-4.69)	<0.001	-	-
Provisional diagnosis (patients with single ILD diagnostic code only)						
PIF	33,445	740 (2.2)	1.00		1.00	
IPF-CS	4,716	270 (5.7)	2.69 (1.96-3.69)	<0.001	2.33 (1.65-3.28)	<0.001
CTD-ILD	523	38 (7.2)	3.43 (1.64-7.18)	0.001	2.15 (0.99-4.67)	0.053
Sarcoid	2,467	10 (0.4)	0.18 (0.04-0.72)	0.015	0.30 (0.07-1.21)	0.090
Other	1,323	14 (1.1)	0.49 (0.15-1.56)	0.225	0.33 (0.10-1.07)	0.066

'Biopsy' codes: ICD-9-CM procedure codes for 'open biopsy of lung' (33.28) or 'thoracoscopic lung biopsy' (33.20; introduced October 2007).
Multivariable analysis excludes type of operation due to lower numbers; type of operation remained significant if included.
Higher Updated Charlson score reflects greater degree of co-morbidity.
Estimated numbers of cases and deaths rounded to nearest integer.
VATS: video-assisted thoracoscopic surgery. OR: Odds Ratio; 95% CI: 95% confidence interval.
PIF: post-inflammatory fibrosis; IPF-CS: idiopathic pulmonary fibrosis clinical-syndrome; CTD-ILD: connective tissue disease related interstitial lung disease; 'Other': hypersensitivity pneumonitis and pneumoconioses (including asbestosis) – grouped due to smaller numbers.

Table 5-20: Multivariable analysis – associations with in-hospital death after surgical lung biopsy – non-elective procedures, 'biopsy' codes only (weighted data)

Variables	Cases	Deaths (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Sex						
Female	14,768	2,644 (17.9)	1.00		1.00	
Male	13,917	3,073 (22.1)	1.30 (1.14-1.47)	<0.001	1.22 (1.06-1.41)	0.005
Age group (years)						
<45	5,086	523 (10.3)	1.00	<0.001 (p for trend)	1.00	<0.001 (p for trend)
45-54	5,222	562 (10.8)	1.05 (0.80-1.38)		0.99 (0.74-1.31)	
55-64	6,632	1,214 (18.3)	2.96 (1.54-2.48)		1.75 (1.36-2.25)	
65-74	6,948	1,895 (27.3)	3.27 (2.60-4.12)		2.79 (2.18-3.58)	
75-84	4,479	1,376 (30.8)	3.87 (3.03-4.95)		3.17 (2.43-4.13)	
>84	318	148 (46.5)	7.58 (4.46-12.87)		7.03 (3.96-12.47)	
Updated Charlson score						
0	8,583	1,379 (16.1)	1.00	<0.001 (p for trend)	1.00	<0.001 (p for trend)
1	8,838	1,376 (15.6)	0.97 (1.81-1.16)		1.02 (0.85-1.24)	
2	4,681	1,178 (25.2)	1.76 (1.45-2.14)		1.55 (1.25-1.90)	
≥3	6,582	1,785 (27.2)	1.95 (1.63-2.33)		1.72 (1.43-2.09)	
Geographical region						
South	10,718	2,088 (19.5)	1.00		1.00	
Northeast	5,829	1,162 (20.0)	1.03 (0.86-1.23)	0.759	0.92 (0.76-1.13)	0.440
Midwest	6,958	1,273 (18.3)	0.92 (0.77-1.11)	0.392	0.83 (0.69-1.01)	0.064
West	5,189	1,194 (23.0)	1.23 (1.03-1.48)	0.026	1.07 (0.88-1.32)	0.488
Year group						
'00-'02	7,744	1,601 (20.7)	1.00	0.065 (p for trend)	1.00	0.240 (p for trend)
'03-'05	8,358	1,769 (21.2)	1.03 (0.87-1.23)		1.09 (0.90-1.33)	
'06-'08	7,113	1,341 (18.9)	0.89 (0.75-1.07)		0.94 (0.77-1.15)	
'09-'11	5,470	1,006 (18.4)	0.86 (0.71-1.06)		0.93 (0.75-1.16)	
Type of operation (post-Oct '07 patients only)						
VATS	3,797	492 (13.0)	1.00		-	-
Open	4,144	1,024 (24.7)	2.21 (1.70-2.86)	<0.001	-	-
Provisional diagnosis (patients with single ILD diagnostic code only)						
PIF	19,736	3,701 (18.8)	1.00		1.00	
IPF-CS	4,052	1,252 (30.9)	1.93 (1.64-2.29)	<0.001	1.85 (1.55-2.20)	<0.001
CTD-ILD	688	123 (17.8)	0.94 (0.61-1.44)	0.770	1.11 (0.70-1.76)	0.648
Sarcoid	1,270	93 (7.3)	0.34 (0.21-0.57)	<0.001	0.51 (0.30-0.85)	0.009
Other	932	60 (6.5)	0.30 (0.17-0.53)	<0.001	0.28 (0.15-0.50)	<0.001

'Biopsy' codes: ICD-9-CM procedure codes for 'open biopsy of lung' (33.28) or 'thoracoscopic lung biopsy' (33.20; introduced October 2007).
Multivariable analysis excludes type of operation due to lower numbers; type of operation remained significant if included.
Higher Updated Charlson score reflects greater degree of co-morbidity.
Estimated numbers of cases and deaths rounded to nearest integer.
VATS: video-assisted thoracoscopic surgery. OR: Odds Ratio; 95% CI: 95% confidence interval.
PIF: post-inflammatory fibrosis; IPF-CS: idiopathic pulmonary fibrosis clinical-syndrome; CTD-ILD: connective tissue disease related interstitial lung disease; 'Other': hypersensitivity pneumonitis and pneumoconioses (including asbestosis) – grouped due to smaller numbers.

Table 5-21: Risk of in-hospital mortality following elective surgical lung biopsy for interstitial lung disease, by age and co-morbidity.

		Age <55 years	Age 55-74 years	Age >74 years
MALES	**Updated Charlson score: 0-1**	0.4% (0.19-0.67)	1.5% (1.20-1.92)	2.7% (1.82-3.86)
	Updated Charlson score: 2 or greater	3.7% (2.29-6.06)	5.4% (4.02-7.12)	10.1% (7.33-13.87)
FEMALES	**Updated Charlson score: 0-1**	0.4% (0.25-0.70)	1.1% (0.87-1.48)	1.9% (1.21-2.94)
	Updated Charlson score: 2 or greater	1.9% (1.00-3.46)	4.0% (2.95-5.48)	5.7% (3.36-9.51)

Figures displayed are percentages (95% confidence intervals)

Table 5-22: Risk of in-hospital mortality following non-elective surgical lung biopsy for interstitial lung disease, by age and co-morbidity.

		Age <55 years	Age 55-74 years	Age >74 years
MALES	**Updated Charlson score: 0-1**	6.3% (5.06-7.91)	15.6% (13.81-17.63)	20.3% (16.85-24.24)
	Updated Charlson score: 2 or greater	16.0% (12.93-19.64)	26.1% (23.28-29.06)	32.8% (28.59-37.21)
FEMALES	**Updated Charlson score: 0-1**	5.6% (4.54-6.85)	13.2% (11.49-15.22)	24.3% (20.16-28.88)
	Updated Charlson score: 2 or greater	12.5% (10.04-15.33)	23.8% (21.12-26.77)	30.3% (25.49-35.61)

Figures displayed are percentages (95% confidence intervals)

5.4 – Discussion

5.4.1 – Summary of findings

This cohort of surgical lung biopsies for interstitial lung disease has shown there to be around 12,000 biopsies performed each year in hospitals across the United States. In-hospital mortality was just under 2% for elective procedures, but significantly higher (16%) for non-elective (urgent and emergency) procedures. There was a strong, if unsurprising, link between increased mortality and increasing age and co-morbidity, but also associations with male sex, open rather than thoracoscopic surgery, and a suspected diagnosis of IPF-CS or CTD-ILD. Procedures classified using 'biopsy' rather than 'excision' codes had a slightly higher mortality, were used slightly more often for non-elective procedures, and were less frequently used over time, although in many respects both codes were similar.

5.4.2 – Strengths

The size of this cohort, at over 30,000 procedures, is the largest reported series of surgical lung biopsies for interstitial lung disease: no previous study has been able to report over 1,000 cases. A further strength is that the NIS database encompasses multiple centres from across a large country, whereas many other series are from single centres. The NIS is also likely to be representative of the wider population, as it includes various categories of patient, including those covered by Medicare and Medicaid, those privately insured and the uninsured.

The focus of this study on later years of the available NIS database (year 2000 onwards) was an important factor: these were likely to have higher data completeness, including increasing numbers of states, and were more likely to reflect current practice. The use of weightings provided by HCUP to adjust for sampling meant that national estimates were likely to be a truer reflection of all the hospitals in the project than using the raw data. Finally, although there

is no universally-agreed standard for assessing co-morbidity using large datasets, the use of a contemporaneous validated score (the updated Charlson score) and published coding guidance helped ensure that the approach taken was reliable, reproducible and relatively easy for others to understand.

5.4.3 – Limitations

The main limitation with using the NIS database was the lack of unique patient identifiers. As a result, it was not possible to explore re-admissions, and there was the possibility that a patient could be included more than once. However, it would be unusual for a patient to undergo a surgical lung biopsy on multiple occasions, and therefore any occurrence would be expected to be rare. The nature of the database meant it was only possible to assess in-hospital mortality, rather than the more familiar 30-day and 90-day mortality measures commonly used in other case series, and since most patients were discharged within 30 days, it is likely that 30-day mortality would be higher than the current estimates to account for deaths at home and after re-admissions.

As with all studies using large databases, there are limitations with regards the reliability of clinical coding. Firstly, the diagnostic codes for surgical lung biopsy, which are reliant on clinical coders' interpretation of operation notes, may not truly reflect the procedures of interest. The use of potentially more specific 'biopsy' codes in addition to the broader definition including 'excision' codes was helpful in that both cohorts yielded similar results, but there were some differences, and it is likely that use of codes varies between centres and over time. The coding of elective and non-elective surgery might also be incorrect; however the results seemed to reflect expected reality in that more urgent cases had higher mortality, likely due to the severity of their underlying illness.

The exclusion of records with a code for lung cancer may have excluded some biopsy patients with co-existent cancer, who are likely to have been at higher

risk. However, it was felt this was a reasonable approach to ensure those with ILD undergoing a biopsy for their cancer were not included: while interesting, this would address a difficult clinical question to the role of diagnostic biopsy for ILD. It is possible that some patients with suspected malignancy but no confirmed diagnostic code were included in the cohort inappropriately, but it is hoped that these would be a small group. A further disadvantage to using discharge records, as opposed to a case series with more clinical details, was the lack of a clear histological diagnosis, and the popularity of the non-specific ICD-9-CM code for post-inflammatory fibrosis – a condition not widely recognised in updated guidelines – limited the ability to assess the impact of the type of ILD.

The fact that each discharge record in the NIS was independent meant that any assessment of co-morbidity was only able to include those codes mentioned in that discharge record: having a longer baseline period of previous admissions would potentially have captured more codes, thereby putting patients in higher risk co-morbidity categories, and potentially lowering the mortality risk associated with higher co-morbidity – however it would be hoped that the more significant co-morbidities used by the updated Charlson score would be highlighted on an inpatient admission. Similarly, the estimates of post-operative complications could not take into account conditions such as myocardial infarctions or arrhythmias, which could have reflected chronic components of the past medical history. Complications were not assessed for non-elective procedures due to concern about coding reliability, and this clearly limits the applicability of this data to planned operations only. One major complication commonly experienced after thoracic surgery is post-operative pain, and this was not assessed in this study, but should remain a key discussion point when counselling patients.

A further limitation in assessing surgical risk was the lack of reliable data on medications such as corticosteroids, immunosuppression and anticoagulation, and importantly pre-operative oxygen requirements, imaging appearances and lung function test results, all of which have been associated with adverse

outcomes in case series (101, 142, 246). The absence of this data limits applicability to the patient in clinic, who may for example have a specific imaging pattern or level of lung function suggesting lower or higher risk. Finally, the nature of the study meant it was not possible to compare those undergoing surgery to those who chose not to undergo a lung biopsy, and therefore, particularly for non-elective biopsies, mortality figures clearly need to be noted alongside the expected mortality of non-surgical management – which for those suffering from an acute exacerbation may be substantial (173).

5.4.4 – Interpretation of findings

Despite the limitations above, the risk tables provided (Table 5-21, Table 5-22) give a reasonable estimate of surgical risk that may be useful in the pre-operative consultation. It is possible that these figures may underestimate true risks for several reasons, including misclassification of elective patients as non-elective, exclusion of patients who were deemed unfit for surgery at the time, and the non-representation of those dying after hospital discharge. However, it is likely that the calculated percentages give a rough guide to the expected risks for the 'average' patient meeting the stated demographic criteria and contemplating surgical diagnosis.

The findings of increased mortality with male sex, increasing age and increasing co-morbidity are not overly surprising and likely true. The differences between regions in the US were not consistent, with a suggestion of reduced in-hospital mortality after elective procedures in the Northeast and increased mortality after non-elective procedures in the West. These observations may reflect variation in clinical practice or the nature of disease, and therefore any conclusions should be made with caution.

There was a clear suggestion that mortality had improved over time, which fits with improved surgical practice and better patient selection. This did not hold true for 'biopsy' codes only, which may reflect changing use of this code

over time. The increased mortality with open surgery may reflect the higher trauma to the body of this approach, but the possibility of confounding needs to be taken into account (more intricate thoracoscopic procedures would be less appealing in sicker patients, therefore leading to a potentially erroneous association between open surgery and higher mortality).

The impact of provisional diagnosis also needs to be interpreted with caution, especially given the widespread use of ICD-9-CM code 515 (post-inflammatory fibrosis). However, results suggest that in those where there is a confident-enough diagnosis of IPF-CS or CTD-ILD to document it in the operative discharge record, in-hospital mortality is increased, and this fits with the more aggressive course of disease expected in most of these patients compared to those with more benign conditions like sarcoidosis (23, 172, 247). It is unclear whether this reflects the presence of a usual interstitial pneumonia (UIP) pattern on imaging: many patients with definite UIP would not be offered surgical biopsy, however it cannot be assumed that the stated mortality figures only apply to non-UIP patients, as this information was not available in the data and surgical practice in the United States may have been to favour biopsy in all patients in earlier years.

While the number of procedures performed yearly remained relatively stable during the study, it is possible that this may reflect decreased utilisation of the procedure in an increasing number of ILD patients who are being diagnosed more commonly using radiology and multi-disciplinary meetings. The overall incidence of ILD over this time period in the US is not clear, but studies of rheumatoid arthritis associated ILD and sarcoidosis suggest it is increasing (248, 249), and the data in Chapter 3 suggests the incidence of IPF is increasing worldwide (187). The less dramatic increase in IPF recently in the US (178, 204) may reflect fewer patients meeting strict American Thoracic Society (ATS) criteria (15), and an increasing number with ‘unclassified’ ILD. More local data from specialist centres comparing numbers of biopsies to numbers of new cases of ILD would be useful.

5.4.5 – Comparison to the literature

There are numerous studies in the wider literature on the role of surgical lung biopsy for interstitial lung disease. These span a considerable time period, and vary in terms of their research aims (for example, safety vs efficacy), case selection (IPF vs any ILD), type of surgery (open vs thoracoscopic) and reporting outcomes (for example, 30-day mortality vs post-operative). These differences limit the ability to compare studies, however mortality estimates range from 0-34%. Studies reporting higher mortality tend to highlight the presence of acute symptoms, older age, pre-operative respiratory failure or mechanical ventilation, and immunosuppression as associated with poor outcomes (104, 112, 133, 141, 143, 144), suggesting more careful case selection could improve outcomes. These studies likely represent the 'non-elective' component of the current study, and supporting this, one US study specifically of patients undergoing biopsy during an acute exacerbation showed survival in only 1 of 7 patients (149).

A recent systematic review by Nguyen and Meyer (120) quoted 'overall mortality' of 3.5% after surgical lung biopsy for ILD (2.1% for thoracoscopic surgery, 4.3% for open surgery), although it was unclear how many of these were elective procedures. Another review by Kreider *et al* in 2007 derived a composite post-operative mortality of 4.5% (142), noting a significantly increased mortality of 47% in those requiring pre-operative ventilation compared to 2.2% in those free from ventilation. In terms of contemporaneous series from the US, one from the Mayo clinic reported a 30-day mortality of 9% (133), while another from Emory University in Atlanta reported a 30-day mortality of 6.7% (152). Both these studies likely included non-elective cases, and therefore the overall in-hospital mortality of 6.4% in the current study seems to fit with these findings.

5.4.6 – Clinical implications

This study highlights the risks of surgical lung biopsy for ILD, particularly for non-elective cases. It is insightful that one in three records in the current

dataset was for a non-elective procedure, suggesting that these higher risk operations are still being performed regularly, despite evidence from case series that these sicker patients have a high chance of an adverse outcome. While it could be argued that patients undergoing non-elective surgery may have a high chance of dying even without surgery (due to the severity of their underlying lung disease), it is important that patients contemplating surgery in these circumstances are aware of the likely mortality.

The recent introduction of anti-fibrotic medications to the armamentarium of the ILD physician means there may be an increased drive to perform surgical lung biopsy, to determine if a patient is suitable for these expensive new treatments. The decrease in procedures for suspected IPF-CS after 2003 (see Figure 5-3) likely reflects publication of ATS guidelines clarifying the diagnostic criteria for IPF and suggesting biopsy is not needed in those with typical radiological appearances (1); whether this pattern will change now there are disease-modifying treatments available is uncertain, but it is clear that increasing numbers of patients with unclassified disease might choose a more 'definitive' test given the potential for intervention. While histological confirmation may allow access to treatments, it may also ensure empirical anti-inflammatory therapies – which may have associated harms in IPF, as suggested by the PANTHER study (164) – are avoided. Clinicians need to counsel patients about the likely benefits and potential risks of a surgical lung biopsy in this situation, and the current study gives some data that may help them do this. Clearly additional factors such as pulmonary function tests will be crucial in adapting the outlook from this data to the individual patient.

5.4.7 – Summary of chapter

This chapter has explored the frequency of surgical lung biopsy for the diagnosis of interstitial lung disease in the United States, using a large, comprehensive secondary care database covering 2000-2011. The overall in-hospital mortality following surgery was estimated at 6.4%, with a notable distinction between elective procedures (in-hospital mortality of 1.7%) and

non-elective procedures (in-hospital mortality of 16.0%). Risk factors for increased mortality, including increasing age and co-morbidity, were highlighted, and various risk estimates according to different demographic combinations were presented. The limitations of the data, including the reliability of coding and lack of clinical data, were noted, although a major strength was the large size of the cohort and its representative nature.

The findings of this study will be useful to clinicians managing patients with interstitial lung disease where the diagnosis is unclear, in conjunction with individual patient data, and the clinical implications are clear that an increased desire to characterise ILD must be balanced with appreciation of surgical risks, particularly for urgent and emergency cases. The following chapter will explore a similar question using a different database from the United Kingdom.

This work was published in the American Journal of Respiratory and Critical Care Medicine with an accompanying editorial in 2016 (236).

Chapter 6 : Risk of surgical lung biopsy for diagnosing interstitial lung disease in the United Kingdom

This chapter examines the use of surgical lung biopsy for diagnosing interstitial lung disease using data from the United Kingdom. This study complements the work of Chapter 5 in addressing surgical risk, whilst also providing additional insights into mortality following hospital discharge and ultimate cause of death.

This work was published in the European Respiratory Journal in 2016 (250).

6.1 – Introduction

6.1.1 – Background

As outlined in Chapter 5, achieving an accurate diagnosis of interstitial lung disease (ILD) is important, as it can help guide treatment options and prognosis (2). This is particularly an issue for idiopathic pulmonary fibrosis (IPF), where the introduction of the anti-fibrotic medications pirfenidone and nintedanib has offered hope to patients who face a median survival of only three years (15, 163). While imaging and multi-disciplinary team discussion can often be enough to make a diagnosis, a surgical lung biopsy may sometimes be required to give histological confirmation (2). However, patients undergoing lung biopsy need information to weigh up the benefits and risks of the procedure.

6.1.2 – Rationale for the study

Most data on morbidity and mortality from surgical lung biopsy come from case series, and therefore have limitations and are not necessarily generalizable to other centres. The study in Chapter 5 assessed the issue of mortality following lung biopsy using a large dataset from the United States, however it was not possible to assess mortality after hospital discharge, and therefore comparison to the 30-day and 90-day mortality figures commonly reported elsewhere is difficult. Furthermore, US practice may be different to that in the UK and Europe, and a complementary study would offer additional evidence on surgical risks.

6.1.3 – Aims and Objectives

This chapter aims to assess the use of surgical lung biopsy for the diagnosis of interstitial lung disease using a secondary care dataset from the United Kingdom. As well as estimating the frequency of the procedure in the UK, it is

planned to link the data to national mortality statistics, to allow estimation of 30-day and 90-day mortality figures. Patient factors impacting on this risk will be assessed, with a further objective being to assess the cause of death in patients who have undergone lung biopsy.

6.2 – Methods

This was an observational study using a large linked clinical database. This section describes the data sources, case selection, outcomes and confounding variables, and statistical methods used.

6.2.1 – Source of data

The primary data source for this study was the Hospital Episodes Statistics (HES) database. This comprises a record of all admissions to National Health Services hospitals in England, and is maintained by the Health and Social Care Information Centre (HSCIC), a body linked to the UK Department of Health (251). Each record reflects an 'episode' of care under a particular consultant, and therefore a typical admission may involve a number of linked episodes. For example, a patient admitted with chest pain may spend time on the acute medical unit, coronary care unit, and rehabilitation ward: each of these periods would comprise a separate episode. As well as inpatient stays, HES also records outpatient and emergency department attendances, and in total collates over 125 million records each year.

Data is collected during a patient's time at hospital, and includes demographic details such as age and sex, dates and methods of admission and discharge, and details of clinical diagnoses and procedures. Diagnoses are coded using the International Classification of Diseases, 10th Revision (ICD-10) (252), and procedures are coded using the OPCS Classification of Interventions and Procedures version 4 (OPCS-4) (253). Details are submitted centrally on a monthly basis to allow hospitals to be paid for the care delivered.

To allow assessment of deaths occurring after discharge from hospital, HES data can be linked to mortality data from the UK Office of National Statistics (ONS) (254). This data originates from death certificates universally completed by physicians after a person's death. Matching of records relies on adequate shared details between the two datasets and follows set

algorithms, and data are then supplied to users in a pseudonymised format. ONS data provides both date of death and underlying cause of death.

Data from 1989-2008 were requested for this study, although records from years prior to 1997 were subsequently excluded as these did not have a unique identifier that allowed pairing with the ONS data. Due to the process of grouping data, this yielded data from April 1997 to March 2009, and the latest date included in linked ONS data was 22 June 2010. Approval for the project was provided by the HSCIC Data Access Advisory Group, and funding for the application came from the University of Nottingham postgraduate support costs fund.

6.2.2 – Case selection

Patients with a diagnosis of interstitial lung disease were selected using the following ICD-10 codes: J84.1 (other interstitial pulmonary disease with fibrosis), J84.8 (other specified interstitial pulmonary diseases), J84.9 (interstitial pulmonary disease, unspecified), D86.0 (sarcoidosis of lung), J67.9 (hypersensitivity pneumonitis due to unspecified organic dust), J99.0 (rheumatoid lung disease), and J99.1 (respiratory disorders in other diffuse connective tissue disorders).

Those patients undergoing surgical lung biopsy were then identified using the following four OPCS-4 procedure codes: E59.3 (biopsy of lesion of lung), E55.2 (open excision of lung), E54.8 (other specified excision of lung) and E54.9 (unspecified excision of lung). The presence of one of these codes anywhere in a record was used as an indicator of the patient having undergone a lung biopsy. To ensure patients undergoing radiological biopsies under the care of respiratory physicians were not included, only those records with a treating speciality of ‘cardiothoracic surgery’ were retained.

6.2.3 – Exclusion criteria

Additional procedure codes suggesting radiologically-guided interventions were queried in the database, and any patient with one of the following codes alongside their biopsy code was excluded: Y53.1 (approach to organ under radiological control), Y53.2 (approach to organ under ultrasonic control), and Y53.3 (approach to organ under computed tomographic control). Three other codes – Y53.6 (approach to organ under video control), Y53.8 (other specified approach to organ under imaging control) and Y53.9 (unspecified approach to organ under imaging control) – could be consistent with video-assisted thoracoscopic surgery (VATS) and any patient with one of these codes was retained, however a sensitivity analysis excluding the two less specific 'imaging' codes was performed.

Any patients undergoing repeat operations were excluded, as were those with additional codes specifying lung resections (lobectomy, pneumonectomy or segmentectomy), those with codes for lung cancer in the current or subsequent record, and those dying of lung cancer within 90 days of surgery. Relevant codes used to identify lung resections and lung cancer are listed in Appendix E.

In the majority of cases, surgical lung biopsy was coded as the first or 'primary' operation, but in other cases it was coded as the second or subsequent operation despite appearing to be the most significant procedure. For this reason, any incidence of a biopsy code in the record was considered relevant; however those records where the biopsy was coded anywhere other than the first position were reviewed individually to ensure the record was consistent with a surgical lung biopsy. Any patients where the nature of the biopsy was in doubt – for example, accompanying a primary code specifying biopsy of a pleural lesion – were excluded.

Finally, any patients without a clear age or sex record were excluded.

6.2.4 – Outcome variables

The main outcome variables were in-hospital, 30-day and 90-day mortality, which were calculated using dates of death available from the ONS and the operation date specified in the HES dataset. An additional outcome for those patients who died was cause of death, which was categorised into broad categories from the underlying causes according to the largest frequencies identified, and recorded for all deaths as well as for each of the three early mortality categories.

Additional outcomes for all biopsy patients were length of stay, post-procedural complications, and re-admission rates. Complications were derived from additional diagnostic codes in the operation record that would be consistent with a post-procedural complication; for conditions that could be a co-morbidity (for example, arrhythmia) these had to be absent from the preceding admission record (if available). Complications explored are listed in Appendix E. Additionally, whether a patient spent time in a critical care area was assessed using the specific variable for this from the HES dataset. Re-admissions were assessed with reference to the subsequent three month time period, with the following data being collected: the number of patients having a re-admission within 3 months, the number of re-admissions per patient, and the likely cause (as determined by the primary diagnosis, grouped into broad categories as per the largest frequencies identified).

6.2.5 – Exposure and confounding variables

Sex and age were recorded for all patients, with age categorised into five groups: less than 45 years, 45-54 years, 55-64 years, 65-74 years, and older than 74 years. There were insufficient numbers of patients aged over 84 years to include this as a separate category. Year of biopsy was noted and grouped into four categories: 1997-1999, 2000-2002, 2003-2005, and 2006-2008 (this grouping excluded the few patients with an operation date in the early part of 2009).

Data on geographical region were obtained using Lower Super Output Area codes available for each patient. Lower Super Output Areas (LSOAs) are small areas of the country with similar social characteristics and a population of around 1,500, used as part of collating census data: there were 32,482 of these in England at the time of this study (255). These were matched to the nine geographical regions in England, but where a match was not possible, the postal district variable was used to allocate to a specific region, with a minority of cases classified as 'other or unknown'. The LSOA was also used to assign a level of deprivation to each patient using the Index of Multiple Deprivation (IMD) score (2010): this score reflects indicators such as income, employment, education and crime, and can be applied to individual LSOAs, with a low score given to areas that are least deprived (256). IMD 2010 data were matched to the HES dataset using the LSOA variable.

Admissions were classified as elective (scheduled) or non-elective (emergency) using a 'waiting time' variable which provided the length of time between the 'decision to admit' and the actual admission date: this variable was only valid for elective admissions, and if missing was assumed to reflect a non-elective admission (these records either had no valid decision-to-admit date or a decision-to-admit date that was identical to the admission date).

Type of operation was assessed where possible by the presence of relevant additional procedural codes. All patients with the biopsy code E55.2 (open excision of lung) or the additional code Y49.3 (thoracotomy) were classified as 'open', assuming there were no other codes suggestive of a VATS procedure. Any patient with one of five codes suggestive of a thoracoscopic or minimal access approach (Y74.1, Y74.2, Y74.4, Y74.8, Y74.9) or the code specifying approach under video control (Y536) were classified as 'VATS', assuming there were no codes suggestive of an open procedure. Any patient with no indicator, or both VATS and open indicators together, was classified as 'unclear or not specified'.

As in Chapter 5, co-morbidity was assessed using the updated Charlson score (242). Information on how to use this score is shown in Table 5-1 and Section

5.2.5. Co-morbidities were derived from additional diagnostic codes present in either the operation record or the previous records, using published guidance as described previously in Chapter 5 (244) and scores were categorised as ‘0’, ‘1’, ’2’, or ‘3 or more’, with higher scores indicating a higher level of co-morbidity.

ILD diagnostic codes were used to assign patients a provisional diagnosis, accepting this might be modified by subsequent histological results. It was not possible to reliably assign a definitive diagnosis based on the latest record present as these were not always consistent. Any patient with more than one diagnostic code was pragmatically coded as code J84.9 (‘unspecified’ ILD).

6.2.6 – Statistical analysis

Statistical analysis was performed using Stata, version 14.0 (StataCorp, College Station, Texas, USA). Logistic regression was used to identify risk factors for early mortality, with a focus on 90-day mortality due to the expected increased numbers of deaths. In the multivariable analysis, adjustment was made for sex, age, level of co-morbidity, level of deprivation, type of operation, and provisional diagnosis. Level of deprivation was analysed as a continuous rather than categorical variable, as the latter was no more effective using the likelihood ratio test. Overall p values and p-for-trend values were calculated using the likelihood ratio test.

Survival was assessed from date of operation using the Cox proportional hazards model, with censoring of survivors on 22 June 2010 (the last date of ONS data) or on date of lung transplantation, which was identified by searching for the relevant procedure codes. The proportional hazards assumption was examined using the Schoenfeld residual test.

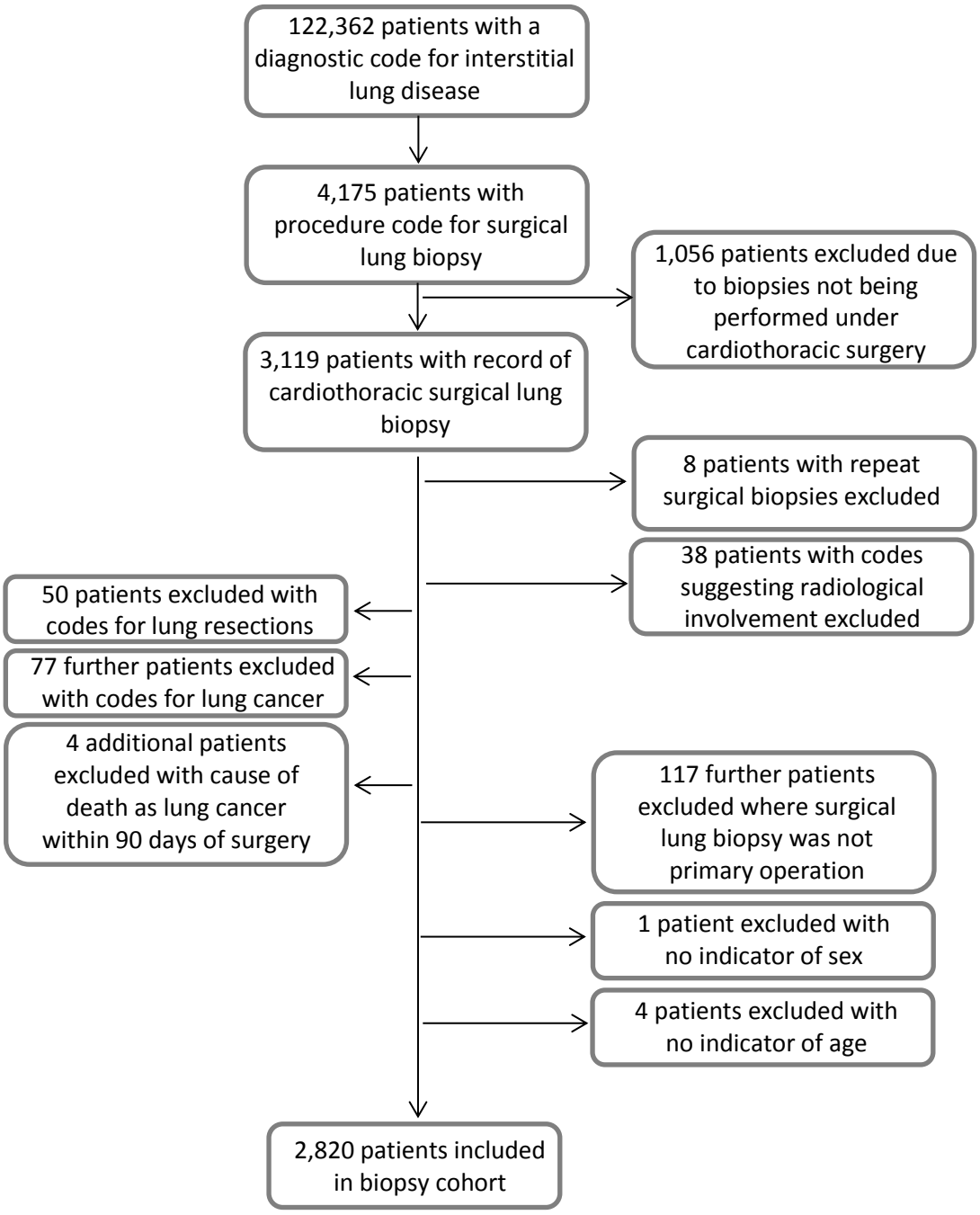
6.3 – Results

This section will outline the selection process for cases with numbers of exclusions at each stage, followed by basic demographics such as age and sex and proportions of other variables, and details of how the number of biopsies changed over time. Post-operative complications and re-admissions data will then be presented, followed by in-hospital, 30-day and 90-day mortality, cause of death data, and risk factors for early mortality. The section will finish with the survival analysis.

6.3.1 – Cohort selection

A flow diagram demonstrating the selection of cases is shown in Figure 6-1. There were 122,362 patients with a diagnostic code for interstitial lung disease in the HES dataset, and 4,175 of these had a procedure code for a surgical lung biopsy. 1,056 were excluded due to being under specialties other than cardiothoracic surgery, 8 were excluded due to repeat operations, and 38 had codes suggesting radiological involvement. 131 further patients were excluded due to the possibility the operation was related to lung cancer, 117 had the biopsy listed as a non-primary operation with some concern about the nature of the procedure, and 5 patients had no age or sex indicator. This resulted in a total of 2,820 patients included in the biopsy cohort.

Figure 6-1: Flow diagram of selection process for patients undergoing surgical lung biopsy for interstitial lung disease in England



6.3.2 – Demographics and other characteristics of cohort

Demographics of the biopsy cohort are shown in Table 6-1. Of the 2,820 patients undergoing surgical lung biopsy for ILD during the twelve year period, 55% were male and 73% were below the age of 65. 81% of biopsies were classified as elective and 19% were non-elective. These groups had similar proportions of demographics, although the non-elective group had a higher proportion with increased co-morbidity and a higher proportion in the youngest age group.

Table 6-1: Demographics of HES biopsy cohort

	Total admissions ***(n=2,820)***	**Elective admissions** ***(n=2,277)***	**Non-elective admissions** ***(n=543)***
	Number (%)	Number (%)	Number (%)
Sex			
Male	1,546 (54.8)	1,250 (54.9)	296 (54.5)
Female	1,274 (45.2)	1,027 (45.1)	247 (45.5)
Age group (years)			
<45	576 (20.4)	444 (19.5)	132 (24.3)
45-54	636 (22.6)	521 (22.9)	115 (21.2)
55-64	843 (29.9)	702 (30.8)	141 (26.0)
65-74	588 (20.9)	482 (21.2)	106 (19.5)
>74	177 (6.3)	128 (5.6)	49 (9.0)
Level of co-morbidity (Updated Charlson score)			
0	1,947 (69.0)	1,617 (71.0)	330 (60.8)
1	717 (25.4)	553 (24.3)	164 (30.2)
2	116 (4.1)	79 (3.5)	37 (6.8)
3 or greater	40 (1.4)	28 (1.2)	12 (2.2)

HES: Hospital Episodes Statistics.
Higher Updated Charlson score = greater co-morbidity.

The biopsy rate ranged from 0.27-0.74 per 100,000 across the English regions (see Table 6-2). To give this some context, the incidence of IPF specifically per region is presented according to the study by Gribbin *et al* (23). There was some correlation between these figures, for example the highest biopsy rate was in the South West where there was the highest incidence of IPF, however in other areas there was a disconnect, for example Yorkshire and Humber where there was the second highest biopsy rate but the lowest incidence of IPF. It is important to note that these numbers do not reflect the incidence of ILD other than IPF.

Table 6-2: Number of biopsies per region of England

Region	Number of cases (%)	Person-years*	Biopsies per 100,000 population	*Crude incidence of IPF per 100,000 (23)*
East Midlands	136 (4.8)	51,073,100	0.27	*3.92*
East of England	378 (13.4)	65,629,300	0.58	*4.75*
London	356 (12.6)	88,620,000	0.40	*3.68*
North East	154 (5.5)	30,615,400	0.50	*5.66*
North West	315 (11.2)	82,006,200	0.38	*5.76*
South East	307 (10.9)	97,228,900	0.32	*3.55*
South West	446 (15.8)	60,020,800	0.74	*5.89*
West Midlands	266 (9.4)	64,073,400	0.42	*4.77*
Yorkshire & Humber	414 (14.7)	60,501,700	0.68	*3.52*
Other / Unknown †	48 (1.7)	-	-	-
OVERALL	*2,820 (100)*	*599,768,800*	*0.47*	*4.6*‡

*Person-years: this was calculated by adding together mid-year population estimates for each region for each year from 1997-2008, rounded to the nearest hundred persons – for example, the mid-year population estimate for the East Midlands for 1997 was 4.1 million, rising to 4.4 million in 2008, giving a cumulative total of 51 million person-years, as shown. Population statistics from the Office of National Statistics, accessed November 2015 from http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-162632 and http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-315018.

Biopsies per 100,000 calculated by dividing cases by person-years for each region, then multiplying by 100,000.

Data on incidence of IPF per region based on Gribbin *et al* (2006) Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax. 61:980-985. doi: 10.1136/thx.2006.062836.

† 'Other' includes patients with a postcode from Scotland or Wales who attended English hospitals.

‡ Overall incidence across *United Kingdom* (ie including Scotland/Wales/N Ireland).

Codes indicating whether an operation was performed via open thoracotomy or video-assisted thoracoscopic surgery (VATS) were available for 38% of operations. Of these, 66% were VATS. No VATS codes were listed prior to 2006, with 80% of patients having a code for the type of operation from 2007 onwards, suggesting the code for VATS came into coding practice at this time. The most common provisional diagnosis was J84.1 (the most specific code for IPF, but also potentially including other idiopathic interstitial pneumonias) which comprised 50.8% of codes, followed by J84.9 ('unspecified ILD') with 28.8% of codes. This included 81 patients with more than one diagnostic code listed.

6.3.3 – Number of biopsies over time

The number of biopsies increased over the years in the study period (see Table 6-3). Numbers increased for both males and females (Figure 6-2), across all age categories (Figure 6-3), and for both elective and non-elective procedures – although to a lesser extent for the non-elective ones (Figure 6-4).

Table 6-3: Number of biopsies by year in England

	Total admissions (n=2,820)	**Elective admissions (n=2,277)**	**Non-elective admissions (n=543)**
	Number (%)	Number (%)	Number (%)
Year			
1997 (April onwards)	104 (3.7)	86 (3.8)	18 (3.3)
1998	169 (6.0)	123 (5.4)	46 (8.5)
1999	191 (6.8)	155 (6.8)	36 (6.6)
2000	185 (6.6)	159 (7.0)	26 (4.8)
2001	213 (7.6)	178 (7.8)	35 (6.5)
2002	195 (6.9)	146 (6.4)	49 (9.0)
2003	197 (7.0)	157 (6.9)	40 (7.4)
2004	239 (8.5)	195 (8.6)	44 (8.1)
2005	262 (9.3)	215 (9.4)	47 (8.7)
2006	261 (9.3)	209 (9.2)	52 (9.6)
2007	345 (12.2)	279 (12.3)	66 (12.2)
2008	367 (13.0)	291 (12.8)	76 (14.0)
2009 (until March)	92 (3.3)	84 (3.7)	8 (1.5)

Figure 6-2: Number of biopsies over time in England, stratified by sex

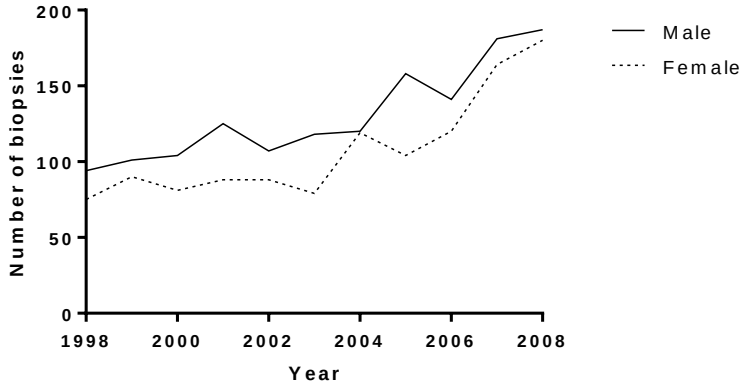


Figure 6-3: Number of biopsies over time in England, stratified by age category

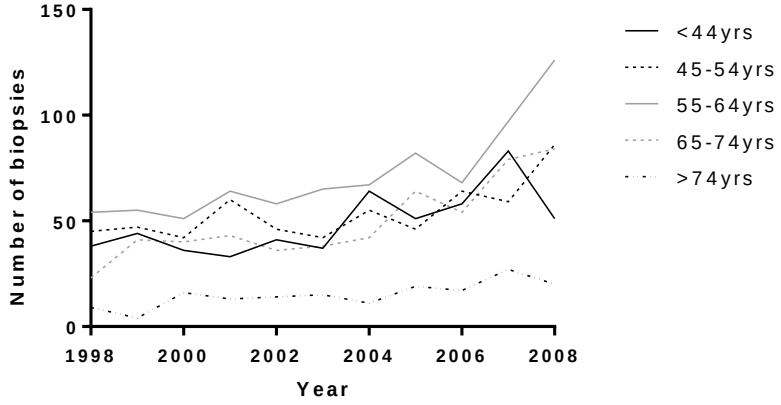
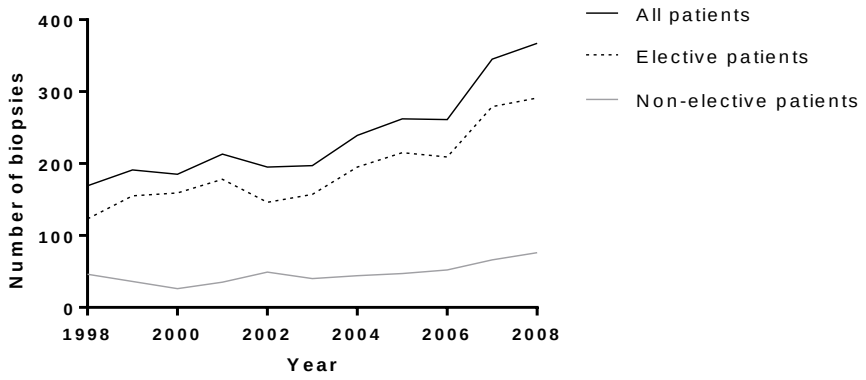


Figure 6-4: Number of biopsies over time in England, by elective vs non-elective status



6.3.4 – Post-operative complications and length of stay

Complications occurred in 13.9% of operations. The most common were pneumothorax (4.2%), pneumonia (2.8%), other unspecified complications of the procedure (1.9%), pleural effusion (1.4%), and failed thoracoscopic approach with conversion to open surgery (1.2%). 8.4% of patients with a valid record for critical care input (87% of the total cohort) spent time in a critical care area: for most this was a single stay but 24 patients had more than one stay. The median length of hospital stay was 4 days (range 0-82).

6.3.5 – Re-admissions

14.1% of patients were re-admitted to hospital within three months, with 28.0% of these having more than one re-admission. Half of initial re-admissions had a primary diagnosis of interstitial lung disease (Table 6-4).

Table 6-4: Cause of re-admissions within three months (for first re-admission only) for patients undergoing surgical lung biopsy for interstitial lung disease in England

Primary diagnosis *(n=397)*	**Number of re-admissions (%)**
Interstitial lung disease	202 (50.9)
Pneumonia/lower respiratory tract infection	38 (9.6)
Pneumothorax	19 (4.8)
Specified post-procedural issue	15 (3.8)
Haemorrhage complicating a procedure	*2 (0.5)*
Infection following a procedure	*5 (1.3)*
Other complication of procedure	*8 (2.0)*
Cardiac problem (for example, myocardial infarction)	16 (4.0)
Other respiratory symptoms (for example, 'cough')	10 (2.5)
Chest pain – not otherwise classified	8 (2.0)
Other infection (for example, urinary tract infection)	7 (1.8)
Pulmonary embolism	5 (1.3)
Pyothorax	2 (0.5)
Pleural effusion / haemothorax	4 (1.0)
Respiratory failure – other	3 (0.8)
Other respiratory – likely unrelated (for example, COPD)	8 (2.0)
Other – unrelated	60 (15.1)

6.3.6 – Early mortality

There were 911 deaths (32% of the cohort) until the end of June 2010. With regards early deaths, in-hospital mortality was 1.7% (47 deaths), 30-day mortality was 2.4% (68 deaths) and 90-day mortality was 3.9% (111 deaths).

Elective biopsies had a lower mortality than non-elective ones: for elective procedures, in-hospital, 30-day and 90-day mortality were 1.0%, 1.5% and 2.8% respectively; for non-elective procedures, the figures were 4.6%, 6.3% and 8.8% respectively.

6.3.7 – Cause of death

For all patients undergoing surgical lung biopsy, the most common cause of death was interstitial lung disease (50% of deaths), followed by cancer (18%) and cardiac disease (8%) (Table 6-5). Interstitial lung disease remained by far the most common cause of death for those dying in-hospital (61.7% of deaths), within 30 days (57.4% of deaths), and within 90 days (61.3% of deaths).

Table 6-5: Cause of death of patients undergoing surgical lung biopsy for interstitial lung disease in England

Cause of death *(n=911)*	**Number of deaths (%)**
Interstitial lung disease	451 (49.5)
Cancer (excluding lung cancer)	94 (10.3)
Lung cancer	71 (7.8)
Ischaemic heart disease or heart failure	53 (5.8)
Chronic obstructive pulmonary disease	35 (3.8)
Pneumonia	35 (3.8)
Other respiratory	29 (3.2)
Connective tissue disease	25 (2.7)
Other cardiac cause	21 (2.3)
Stroke	13 (1.4)
Other	65 (7.1)
No data	19 (2.1)

6.3.8 – Risk factors for early mortality

Risk factors for death within 90 days of biopsy (the time period yielding the most power) were identified as male sex, increasing age, increasing co-morbidity, and use of open thoracotomy (Table 6-6). Results were broadly similar for deaths within 30 days or in-hospital, although the effect of co-morbidity was stronger for in-hospital deaths (Table 6-7, Table 6-8).

Risk factors were less significant when non-elective patients were excluded (Table 6-9, Table 6-10, Table 6-11). In a sensitivity analysis excluding 593 patients who had an additional procedure code specifying 'approach to organ under imaging control' (which could be applied to VATS but was non-specific and therefore unclear), mortality was slightly higher at 1.9% (in-hospital), 2.7% (30 day) and 4.2% (90 day).

After splitting admissions into four time periods, mortality was lowest in the latest time period (2006-2008) for in-hospital, 30-day and 90-day mortality measures; in-hospital mortality of 1.0% in 2006-2008 vs 1.7% in 1997-1999; 30-day mortality of 1.8% in 2006-2008 vs 3.0% in 1997-1999; and 90-day mortality of 2.8% in 2006-2008 vs 4.3% in 1997-1999. Risk factors for death within 90 days of biopsy for the period 2005 onwards are presented in Table 6-12, although these data were limited by small numbers.

Table 6-6: Multivariable analysis – associations with death within 90 days of surgical lung biopsy for interstitial lung disease

Variables	Cases	Deaths (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Sex						
Female	1,274	36 (2.8)	1.00	0.005	1.00	0.038
Male	1,546	75 (4.9)	1.75 (1.17-2.63)		1.54 (1.02-2.34)	
Age group (years)						
<45	576	10 (1.7)	1.00	<0.001 (p for trend)	1.00	<0.001 (p for trend)
45-54	636	21 (3.3)	1.93 (0.90-4.14)		1.72 (0.79-3.72)	
55-64	843	31 (3.7)	2.16 (1.05-4.44)		1.85 (0.89-3.82)	
65-74	588	32 (5.4)	3.26 (1.59-6.69)		2.81 (1.35-5.82)	
>74	177	17 (9.6)	6.01 (2.70-13.39)		4.33 (1.90-9.89)	
Updated Charlson score						
0	1,947	75 (3.9)	1.00	0.082 (p for trend)	1.00	0.037 (p for trend)
1	717	23 (3.2)	0.83 (0.51-1.33)		1.02 (0.61-1.69)	
2	116	8 (6.9)	1.85 (0.87-3.93)		1.63 (0.75-3.54)	
≥3	40	*	3.57 (1.36-9.36)		3.88 (1.43-10.58)	
IMD score						
	2,760	109 (4.0)	0.99 (0.98-1.01)	0.381	1.00 (0.98-1.01)	0.521
Type of operation						
VATS	703	14 (2.0)	1.00	0.002	1.00	0.004
Open	362	21 (5.8)	3.03 (1.52-6.03)		2.94 (1.41-6.11)	
Unclear or n/s	1,755	76 (4.3)	2.23 (1.25-3.97)		2.37 (1.29-4.36)	
Provisional diagnosis						
J84.1	1,433	76 (5.3)	1.00	<0.001	1.00	0.008
J84.9	812	28 (3.5)	0.64 (0.41-0.99)		0.76 (0.48-1.20)	
J84.8	99	*	0.18 (0.03-1.32)		0.23 (0.03-1.65)	
RA-ILD	16	0	-		-	
CTD-ILD	38	*	0.99 (0.23-4.20)		0.91 (0.21-3.94)	
HP	162	*	0.34 (0.11-1.08)		0.45 (0.13-1.55)	
Sarcoid	260	*	0.07 (0.01-0.50)		0.10 (0.01-0.74)	

'*' in this table means a number between 1 and 5 – small numbers hidden to aid confidentiality.

Higher updated Charlson score reflects greater degree of co-morbidity.

95% CI: 95% confidence interval; IMD: index of multiple deprivation (lower score = least deprived); VATS: video-assisted thoracoscopic surgery; n/s: not specified.

J84.1: other interstitial pulmonary disease with fibrosis; J84.9: interstitial pulmonary disease, unspecified; J84.8: other specified interstitial pulmonary disease; RA-ILD (J99.0): rheumatoid lung disease; CTD-ILD (J99.1): respiratory disorders in other diffuse connective tissue disorders; HP (J67.9): hypersensitivity pneumonitis due to unspecified organic dust; Sarcoid (D86.0): sarcoidosis of lung.

For type of operation, 'unclear or not specified' mainly reflects older data from before a specific code for VATS was available. These cases are likely to be a combination of open and VATS procedures, with increasing numbers of VATS in later years.

Table 6-7: Multivariable analysis – associations with death within 30 days of surgical lung biopsy for interstitial lung disease

Variables	Cases	Deaths (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Sex						
Female	1,274	24 (1.9)	1.00	0.094	1.00	0.205
Male	1,546	44 (2.9)	1.53 (0.92-2.52)		1.40 (0.83-2.35)	
Age group (years)						
<45	576	6 (1.0)	1.00	<0.001 (p for trend)	1.00	<0.001 (p for trend)
45-54	636	12 (1.9)	1.83 (0.68-4.90)		1.64 (0.61-4.43)	
55-64	843	16 (1.9)	1.84 (0.71-4.73)		1.53 (0.59-3.97)	
65-74	588	21 (3.6)	3.52 (1.41-8.78)		2.96 (1.18-7.46)	
>74	177	13 (7.3)	7.53 (2.82-20.12)		5.23 (1.90-14.39)	
Updated Charlson score						
0	1,947	45 (2.3)	1.00	0.042 (p for trend)	1.00	0.039 (p for trend)
1	717	13 (1.8)	0.78 (0.42-1.46)		0.85 (0.43-1.68)	
2	116	6 (5.2)	2.31 (0.96-5.52)		1.93 (0.79-4.75)	
≥3	40	*	4.70 (1.60-13.75)		4.80 (1.58-14.54)	
IMD score						
	2,760	67 (2.4)	1.00 (0.98-1.02)	0.985	1.00 (0.99-1.02)	0.841
Type of operation						
VATS	703	11 (1.6)	1.00	0.154	1.00	0.181
Open	362	12 (3.3)	2.16 (0.94-4.94)		2.14 (0.89-5.15)	
Unclear or n/s	1,755	45 (2.6)	1.66 (0.85-3.22)		1.72 (0.85-3.49)	
Provisional diagnosis						
J84.1	1,433	47 (3.3)	1.00	0.142	1.00	0.499
J84.9	812	15 (1.9)	0.56 (0.31-1.00)		0.66 (0.36-1.20)	
J84.8	99	*	0.30 (0.04-2.20)		0.37 (0.05-2.75)	
RA-ILD	16	0	-		-	
CTD-ILD	38	*	1.64 (0.38-7.01)		1.48 (0.34-6.55)	
HP	162	*	0.56 (0.17-1.81)		0.84 (0.23-3.05)	
Sarcoid	260	0	-		-	

'*' in this table means a number between 1 and 5 – small numbers hidden to aid confidentiality.

Higher updated Charlson score reflects greater degree of co-morbidity.

95% CI: 95% confidence interval; IMD: index of multiple deprivation (lower score = least deprived); VATS: video-assisted thoracoscopic surgery; n/s: not specified.

J84.1: other interstitial pulmonary disease with fibrosis; J84.9: interstitial pulmonary disease, unspecified; J84.8: other specified interstitial pulmonary disease; RA-ILD (J99.0): rheumatoid lung disease; CTD-ILD (J99.1): respiratory disorders in other diffuse connective tissue disorders; HP (J67.9): hypersensitivity pneumonitis due to unspecified organic dust; Sarcoid (D86.0): sarcoidosis of lung.

For type of operation, 'unclear or not specified' mainly reflects older data from before a specific code for VATS was available. These cases are likely to be a combination of open and VATS procedures, with increasing numbers of VATS in later years.

Table 6-8: Multivariable analysis – associations with in-hospital death following surgical lung biopsy for interstitial lung disease

Variables	Cases	Deaths (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Sex						
Female	1,274	17 (1.3)	1.00	0.207	1.00	0.414
Male	1,546	30 (1.9)	1.46 (0.80-2.67)		1.29 (0.70-2.38)	
Age group (years)						
<45	576	*	1.00	0.002	1.00	0.006
45-54	636	9 (1.4)	2.05 (0.63-6.70)	(p for trend)	1.91 (0.58-6.31)	(p for trend)
55-64	843	13 (1.5)	2.24 (0.73-6.90)		1.98 (0.64-6.15)	
65-74	588	14 (2.4)	3.49 (1.14-10.66)		3.10 (1.00-9.58)	
>74	177	7 (4.0)	5.89 (1.70-20.35)		4.85 (1.37-17.11)	
Updated Charlson score						
0	1,947	25 (1.3)	1.00	0.002	1.00	0.002
1	717	14 (2.0)	1.53 (0.79-2.96)	(p for trend)	1.83 (0.91-3.68)	(p for trend)
2	116	*	3.46 (1.30-9.22)		2.94 (1.08-8.01)	
≥3	40	*	6.23 (1.80-21.56)		6.51 (1.82-23.26)	
IMD score						
	2,760	47 (1.7)	1.00 (0.98-1.02)	0.876	1.00 (0.98-1.02)	0.803
Type of operation						
VATS	703	*	1.00	0.011	1.00	0.025
Open	362	9 (2.5)	4.46 (1.36-14.57)		3.89 (1.16-13.06)	
Unclear or n/s	1,755	34 (1.9)	3.45 (1.22-9.76)		3.31 (1.15-9.51)	
Provisional diagnosis						
J84.1	1,433	34 (2.4)	1.00	0.214	1.00	0.508
J84.9	812	9 (1.1)	0.46 (0.22-0.97)		0.57 (0.27-1.21)	
J84.8	99	*	0.42 (0.06-3.10)		0.52 (0.07-3.86)	
RA-ILD	16	0	-		-	
CTD-ILD	38	*	1.11 (0.15-8.34)		0.88 (0.11-6.75)	
HP	162	*	0.51 (0.12-2.16)		0.47 (0.10-2.13)	
Sarcoid	260	0	-		-	

'*' in this table means a number between 1 and 5 – small numbers hidden to aid confidentiality.

Higher updated Charlson score reflects greater degree of co-morbidity.

95% CI: 95% confidence interval; IMD: index of multiple deprivation (lower score = least deprived); VATS: video-assisted thoracoscopic surgery; n/s: not specified.

J84.1: other interstitial pulmonary disease with fibrosis; J84.9: interstitial pulmonary disease, unspecified; J84.8: other specified interstitial pulmonary disease; RA-ILD (J99.0): rheumatoid lung disease; CTD-ILD (J99.1): respiratory disorders in other diffuse connective tissue disorders; HP (J67.9): hypersensitivity pneumonitis due to unspecified organic dust; Sarcoid (D86.0): sarcoidosis of lung.

For type of operation, 'unclear or not specified' mainly reflects older data from before a specific code for VATS was available. These cases are likely to be a combination of open and VATS procedures, with increasing numbers of VATS in later years.

Table 6-9: Multivariable analysis – associations with death within 90 days of surgical lung biopsy for interstitial lung disease – elective patients only

Variables	Cases	Deaths (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Sex						
Female	1,027	23 (2.2)	1.00	0.161	1.00	0.321
Male	1,250	40 (3.2)	1.44 (0.86-2.43)		1.31 (0.77-2.23)	
Age group (years)						
<45	444	8 (1.8)	1.00	0.169 (p for trend)	1.00	0.408 (p for trend)
45-54	521	16 (3.1)	1.73 (0.73-4.07)		1.42 (0.59-3.41)	
55-64	702	20 (2.9)	1.60 (0.70-3.66)		1.32 (0.57-3.05)	
65-74	482	12 (2.5)	1.39 (0.56-3.44)		1.12 (0.45-2.79)	
>74	128	7 (5.5)	3.15 (1.12-8.87)		2.33 (0.81-6.68)	
Updated Charlson score						
0	1,617	43 (2.7)	1.00	0.112 (p for trend)	1.00	0.036 (p for trend)
1	553	14 (2.5)	0.95 (0.52-1.75)		1.21 (0.63-2.33)	
2	79	*	0.95 (0.23-4.00)		1.00 (0.24-4.27)	
≥3	28	*	6.10 (2.03-18.35)		7.20 (2.28-22.75)	
IMD score						
	2,226	62 (2.8)	0.99 (0.97-1.01)	0.288	0.99 (0.97-1.01)	0.223
Type of operation						
VATS	583	8 (1.4)	1.00	0.036	1.00	0.039
Open	275	8 (2.9)	2.15 (0.80-5.80)		1.87 (0.65-5.33)	
Unclear or n/s	1,419	47 (3.3)	2.46 (1.16-5.24)		2.49 (1.15-5.38)	
Provisional diagnosis						
J84.1	1,151	40 (3.5)	1.00	0.411	1.00	0.568
J84.9	664	20 (3.0)	0.86 (0.50-1.49)		0.94 (0.53-1. 66)	
J84.8	81	*	0.35 (0.05-2.56)		0.41 (0.06-3.05)	
RA-ILD	12	0	-		-	
CTD-ILD	26	0	-		-	
HP	125	*	0.45 (0.11-1.89)		0.47 (0.10-2.15)	
Sarcoid	218	0	-		-	

'*' in this table means a number between 1 and 5 – small numbers hidden to aid confidentiality.

Higher updated Charlson score reflects greater degree of co-morbidity.

95% CI: 95% confidence interval; IMD: index of multiple deprivation (lower score = least deprived); VATS: video-assisted thoracoscopic surgery; n/s: not specified.

J84.1: other interstitial pulmonary disease with fibrosis; J84.9: interstitial pulmonary disease, unspecified; J84.8: other specified interstitial pulmonary disease; RA-ILD (J99.0): rheumatoid lung disease; CTD-ILD (J99.1): respiratory disorders in other diffuse connective tissue disorders; HP (J67.9): hypersensitivity pneumonitis due to unspecified organic dust; Sarcoid (D86.0): sarcoidosis of lung.

For type of operation, 'unclear or not specified' mainly reflects older data from before a specific code for VATS was available. These cases are likely to be a combination of open and VATS procedures, with increasing numbers of VATS in later years.

Table 6-10: Multivariable analysis – associations with death within 30 days of surgical lung biopsy for interstitial lung disease – elective patients only

Variables	Cases	Deaths (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Sex						
Female	1,027	13 (1.3)	1.00	0.415	1.00	0.456
Male	1,250	21 (1.7)	1.33 (0.66-2.67)		1.31 (0.64-2.67)	
Age group (years)						
<45	444	*	1.00	0.552 (p for trend)	1.00	0.860 (p for trend)
45-54	521	11 (2.1)	2.37 (0.75-7.50)		2.09 (0.65-6.67)	
55-64	702	10 (1.4)	1.59 (0.50-5.10)		1.31 (0.41-4.25)	
65-74	482	*	1.15 (0.31-4.32)		0.94 (0.25-3.58)	
>74	128	*	3.55 (0.87-14.39)		2.74 (0.66-11.42)	
Updated Charlson score						
0	1,617	22 (1.4)	1.00	0.064 (p for trend)	1.00	0.046 (p for trend)
1	553	8 (1.5)	1.06 (0.47-2.40)		1.15 (0.47-2.84)	
2	79	*	0.93 (0.12-6.98)		0.96 (0.13-7.31)	
≥3	28	*	8.70 (2.44-30.96)		9.33 (2.50-34.85)	
IMD score						
	2,226	34 (1.5)	0.99 (0.97-1.02)	0.609	0.99 (0.97-1.02)	0.476
Type of operation						
VATS	583	*	1.00	0.279	1.00	0.281
Open	275	*	1.71 (0.45-6.40)		1.76 (0.46-6.84)	
Unclear or n/s	1,419	25 (1.8)	2.07 (0.79-5.44)		2.11 (0.79-5.66)	
Provisional diagnosis						
J84.1	1,151	20 (1.7)	1.00	0.987	1.00	0.995
J84.9	664	11 (1.7)	0.95 (0.45-2.00)		1.09 (0.51-2.33)	
J84.8	81	*	0.71 (0.09-5.33)		0.87 (0.11-6.68)	
RA-ILD	12	0	-		-	
CTD-ILD	26	0	-		-	
HP	125	*	0.92 (0.21-3.98)		1.00 (0.20-5.05)	
Sarcoid	218	0	-		-	

'*' in this table means a number between 1 and 5 – small numbers hidden to aid confidentiality.

Higher updated Charlson score reflects greater degree of co-morbidity.

95% CI: 95% confidence interval; IMD: index of multiple deprivation (lower score = least deprived); VATS: video-assisted thoracoscopic surgery; n/s: not specified.

J84.1: other interstitial pulmonary disease with fibrosis; J84.9: interstitial pulmonary disease, unspecified; J84.8: other specified interstitial pulmonary disease; RA-ILD (J99.0): rheumatoid lung disease; CTD-ILD (J99.1): respiratory disorders in other diffuse connective tissue disorders; HP (J67.9): hypersensitivity pneumonitis due to unspecified organic dust; Sarcoid (D86.0): sarcoidosis of lung.

For type of operation, 'unclear or not specified' mainly reflects older data from before a specific code for VATS was available. These cases are likely to be a combination of open and VATS procedures, with increasing numbers of VATS in later years.

Table 6-11: Multivariable analysis – associations with in-hospital death following surgical lung biopsy for interstitial lung disease – elective patients only

Variables	Cases	Deaths (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Sex						
Female	1,027	10 (1.0)	1.00	0.974	1.00	0.998
Male	1,250	12 (1.0)	0.99 (0.42-2.29)		1.00 (0.42-2.37)	
Age group (years)						
<45	444	*	1.00	0.522 (p for trend)	1.00	0.670 (p for trend)
45-54	521	7 (1.3)	3.01 (0.62-14.56)		2.59 (0.53-12.71)	
55-64	702	7 (1.0)	2.23 (0.46-10.76)		1.95 (0.40-9.51)	
65-74	482	*	1.85 (0.34-10.15)		1.54 (0.28-8.59)	
>74	128	*	3.51 (0.49-25.15)		3.05 (0.41-22.67)	
Updated Charlson score						
0	1,617	11 (0.7)	1.00	0.011 (p for trend)	1.00	0.007 (p for trend)
1	553	8 (1.5)	2.14 (0.86-5.36)		2.73 (1.04-7.16)	
2	79	*	1.87 (0.24-14.68)		2.04 (0.25-16.34)	
≥3	28	*	11.23 (2.37-53.21)		6.51 (1.82-23.26)	
IMD score						
	2,226	22 (1.0)	1.00 (0.97-1.03)	0.894	0.99 (0.97-1.02)	0.715
Type of operation						
VATS	583	*	1.00	0.102	1.00	0.083
Open	275	*	2.13 (0.30-15.19)		2.15 (0.29-15.85)	
Unclear or n/s	1,419	18 (1.3)	3.73 (0.86-16.14)		4.02 (0.91-17.76)	
Provisional diagnosis						
J84.1	1,151	14 (1.2)	1.00	0.916	1.00	0.824
J84.9	664	6 (0.9)	0.74 (0.28-1.94)		0.87 (0.33-2.33)	
J84.8	81	*	1.02 (0.13-7.82)		1.21 (0.15-9.59)	
RA-ILD	12	0	-		-	
CTD-ILD	26	0	-		-	
HP	125	*	0.65 (0.09-5.02)		0.41 (0.05-3.43)	
Sarcoid	218	0	-		-	

'*' in this table means a number between 1 and 5 – small numbers hidden to aid confidentiality.

Higher updated Charlson score reflects greater degree of co-morbidity.

95% CI: 95% confidence interval; IMD: index of multiple deprivation (lower score = least deprived); VATS: video-assisted thoracoscopic surgery; n/s: not specified.

J84.1: other interstitial pulmonary disease with fibrosis; J84.9: interstitial pulmonary disease, unspecified; J84.8: other specified interstitial pulmonary disease; RA-ILD (J99.0): rheumatoid lung disease; CTD-ILD (J99.1): respiratory disorders in other diffuse connective tissue disorders; HP (J67.9): hypersensitivity pneumonitis due to unspecified organic dust; Sarcoid (D86.0): sarcoidosis of lung.

For type of operation, 'unclear or not specified' mainly reflects older data from before a specific code for VATS was available. These cases are likely to be a combination of open and VATS procedures, with increasing numbers of VATS in later years.

Table 6-12: Multivariable analysis – associations with death within 90 days of surgical lung biopsy for interstitial lung disease – data from 2005-2008 only

Variables	Cases	Deaths (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Sex						
Female	568	17 (3.0)	1.00	0.652	1.00	0.905
Male	667	23 (3.5)	1.16 (0.61-2.19)		0.96 (0.49-1.90)	
Age group (years)						
<45	243	*	1.00	0.001	1.00	0.010
45-54	255	*	0.95 (0.27-3.33)	(p for trend)	0.93 (0.26-3.32)	(p for trend)
55-64	373	11 (3.0)	1.45 (0.50-4.22)		1.46 (0.49-4.38)	
65-74	281	9 (3.2)	1.58 (0.52-4.76)		1.50 (0.48-4.69)	
>74	83	10 (12.1)	6.52 (2.16-19.69)		4.97 (1,53-16.19)	
Updated Charlson score						
0	798	26 (3.3)	1.00	0.192	1.00	0.077
1	366	9 (2.5)	0.75 (0.35-1.61)	(p for trend	1.05 (0.47-2.31)	(p for trend)
2	45	*	0.67 (0.09-5.09)		0.62 (0.08-4.84)	
≥3	26	*	5.40 (1.74-16.79)		6.87 (2.02-23.39)	
IMD score						
	1,196	39 (3.3)	1.00 (0.97-1.02)	0.733	1.00 (0.97-1.02)	0.819
Type of operation						
VATS	631	14 (2.2)	1.00	0.071	1.00	0.119
Open	137	8 (5.8)	2.73 (1.12-6.65)		2.60 (1.01-6.71)	
Unclear or n/s	467	18 (3.9)	1.77 (0.87-3.59)		1.74 (0.83-3.67)	
Provisional diagnosis						
J84.1	548	25 (4.6)	1.00	0.128	1.00	0.531
J84.9	459	14 (3.1)	0.66 (0.34-1.28)		0.83 (0.41-1.68)	
J84.8	43	0	-		-	
RA-ILD	*	0	-		-	
CTD-ILD	14	0	-		-	
HP	73	0	-		-	
Sarcoid	93	*	0.23 (0.03-1.70)		0.38 (0.05-2.92)	

'*' in this table means a number between 1 and 5 – small numbers hidden to aid confidentiality.

Higher updated Charlson score reflects greater degree of co-morbidity.

95% CI: 95% confidence interval; IMD: index of multiple deprivation (lower score = least deprived); VATS: video-assisted thoracoscopic surgery; n/s: not specified.

J84.1: other interstitial pulmonary disease with fibrosis; J84.9: interstitial pulmonary disease, unspecified; J84.8: other specified interstitial pulmonary disease; RA-ILD (J99.0): rheumatoid lung disease; CTD-ILD (J99.1): respiratory disorders in other diffuse connective tissue disorders; HP (J67.9): hypersensitivity pneumonitis due to unspecified organic dust; Sarcoid (D86.0): sarcoidosis of lung.

For type of operation, 'unclear or not specified' mainly reflects older data from before a specific code for VATS was available. These cases are likely to be a combination of open and VATS procedures, with increasing numbers of VATS in later years.

6.3.9 – Survival analysis

Looking at survival, it was calculated that the rate of death for patients undergoing surgical lung biopsy was 6.81 per 100 person-years (95% confidence interval (CI) 6.38-7.27), suggesting that about 6% of patients would die in the first year after surgery. For those aged 65 and over, the rate of death was 13.14 per 100 person-years (95% CI 11.86-14.55) suggesting about 13% of patients would die in the first year.

Using Cox regression, it was estimated that males had a 52% increased risk of death compared to females, there was a 2-7 fold increased risk of death with increasing age compared to the lowest age category, there was an 2.3 fold increased risk of death with an updated Charlson score of 3 or more compared to 0, and a 61% increased risk of death with open surgery compared to VATS (Table 6-13).

Table 6-13: Cox regression model for survival following surgical lung biopsy for interstitial lung disease

Variables	Number of deaths / total	Hazard ratio (95% CI)	p value
Sex			
Female	331 / 1,274	1.00	<0.001
Male	577 / 1,546	1.52 (1.33-1.74)	
Age group (years)			
<45	78 / 576	1.00	<0.001
45-54	167 / 636	2.14 (1.63-2.80)	(p for trend)
55-64	295 / 843	3.17 (2.47-4.07)	
65-74	263 / 588	4.80 (3.73-6.19)	
>74	105 / 177	7.27 (5.41-9.77)	
Updated Charlson score			
0	640 / 1,947	1.00	0.029
1	200 / 717	0.92 (0.78-1.08)	(p for trend)
2	48 / 116	1.40 (1.04-1.88)	
≥3	20 / 40	2.25 (1.44-3.52)	
Type of operation			
VATS	99 / 703	1.00	<0.001
Open	133 / 362	1.61 (1.23-2.09)	
Unclear or n/s	676 / 1,755	1.57 (1.26-1.96)	

Higher updated Charlson score reflects greater degree of co-morbidity.

95% CI: 95% confidence interval; VATS: video-assisted thoracoscopic surgery; n/s: not specified.

Multivariable model adjusted for gender, age, updated Charlson score and type of operation.

For type of operation, 'unclear or not specified' mainly reflects older data from before a specific code for VATS was available. These cases are likely to be a combination of open and VATS procedures, with increasing numbers of VATS in later years.

6.4 – Discussion

6.4.1 – Summary of findings

This study has shown that an increasing number of surgical lung biopsies for interstitial lung disease were performed in England from 1997-2008, with variation according to geographical region. The figure of 367 biopsies in 2008 would equate to an average of 13 annual biopsies per thoracic surgical centre in England (see Appendix E). Assuming the estimate of 51% of biopsies being for a provisional diagnosis of J84.1 (most specific for idiopathic pulmonary fibrosis, but possibly including other idiopathic interstitial pneumonias) this would equate to around 187 biopsies per year for IPF-clinical syndrome, or 4.5% of the new cases per year in England (based on 5,000 new cases per year in the UK (24), with England comprising 84% of the UK population).

In-hospital mortality was 1.7%, 30-day mortality was 2.4%, and 90-day mortality was 3.9%. Complications were reasonably common, and the most common cause for re-admission and death was interstitial lung disease – likely (but not certain) to represent acute exacerbations. Unsurprisingly there was a higher mortality in non-elective admissions. Male sex, increasing age, increasing co-morbidity and open surgery were risk factors for early mortality.

6.4.2 – Strengths

Although not as vast as the US cohort reported in Chapter 5, this cohort of almost 3,000 patients is still larger than most case series of surgical lung biopsies for interstitial lung disease. Furthermore, like the US study, this database encompasses multiple centres from across a country, and complements this earlier work by assessing the issue in a different health system. The Hospital Episodes Statistics database allowed comprehensive capture of all records of admissions to National Health Service hospitals, representing the vast majority of patients who receive healthcare in England,

and therefore the study is likely to be highly representative of the underlying population.

The ability to link with national cause of death data ensured reliable assessment of mortality after discharge, and therefore, unlike other series, it was possible to assess mortality at several time stages as well as re-admissions, complications, and ultimate cause of death for patients treated across a large number of surgical units. The added detail from previous admission records also strengthened data on co-morbidities, which were assessed using a contemporaneous validated score as in Chapter 5.

6.4.3 – Limitations

One of the key limitations to this analysis was the lack of a clear unique diagnostic code for surgical lung biopsy in the OPCS-4 system, meaning that some procedures may have been performed by other means, such as medical thoracoscopy or computed tomography guided percutaneous needle biopsy. Although these would be unusual diagnostic approaches for ILD, it is feasible that patients with underlying ILD could undergo these procedures for another means, such as investigation of a pulmonary nodule. Attempts to exclude such cases by limiting the speciality as cardiothoracic surgery will have reduced the chance of including non-surgical patients, but it is possibly that miscoding could result in some inaccurate procedures being retained.

A further possibility is that some patients undergoing a diagnostic surgical biopsy for malignancy may have been included, despite the exclusion of all patients with codes for lung cancer. Reassuringly, excluding all patients who subsequently died from cancer made little difference to the results. The provisional diagnosis data should be interpreted with caution as this originated from the index admission where final histology would likely not be available prior to discharge, and therefore the confidence of this presumptive diagnosis may vary depending on the experience of the doctor completing discharge paperwork and the translation of any record by clinical coders. On a similar vein, cause of death data will have relied on the accuracy of death

certification, and the underlying cause specified may not reflect the *mode* of death – for example, the majority of cases of 'interstitial lung disease' may have had pneumonia, acute exacerbations or progressive respiratory failure as a final common pathway.

The assessment of co-morbidity in this study was aided by the availability of previous records as a source of additional diagnoses, but it is still possible that not all medical problems will have been coded, and therefore co-morbidity may have been underestimated. However, as with the US study in Chapter 5, it would be assumed that most significant medical conditions would be listed during an inpatient admission. Similarly to the US study, it was not possible to assess the use of medications such as corticosteroids, anticoagulation, and immunosuppression, and importantly there were no data on pre-operative oxygen requirements, imaging appearances or lung function tests, all of which have been shown to affect individual surgical risk in case series (101, 142, 246). It was not possible to compare those undergoing a biopsy with those that did not have the procedure, a group which may also have had an elevated mortality compared to the baseline population (particularly the non-elective cases). A final limitation of this study was that the data covered a time period lasting until 2008, and therefore it is likely that surgical practice and patient selection may have changed slightly since this time.

6.4.4 – Interpretation of findings

The increasing number of biopsies over time in this study suggests an increasing desire to achieve a firm diagnosis in ILD, however it may simply reflect a stable biopsy rate on the background of a rising incidence of ILD in the UK (24, 178) (see Chapters 2 and 3). Overall, the proportion of cases of IPF undergoing surgical biopsy seems low, but this may be consistent with local clinical practice where surgical lung biopsy is only used infrequently if imaging is supportive. The proportion of younger patients undergoing biopsy seems higher than might be expected, but again this is consistent with the observation that biopsy may be more readily attempted in younger patients

with low co-morbidity, whereas clinicians may be more reluctant to offer the procedure to older patients. It is however possible that the cohort in this study will include a greater proportion of younger patients with an inflammatory type of ILD.

The risk factors for early mortality are all consistent with findings in the US dataset and seem plausible. It is notable that only age and co-morbidity were significantly associated with all three markers of early mortality, and that only co-morbidity was significant when focussing on elective patients – this may in part reflect the lower numbers in the study, but also likely reflects these being the main determinants of risk. The lack of an association with age for elective procedures may be a result of only 'biologically younger' older patients being put forward for surgery from the outpatient clinic. As with the US data, the regional variation may reflect geographic differences in incidence, but also an element of different clinical practice.

Given patients with a diagnosis of lung cancer were excluded, it was surprising that so many patients ended up with lung cancer as a cause of death. This may reflect un-coded disease before biopsy, but also that lung cancer is more common in patients with IPF (257) and may develop later on. As noted in the discussion of limitations above, if all patients who ultimately died of any type of cancer were omitted, overall mortality was essentially no different (in-hospital, 30-day and 90-day mortality of 1.7%, 2.4% and 4.0% respectively). It is unfortunate that there were not more data available on the type of operation, however the 'unspecified' results are located midway between open surgery and VATS, and it is therefore likely that these represent a mix of the two procedures, with a likely higher proportion of VATS in later years. Given the dataset includes patients undergoing open surgery, it is likely that overall figures will slightly over-estimate the expected mortality from a VATS procedure carried out today.

6.4.5 – Comparison to other data

The similarities to the data from the United States reported in Chapter 5 give weight to the findings, although there are some disparities that likely relate to differences in clinical practice. The overall in-hospital mortality of 1.7% is identical to that for elective patients in the US data, which may suggest these are similar populations. Although the distinction between whether biopsies were elective or non-elective was less robust in the UK study, the estimate for elective in-hospital mortality of 1.0% being lower than the US data may reflect a more cautious approach to patient selection for biopsies in the UK. Furthermore, the proportion of non-elective biopsies was lower in the UK.

The overall figure of 2.4% 30-day mortality is similar to that reported by Carrillo *et al* in the next largest series, of 722 patients in Mexico from 1986-1990 (148), and also Sigurdsson *et al* in a smaller nationwide series from Iceland from 1986-2007 (101), although slightly higher than the 2.1% estimate for VATS procedures from the systematic review by Nguyen and Meyer (120), likely reflecting the fact that the current study includes some older cases undergoing open surgery. In terms of other contemporaneous case series from the UK, Ooi *et al* reported in-hospital mortality of 1.4% from a retrospective series of 70 patients undergoing surgical lung biopsy from Cambridge from 1998-2003 (79% VATS) (111) and Greenwood *et al* noted an 'overall' mortality of 0.9% in 224 patients undergoing lung biopsy in Liverpool from 2001-2008 (73% VATS) (110). There were limited details on how many cases were elective or non-elective in each series, but the results are fairly similar to the in-hospital mortality data from the current study, albeit slightly better as might be expected from case series. Two more recent studies from Scotland reported 30-day mortality of 4.9% (n=103, 79% VATS) and 1.5% (n=66, 100% VATS) respectively (109, 129), either side of the 30-day figure from the current study.

The increasing number of cases in later years in this study contrasts with a decrease in other studies (132) attributed to the publication of previous American Thoracic Society and European Respiratory Society consensus

criteria (1). As noted, this may however reflect increasing numbers of patients with ILD and a stable rate of biopsy. It would be interesting to see how trends have continued in more recent years with the advent of anti-fibrotic treatment for IPF.

6.4.6 – Clinical Implications

This study adds to previous work in identifying risks associated with surgical lung biopsy for ILD. The overall 30 day mortality of 2.4% is comparable to the 30 day mortality following lobectomy for non-small cell lung cancer (2.3%) (258) – a potentially curative rather than diagnostic operation – which highlights that this is not a minor procedure, and may lead to harm in a minority of cases.

As with the US data, it was possible to calculate risk estimates stratified by age and co-morbidity, and these suggest that a patient aged under 65 with no significant co-morbidities has a 30-day mortality of 1.6%, whereas a patient aged over 65 with co-morbidities has a 30-day mortality of 4.7%. While individual patient characteristics are clearly highly relevant, these data are likely to be useful for clinicians counselling patients on whether to undergo surgery or not. The finding that a large number of patients undergoing biopsy for ILD will be re-admitted with their disease and subsequently die from it highlights that ILD is a significant clinical problem, and the key question for clinicians is whether the result of the biopsy will affect long-term patient management: if the multi-disciplinary team are reasonably confident of a diagnosis after radiological imaging, then it could well be argued that a surgical biopsy is not required, and management (whether disease modifying therapy or supportive care) should be instituted empirically. On the other hand, in selected patients, a biopsy may alter management significantly.

Given the mortality associated with surgical lung biopsy, combined with improvements and greater experience in imaging studies, the key message is perhaps that the decision to undergo biopsy should be taken very carefully in older patients with co-morbidities, with clear counselling of risks and

awareness of factors associated with poorer outcomes. The limited number of biopsies performed annually per surgical centre in England suggests a national audit would be an effective means of monitoring outcomes: the Society for Cardiothoracic Surgeons now collates some of this data for UK centres, and this could be used to monitor local practice. The impact of anti-fibrotic therapy for IPF on rates of biopsy in ILD needs careful assessment to ensure that the level of certainty required for a diagnosis does not change dramatically purely to accommodate potential new treatment options.

6.4.7 – Summary of chapter

In summary, this study supports and expands on the work in Chapter 5 in assessing the risk to patients following surgical lung biopsy for ILD, by examining a large representative secondary care database from England linked to national mortality statistics. Key findings include a rising number of biopsies over time from 1997-2008, with 4-5% of new cases of IPF-clinical syndrome being biopsied, and overall mortality statistics of 1.7% (in-hospital), 2.4% (30-day mortality), and 3.9% (90-day mortality), with the main risk factors for early mortality being age and level of co-morbidity. Limitations of the data including coding accuracy were countered by the ability to assess subsequent admissions and ultimate cause of death, both of which were dominated by the diagnosis of interstitial lung disease.

Overall, this study adds weight to the conclusions of Chapter 5, and will be valuable to clinicians contemplating whether a histological diagnosis of interstitial lung disease is required to manage the individual patient in front of them. Risk factors highlighted here, combined with additional clinical data, should be taken into account when considering the benefits and risks of a surgical diagnosis.

This work was published in the European Respiratory Journal in 2016 (250).

Chapter 7 : Mortality of people with idiopathic pulmonary fibrosis undergoing major surgery

This chapter considers the risks to people with idiopathic pulmonary fibrosis undergoing major surgical procedures, using secondary care data from the United States. Possible reasons for the varying risks of different procedures are explored.

7.1 – Introduction

7.1.1 – Background

Acute exacerbations of idiopathic pulmonary fibrosis are associated with a high mortality (173). The aetiology of these events is not always clear, but one widely reported risk factor is the use of diagnostic surgical lung biopsy (112, 146, 259), a driver behind much of the work looking at the safety of this procedure, and explored further in the previous two chapters.

Other pulmonary surgery has also been implicated, and there is a growing body of evidence, mainly from Japan, about the impact of lobectomy for lung cancer in terms of triggering acute exacerbations and causing other post-operative morbidity (136, 260-262). There are also case reports of exacerbations following non-pulmonary surgery (60, 230, 263), however these are not commonly reported, and a recent review failed to find any additional cases in the literature (263).

7.1.2 – Rationale for the study

With an increasing incidence of IPF (24, 187), it is likely that an increasing number of people with the disease will present to clinicians with other conditions which may require surgical treatment. The risk of acute exacerbations following surgical procedures, as well as a possible increased risk of other complications such as pneumonia and myocardial infarction, means that short-term mortality may be higher for patients with IPF undergoing such surgery than the general population. While clinicians and patients may intuitively assume that the presence of lung disease will increase the risks of surgery, there are no reliable data available to provide guidance on how this compares to patients without IPF, and the effect of different types of surgery is not known.

The hypothesis for this chapter is that people with IPF will have increased mortality following major surgery than people without IPF.

7.1.3 – Aims and Objectives

This chapter aims to assess the in-hospital mortality following major surgical procedures in patients with IPF in the United States. The impact of both pulmonary and non-pulmonary procedures will be assessed, with an assessment of core patient factors impacting on this risk.

7.2 – Methods

This was an observational study using a large clinical database. This chapter describes the data source, how patients with IPF were selected, and the process of choosing major surgical procedures, before outlining outcome measures and the statistical methods used.

7.2.1 – Source of data

This study used the 2000-2011 Nationwide Inpatient Sample (NIS), part of the Healthcare Cost and Utilization Project (HCUP), which is sponsored by the Agency for Healthcare Research and Quality (AHRQ) (237). This large, anonymised, representative database from the United States was used in Chapter 5 and is described in detail in Section 5.2.1. Briefly, it comprises a record of all discharges from a stratified 20% sample of US community hospitals, with details of diagnoses and procedures provided using the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) system.

7.2.2 – Case selection

Cases of pulmonary fibrosis were identified as those records containing the following two ICD-9-CM diagnostic codes: 515 (post-inflammatory pulmonary fibrosis) and 516.3 (idiopathic fibrosing alveolitis). Any record containing either of these codes, but no other codes for interstitial lung disease (517.2 - lung involvement in systemic sclerosis; 714.81 - rheumatoid lung; 517.8 - lung involvement in diseases classified elsewhere; 495 - extrinsic allergic alveolitis; 500-505 - pneumoconiosis, including asbestosis; 135 – sarcoidosis) was labelled as a 'broad' definition of idiopathic pulmonary fibrosis clinical syndrome (IPF-CS). Any record containing only code 516.3, but no other code for ILD, was labelled as a 'narrow' definition of IPF-CS.

The use of broad and narrow classifications of IPF has been used previously in large database studies (25, 186, 264), and the definitions used here are similar but not identical to those used elsewhere in the literature. Overall the current definitions are slightly more inclusive, and the term IPF-clinical syndrome reflects this difference: this has been used previously (24, 178, 181) and indicates that some of these cases may not be 'true' IPF, given that other idiopathic interstitial pneumonias and unspecified fibrosis may be classified under these codes. Nevertheless these codes likely represent the majority of patients seen in clinics with possible IPF, with the narrow definition being the most specific.

7.2.3 – Choice of procedures

Three major classes of surgical procedure were chosen to assess the risk of surgery: coronary revascularisation, joint replacement and pulmonary resection. These were chosen for three reasons: they are all considered major surgery (265), they are likely to be reasonably common in the age groups most affected by IPF, and have all also been previously noted to cause acute exacerbations (263).

For coronary revascularisation, records containing a code for coronary artery bypass grafting were selected, although those with contemporaneous heart valve surgery were excluded, to ensure a more homogeneous population. Records with codes for percutaneous coronary angioplasty were also selected, as a comparator procedure with different anaesthetic implications.

For joint replacement, all cases of hip and knee replacement were selected, including revisions. For pulmonary resection, only lobectomy was selected, as it was anticipated that this would be the most common procedure with the greatest power. Full ICD-9-CM codes used are listed in Appendix D. Only elective records were selected, to ensure a more consistent patient cohort and ensure results were more applicable to the clinician in the outpatient

setting. The distinction between elective and non-elective records in the NIS is described in Section 5.2.5.

7.2.4 – Outcomes, exposures and confounding variables

The primary outcome used was in-hospital mortality. Numbers of deaths in-hospital and percentage mortality were estimated on a national basis using sample weightings available within the NIS.

Key factors assessed were sex, age, level of co-morbidity and time period, with similar categorisation to that used in Chapter 5 (see Section 5.2.5). In summary, age was categorised into six groups: less than 45 years, 45-54 years, 55-64 years, 65-74 years, 75-84 years, and older than 84 years. Co-morbidity was assessed using the updated Charlson score (242, 244), based on additional diagnoses listed in the discharge record. Time periods were classified into four groups: 2000-2002, 2003-2005, 2006-2008, and 2009-2011.

7.2.5 – Statistical analysis

Statistical analysis was performed using Stata, version 14.0 (StataCorp, Collage Station, Texas, USA). To account for the complex stratified sample design of the NIS, estimates were calculated using the specialized survey commands, taking account of year and strata, and using weights to create national estimates (245). Logistic regression was used to estimate odds ratios for mortality, with adjustment for sex, age, co-morbidity and time period.

Frequencies of cases ≤10 were omitted for reasons of confidentiality as per the data-use agreement.

7.3 – Results

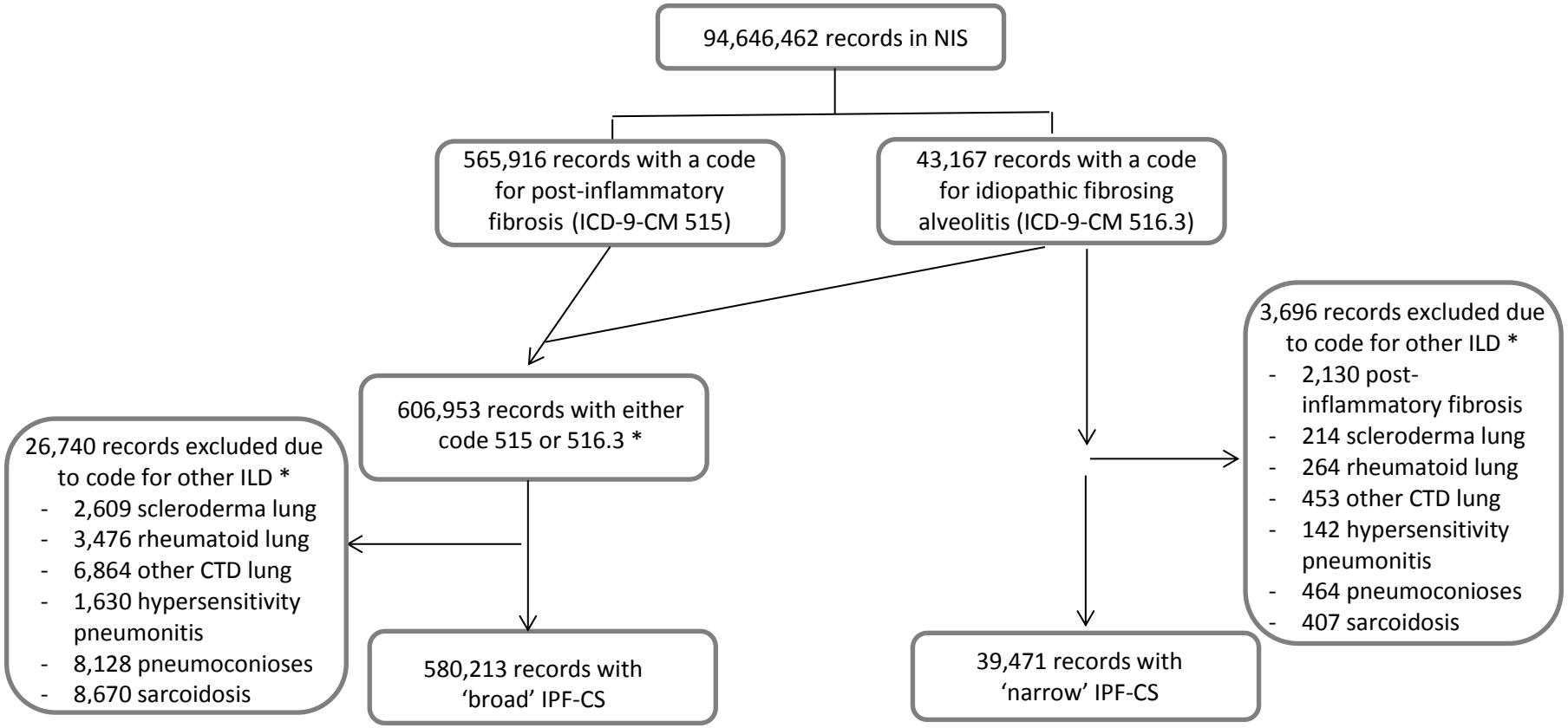
This section will describe the numbers of cases with pulmonary fibrosis undergoing each type of surgery and their demographics, followed by in-hospital mortality for each procedure and odds ratios calculated by multivariable logistic regression. Demographic details will be presented using unweighted data for ease of understanding; mortality data will be presented using weighted data to account for the sampling process.

7.3.1 – Cohort selection

A flow diagram outlining the number of records for patients with both broadly and narrowly defined idiopathic pulmonary fibrosis clinical syndrome (IPF-CS) is shown in Figure 7-1. Out of over 94 million records in the NIS, 580,213 had codes consistent with 'broad' IPF-CS, and 39,471 had codes consistent with 'narrow' IPF-CS.

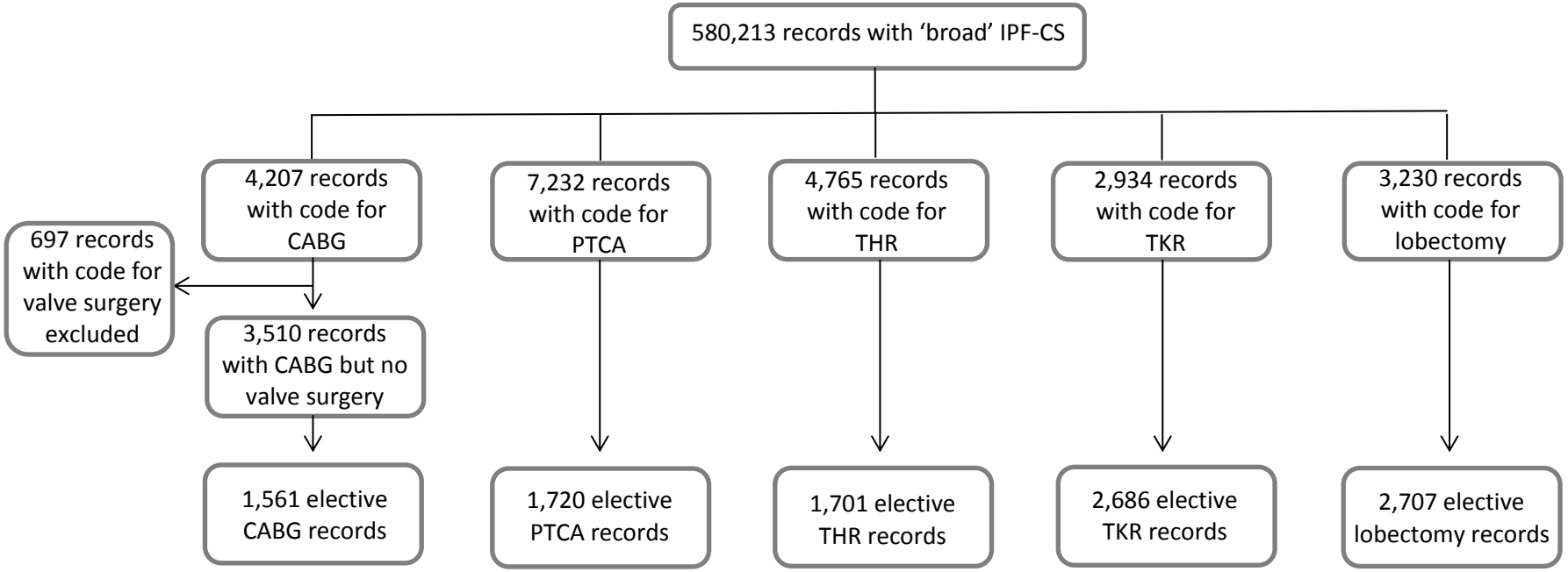
There were over 1,000 records for each procedure in the 'broad' category (from 1,561 for coronary artery bypass grafting, to 2,707 for lobectomy) but notably fewer in the 'narrow' category (only 72 for hip replacement, with lobectomy again the largest group with 194 records). Selection of records is displayed in Figure 7-2 for 'broad' cases, and Figure 7-3 for 'narrow' cases.

Figure 7-1: Flow diagram of selection of records with broadly and narrowly defined idiopathic pulmonary fibrosis clinical syndrome (IPF-CS)



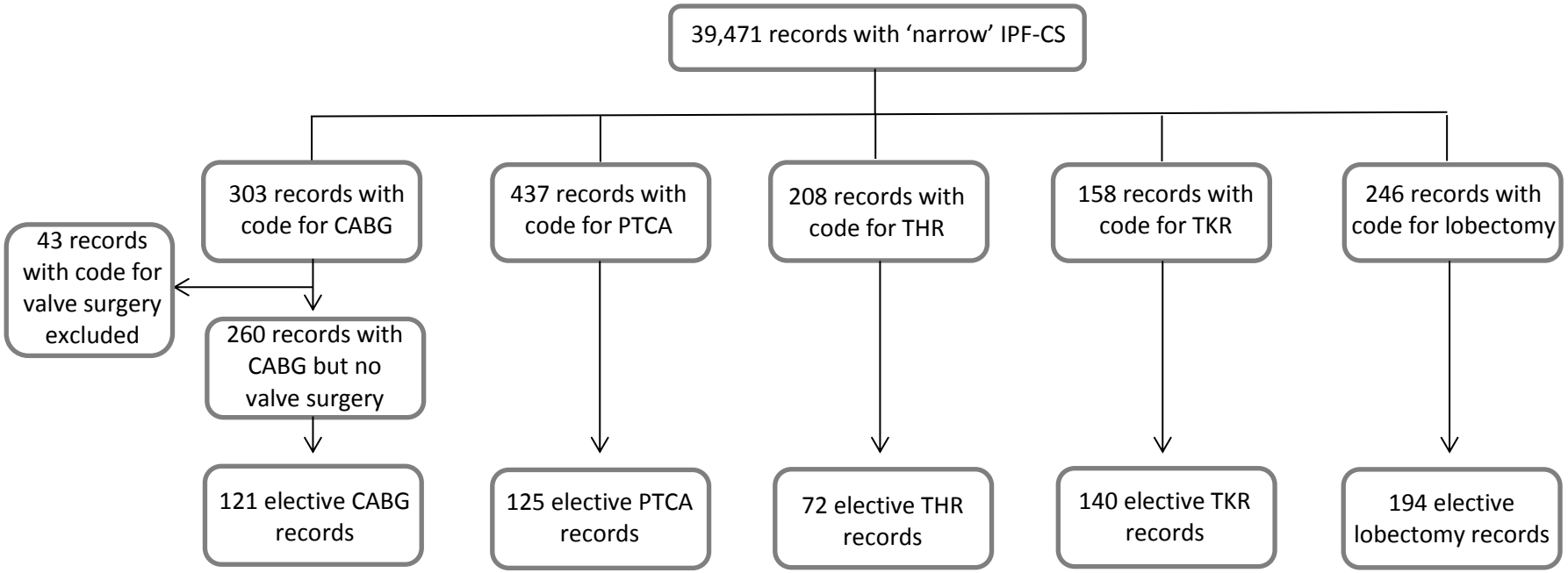
*Records can have more than one ILD code listed.
NIS: Nationwide Inpatient Sample; ILD: interstitial lung disease; CTD: connective tissue disease. For relevant ICD-9-CM codes, see main text.

Figure 7-2: Flow diagram of selection of records with five classes of operation for patients with broadly-defined idiopathic pulmonary fibrosis clinical syndrome (IPF-CS)



CABG: coronary artery bypass grafting; PTCA: percutaneous transluminal coronary angioplasty; THR: total hip replacement; TKR: total knee replacement.
See Appendix D for codes used to select these categories.

Figure 7-3: Flow diagram of selection of records with five classes of operation for patients with narrowly-defined idiopathic pulmonary fibrosis clinical syndrome (IPF-CS)



CABG: coronary artery bypass grafting; PTCA: percutaneous transluminal coronary angioplasty; THR: total hip replacement; TKR: total knee replacement.
See Appendix D for codes used to select these categories.

7.3.2 – Demographics of cohort

Unweighted demographic details of records for both 'broad' and 'narrow' cohorts are shown in Table 7-1 and Table 7-2 respectively. For comparison, percentages for each demographic for those patients undergoing major elective surgical procedures in the database *without* any code for IPF-CS are provided in Table 7-3.

For patients in both broad and narrow IPF-CS cohorts, males were more commonly represented for coronary revascularisation and lobectomy, whereas females were more commonly represented for joint replacements. Lobectomy had the highest proportion of patients in the highest co-morbidity category. The use of lobectomy in both cohorts decreased over time (unlike in the wider database), whereas the use of knee replacement increased for the 'broad' cohort (similar to the wider database).

Table 7-1: Unweighted demographic details of records for patients with 'broad' idiopathic pulmonary fibrosis clinical syndrome (IPF-CS) undergoing major elective surgical procedures in this study

	CABG cohort	PTCA cohort	THR cohort	TKR cohort	Lobectomy cohort
	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
Sex					
Male	1,139 (73.0)	1,101 (64.0)	696 (40.9)	1,022 (38.1)	1,421 (52.5)
Female	422 (27.0)	618 (35.9)	1,005 (59.1)	1,664 (62.0)	1,286 (47.5)
Age group (years)					
0-44	14 (0.9)	21 (1.2)	44 (2.6)	26 (1.0)	167 (6.2)
45-54	106 (6.8)	96 (5.6)	98 (5.8)	131 (4.9)	333 (12.3)
55-64	330 (21.1)	291 (16.9)	223 (13.1)	424 (15.8)	648 (23.9)
65-74	560 (35.9)	587 (34.1)	496 (29.2)	930 (34.6)	969 (35.8)
75-84	510 (32.7)	613 (35.6)	611 (35.9)	1,016 (37.8)	554 (20.5)
>84	41 (2.6)	112 (6.5)	229 (13.5)	159 (5.9)	36 (1.3)
Level of co-morbidity (Updated Charlson score)					
0	523 (33.5)	626 (36.4)	700 (41.2)	1,277 (47.5)	521 (19.3)
1	519 (33.3)	502 (29.2)	589 (34.6)	889 (33.1)	547 (20.2)
2	208 (13.3)	244 (14.2)	217 (12.8)	302 (11.2)	466 (17.2)
3 or more	311 (19.9)	348 (20.2)	195 (11.5)	218 (8.1)	1,173 (43.3)
Year group					
2000-2002	410 (26.3)	319 (18.6)	320 (18.8)	407 (15.2)	751 (27.7)
2003-2005	418 (26.8)	479 (27.9)	474 (27.9)	653 (24.3)	728 (26.9)
2006-2008	410 (26.3)	585 (34.0)	456 (26.8)	787 (29.3)	669 (24.7)
2009-2011	323 (20.7)	337 (19.6)	451 (26.5)	839 (31.2)	559 (20.7)

Percentages rounded to 1 decimal place. Minority of patients not coded for sex.
CABG: coronary artery bypass grafting; PTCA: percutaneous transluminal coronary angioplasty; THR: total hip replacement; TKR: total knee replacement.
'Broad' IPF-CS: ICD-9-CM codes 515 (post-inflammatory fibrosis) and 516.3 (idiopathic fibrosing alveolitis), without additional codes for other ILD.

Table 7-2: Unweighted demographic details of records for patients with 'narrow' idiopathic pulmonary fibrosis clinical syndrome (IPF-CS) undergoing major elective surgical procedures in this study

	CABG cohort	PTCA cohort	THR cohort	TKR cohort	Lobectomy cohort
	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
Sex					
Male	86 (71.1)	83 (66.4)	26 (36.1)	56 (40.0)	104 (53.6)
Female	35 (28.9)	42 (33.6)	46 (63.9)	84 (60.0)	90 (46.4)
Age group (years)					
0-44	*	*	*	*	*
45-54	*	*	*	*	18 (9.3)
55-64	32 (26.5)	33 (26.4)	13 (18.1)	21 (15.0)	37 (19.1)
65-74	36 (29.8)	31 (24.8)	18 (25.0)	50 (35.7)	91 (46.9)
75-84	43 (35.5)	46 (36.8)	29 (40.3)	56 (40.0)	39 (20.1)
>84	*	*	*	*	*
Level of co-morbidity (Updated Charlson score)					
0	43 (35.5)	49 (39.2)	37 (51.4)	62 (44.3)	16 (8.3)
1	34 (28.1)	33 (26.4)	20 (27.8)	47 (33.6)	26 (13.4)
2	16 (13.2)	22 (17.6)	*	16 (11.4)	40 (20.6)
3 or more	28 (23.1)	21 (16.8)	10 (13.9)	15 (10.7)	112 (57.7)
Year group					
2000-2002	38 (31.4)	30 (24.0)	18 (25.0)	31 (22.1)	90 (46.4)
2003-2005	37 (30.6)	27 (21.6)	19 (26.4)	46 (32.9)	52 (26.8)
2006-2008	23 (19.0)	49 (39.2)	16 (22.2)	34 (24.3)	29 (15.0)
2009-2011	23 (19.0)	19 (15.2)	19 (26.4)	29 (20.7)	23 (11.9)

*Value less than or equal to 10 records – omitted for confidentiality reasons.
Percentages rounded to 1 decimal place. Minority of patients not coded for sex.
CABG: coronary artery bypass grafting; PTCA: percutaneous transluminal coronary angioplasty; THR: total hip replacement; TKR: total knee replacement.
'Narrow' IPF-CS: ICD-9-CM code 516.3 (idiopathic fibrosing alveolitis) only.

Table 7-3: Unweighted demographic details of records for patients without any code for idiopathic pulmonary fibrosis clinical syndrome (IPF-CS) undergoing elective major surgical procedures

	CABG (total 291,034) %	**PTCA** (total 576,541) %	**THR** (total 578,937) %	**TKR** (total 1,135,277) %	**Lobectomy** (total 72,505) %
Sex					
Male	73.8	66.6	43.0	36.6	48.8
Female	26.2	33.4	56.6	63.2	51.2
Age group (years)					
0-44	2.6	3.7	6.2	2.0	4.9
45-54	13.3	14.5	14.3	11.4	11.0
55-64	28.7	26.2	23.4	27.4	24.4
65-74	34.6	31.4	28.1	34.4	36.2
75-84	19.4	20.9	22.7	21.9	21.8
>84	1.4	3.3	5.3	2.9	1.7
Level of co-morbidity (Updated Charlson score)					
0	61.0	73.0	75.7	76.9	4.2
1	18.4	12.9	15.9	16.6	3.1
2	11.9	8.9	5.4	4.6	32.6
3 or more	8.6	5.3	3.0	1.9	60.2
Year group					
2000-2002	32.0	26.8	20.1	16.0	21.6
2003-2005	26.8	31.0	24.9	23.3	24.7
2006-2008	22.4	28.1	25.6	28.3	26.9
2009-2011	18.8	14.1	29.5	32.5	26.9

Percentages rounded to 1 decimal place. Minority of patients not coded for sex.
CABG: coronary artery bypass grafting; PTCA: percutaneous transluminal coronary angioplasty; THR: total hip replacement; TKR: total knee replacement.
'Narrow' IPF-CS: ICD-9-CM code 516.3 (idiopathic fibrosing alveolitis) only.

7.3.3 – Overall in-hospital mortality

Overall in-hospital mortality in the entire dataset (all discharges) was 2.1%.

For patients with 'broad' IPF-CS, this was 7.3%, and for 'narrow' IPF-CS, this was 11.3%.

7.3.4 – Mortality after coronary revascularisation

The in-hospital mortality rate for patients without any code for IPF-CS undergoing coronary artery bypass grafting (excluding co-existing valve surgery) was 1.7%. For patients with 'broad' IPF-CS, in-hospital mortality was estimated at 3.8%, and for those with 'narrow' IPF-CS, this was 6.6%. Adjusted odds ratios for mortality were 1.57 for 'broad' IPF-CS vs no IPF-CS (95% CI 1.19-2.06, p=0.001) and 2.46 for 'narrow' IPF-CS vs no IPF-CS (95% CI 1.16-5.23, p=0.019) (see Table 7-4).

For percutaneous coronary angioplasty, the in-hospital mortality in those without any code for IPF-CS was 0.5%, whereas this was over five times higher in those with both broadly and narrowly defined disease, at 2.7% and 3.3% respectively. Co-morbidity was the main confounder factor impacting on mortality for both procedures.

7.3.5 – Mortality after joint replacement

For hip replacement, in-hospital mortality for those without IPF-CS was 0.2%. Mortality was estimated at 1.1% for 'broad' IPF-CS, and 2.7% for 'narrow' IPF-CS. Adjusted odds ratios for mortality for the broader definition were significantly increased (odds ratio 1.90, 95% CI 1.19-3.02, p=0.007) (see Table 7-5).

For knee replacement, in-hospital mortality was 0.8% for 'broad' IPF-CS, and 1.3% for 'narrow' IPF-CS, against a non-IPF-CS rate of 0.1%. Adjusted odds ratios were significantly increased for both. Co-morbidity, and to a lesser extent age, were the key modifiers of risk.

Table 7-4: In-hospital mortality after coronary revascularisation for patients with idiopathic pulmonary fibrosis clinical syndrome (IPF-CS)

		Total cases Number (95% CI)	**In-hospital deaths** Number (95% CI)	**In-hospital mortality** % (95% CI)	**Unadjusted OR** (95% CI)	**Adjusted OR†** (95% CI)	**p value**
Cases of 'broad' IPF-CS	**CABG**	7,358 (6,862-7,854)	279 (205-354)	3.8% (2.95-4.91)	2.32 (1.78-3.03)	1.57 (1.19-2.06)	0.001
	PTCA	8,084 (7,501-8,668)	220 (154-285)	2.7% (2.03-3.62)	5.41 (4.01-7.30)	2.60 (1.91-3.55)	<0.001
Cases of 'narrow' IPF-CS	**CABG**	571 (464-679)	38 (12-64)	6.6% (3.34-12.68)	4.15 (2.03-8.52)	2.46 (1.16-5.23)	0.019
	PTCA	593 (472-715)	20 (0-39)	3.3% (1.24-8.47)	6.61 (2.43-17.94)	3.42 (1.24-9.45)	0.018

† Adjusted for sex, age, co-morbidity (updated Charlson score), and time period (year categories).
Numbers of cases and deaths rounded to nearest integers.
CABG: coronary artery bypass grafting; PTCA: percutaneous transluminal coronary angioplasty; OR: odds ratio; 95% CI: 95% confidence intervals.
'Broad' IPF-CS: ICD-9-CM codes 515 (post-inflammatory fibrosis) and 516.3 (idiopathic fibrosing alveolitis) without any other code for ILD;
'Narrow' IPF-CS: ICD-9-CM code 516.3 only without any other code for ILD.
Cases of 'narrow' IPF-CS compared against those *without* any IPF – ie does not include those with broad but not narrow coding

Table 7-5: In-hospital mortality after joint replacement for patients with idiopathic pulmonary fibrosis clinical syndrome (IPF-CS)

		Total cases Number (95% CI)	In-hospital deaths Number (95% CI)	In-hospital mortality % (95% CI)	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)	p value
Cases of 'broad' IPF-CS	**THR**	8,037 (7,563-8,512)	89 (49-129)	1.1% (0.71-1.74)	5.04 (3.19-7.95)	1.90 (1.19-3.02)	0.007
	TKR	12,733 (12,072-13,394)	99 (57-141)	0.8% (0.51-1.19)	7.91 (5.14-12.16)	3.84 (2.47-5.95)	<0.001
Cases of 'narrow' IPF-CS	**THR**	343 (261-424)	* (-3-22)	2.7% (0.68-9.91)	12.29 (3.06-49.43)	4.61 (0.92-23.06)	0.063
	TKR	680 (561-798)	* (-4-22)	1.3% (0.34-5.24)	13.79 (3.40-55.92)	5.10 (1.15-22.64)	0.032

* Value less than or equal to 10 records – omitted for confidentiality reasons.
† Adjusted for sex, age, co-morbidity (updated Charlson score), and time period (year categories).
Numbers of cases and deaths rounded to nearest integers.
THR: total hip replacement; TKR: total knee replacement; OR: odds ratio; 95% CI: 95% confidence intervals.
'Broad' IPF-CS: ICD-9-CM codes 515 (post-inflammatory fibrosis) and 516.3 (idiopathic fibrosing alveolitis) without any other code for ILD;
'Narrow' IPF-CS: ICD-9-CM code 516.3 only without any other code for ILD.
Cases of 'narrow' IPF-CS compared against those *without* any IPF – ie does not include those with broad but not narrow coding

7.3.6 – Mortality after pulmonary resection

The in-hospital mortality rate following lobectomy in those without IPF-CS was 2.3%. Mortality was higher for both 'broad' and 'narrow' IPF-CS, at 3.4% and 5.1% respectively, and adjusted odds ratios were significant for both – 1.53 for 'broad' vs no IPF-CS (95% CI 1.22-1.91, p=<0.001); 1.96 for 'narrow' vs no IPF-CS (95% CI 1.01-3.83, p=0.047) (see Table 7-6). Adjustment for age and co-morbidity had less of an impact for lobectomy.

Table 7-6: In-hospital mortality after pulmonary resection for patients with idiopathic pulmonary fibrosis clinical syndrome (IPF-CS)

	Total cases Number (95% CI)	**In-hospital deaths** Number (95% CI)	**In-hospital mortality** % (95% CI)	**Unadjusted OR** (95% CI)	**Adjusted OR†** (95% CI)	**p value**
Cases of 'broad' IPF-CS	12,855 (11,909-13,801)	433 (343-523)	3.4% (2.76-4.10)	1.50 (1.21-1.85)	1.53 (1.22-1.91)	<0.001
Cases of 'narrow' IPF-CS	913 (747-1,079)	46 (18-75)	5.1% (2.71-9.29)	2.29 (1.19-4.40)	1.96 (1.01-3.83)	0.047

* Value less than or equal to 10 records – omitted for confidentiality reasons.

† Adjusted for sex, age, co-morbidity (updated Charlson score), and time period (year categories).

Numbers of cases and deaths rounded to nearest integers. OR: odds ratio; 95% CI: 95% confidence intervals.

'Broad' IPF-CS: ICD-9-CM codes 515 (post-inflammatory fibrosis) and 516.3 (idiopathic fibrosing alveolitis) without any other code for ILD;

'Narrow' IPF-CS: ICD-9-CM code 516.3 only without any other code for ILD.

Cases of 'narrow' IPF-CS compared against those *without* any IPF – ie does not include those with broad but not narrow coding

7.4 – Discussion

7.4.1 – Summary of findings

For all procedures, in-hospital mortality was higher for broadly- defined IPF-CS than the general population, and mortality was even higher for the more specific narrowly-defined IPF-CS. Although absolute risks were low, the differences were particularly notable for joint replacement, whereas the differences were least for lobectomy.

Table 7-7 summarises the key results (in-hospital mortality with adjusted odds ratios) for all five procedures examined.

7.4.2 – Strengths

The key strength of this study is the large number of cases, from multiple centres across the United States. The NIS database has been used for a number of different clinical conditions (238-241), including interstitial lung disease (see Chapter 5) (236), and is likely to be representative of the general population given its composition of private, Medicare, Medicaid and uninsured patients. It is particularly suitable for this clinical question, as the number of patients with IPF undergoing each type of major surgery at individual centres is likely to be small.

The choice of procedures studied gives a flavour of various types of major surgery, which may by their nature offer differing risk profiles in the context of IPF – for example, the distinction between pulmonary and non-pulmonary surgery. The use of broader and narrower codes for IPF has been employed previously (albeit with slightly different criteria) and while these vary in terms of their specificity, it is likely that the selected codes represent patients commonly seen in hospital or the outpatient setting with probable or possible IPF (17, 204).

Table 7-7: In-hospital mortality of patients with idiopathic pulmonary fibrosis clinical syndrome (IPF-CS) after selected procedures

	Non-IPF-CS	Broadly-defined IPF-CS		Narrowly-defined IPF-CS	
	In-hospital mortality % (95% CI)	**In-hospital mortality** % (95% CI)	**Adjusted OR*** (95% CI)	**In-hospital mortality** % (95% CI)	**Adjusted OR*** (95% CI)
Coronary artery bypass grafting	1.7% (1.62-1.74)	3.8% (2.95-4.91)	1.57 (1.19-2.06)	6.6% (3.34-12.68)	2.46 (1.16-5.23)
Percutaneous coronary angioplasty	0.5% (0.49-0.54)	2.7% (2.03-3.62)	2.60 (1.91-3.55)	3.3% (1.24-8.47)	3.42 (1.24-9.45)
Total hip replacement	0.2% (0.21-0.24)	1.1% (0.71-1.74)	1.90 (1.19-3.02)	2.7% (0.68-9.91)	4.61 (0.92-23.06)
Total knee replacement	0.8% (0.09-0.11)	0.8% (0.51-1.19)	3.84 (2.47-5.95)	1.3% (0.34-5.24)	5.10 (1.15-22.64)
Lobectomy	2.3% (2.16-2.40)	3.4% (2.76-4.10)	1.53 (1.22-1.91)	5.1% (2.71-9.29)	1.96 (1.01-3.83)

* Adjusted for sex, age, co-morbidity (updated Charlson score), and time period (year categories).
Coronary artery bypass grafting cohort excludes patients undergoing contemporaneous valve surgery.
OR: odds ratio; 95% CI: 95% confidence intervals.
Non-IPF-CS: patients without 'broadly'-defined idiopathic pulmonary fibrosis clinical syndrome (see below).
'Broad' IPF-CS: ICD-9-CM codes 515 (post-inflammatory fibrosis) and 516.3 (idiopathic fibrosing alveolitis) without any other code for ILD.
'Narrow' IPF-CS: ICD-9-CM code 516.3 only without any other code for ILD.
Cases of 'narrow' IPF-CS compared against those *without* any IPF – ie does not include those with broad but not narrow coding.

7.4.3 – Limitations

As noted in Chapter 5, there are certain limitations to using the NIS. For confidentiality reasons, the database lacks unique identifiers, and therefore it was not possible to link multiple records for a single patient. As a result, it is possible that patients could be included more than once – for example, having had coronary artery bypass grafting after a hip replacement the year before, with both episodes being included. Similarly, it was not possible to assess the impact of any events during preceding admissions that might have influenced surgical risk, or re-admissions which might have revealed mortality after discharge but within the relative post-operative period. Furthermore, assessment of co-morbidity relied on codes included only once in the discharge record, and therefore this may have underestimated the level of co-morbidity by missing previously coded conditions – however, it would be hoped that the conditions contributing to the updated Charlson score would be notable enough to accompany a discharge summary after major surgery.

Selection of cases was dependent on the codes used, which will have been determined by both clinical coders' interpretation of medical records, and the confidence of the clinicians involved. For the time period of this study, there was not one clear code for IPF: the codes selected are the most sensitive and have been used elsewhere but may include some cases that are not true IPF. It was not possible for the broad and narrow definitions of IPF used here to match those proposed by Raghu (25) and used elsewhere in the literature (186, 264), as the nature of the NIS means it was not possible to link records and identify previous diagnostic tests, a proviso of the narrow definitions used before. The narrowest definition in the current study therefore corresponds to the broader definitions used elsewhere, limiting direct comparison, however the broad definition in this study does correspond to the initial cohort used in a later Medicare study by Raghu (204), where it was acknowledged that many patients with code 515 were likely to have IPF. The use of the term IPF-clinical syndrome in the current study also helps highlight the slightly more inclusive population studied.

In terms of procedures, the selection of only elective operations may have excluded some cases that were planned at short notice and therefore classed as non-elective, but is likely to have ensured a more homogeneous case mix. For example, the larger difference between elective and overall procedures highlighted for coronary revascularisation and hip replacement in Figure 7-2 likely reflects a higher proportion of non-elective procedures due to worsening angina and traumatic hip fractures respectively, and it is therefore appropriate that these were not included.

Despite the size of the dataset, there were limited numbers of cases for the more specific 'narrow' definition. This may reflect the fact that patients with 'clear' IPF often avoid major surgery, while those with more undefined and less aggressive disease are still referred, or could simply reflect lower use of the more specific code. Either way, it is difficult to draw conclusions for these patients due to the low numbers and wide confidence intervals. Finally, a major limitation of the NIS for this clinical question is the lack of data on lung function such as spirometry and transfer factor, which would almost certainly be a key determinant of whether a patient undergoes surgery or not (particularly for pulmonary surgery) and a major factor influencing the risk of post-operative pulmonary complications.

7.4.4 – Interpretation of findings

The increase in in-hospital mortality for patients with IPF-CS compared to the general population is perhaps not surprising, as impaired lung function might be expected to result in increased complications after general anaesthesia. However, the extent of the increased mortality – rather than simply morbidity – was notable. The increased risk with more specific disease fits with more precisely-defined 'true' IPF having worse outcomes than other non-specific fibrosis (2, 266). Although it was not possible to determine from this data if higher mortality was a result of acute exacerbations or alternative causes, the exact mode of death is likely to be less important to patients than their underlying chances of surviving surgery.

The most dramatic variation in mortality was seen for non-pulmonary surgery. This is perhaps surprising as most evidence in the literature reports adverse outcomes following surgical lung biopsy or surgery for lung cancer, with theories such as instrumentation of the lung or single lung ventilation being responsible (136, 146, 267-269). However, other factors may be important, including the type of anaesthesia used, the role of circulating fibrocytes (263), manipulation of coagulation pathways (57), susceptibility to infections (269), or aspiration of gastric contents (269). These will briefly be discussed below.

The adverse effects of general anaesthesia are well known, and attempts have been made to develop thoracic surgery in non-intubated patients (270), which might reduce the risk of morbidity and mortality. Unfortunately it was not possible to determine the type of anaesthesia used for cases in the NIS database, although it is likely that some cases of joint replacement will have had regional anaesthesia, and elective coronary angioplasty is likely to have been performed without anaesthetic involvement. This might argue against anaesthesia being a major contributory factor in terms of adverse effects of surgery in patients with IPF, and further work on the effect of different types of anaesthesia on mortality and the impact of other non-surgical procedures would be useful.

Ghatol *et al* (263) have previously discussed the potential role of circulating fibrocytes in post-operative acute exacerbations of IPF. These bone marrow derived cells concentrate in wound tissue and contribute to wound repair, and have been shown to be present in higher concentrations in patients undergoing acute exacerbations (271). The theory is that an increased number of these cells after major surgery could then be drawn to the lung as a result of oxygen-mediated injury or mechanical damage as a result of ventilation (263), although whether this would occur in patients avoiding general anaesthesia is unclear.

There have been a number of studies assessing the role of coagulation pathways in IPF, particularly the role that these pathways play in wound

healing and repair (57). Navaratnam *et al* identified that patients with IPF were more likely to have a prothrombotic state than controls in a population-based study (58), however trials of warfarin in IPF have suggested that anticoagulation is associated with increased mortality (63) – implying that interfering with the clotting process is harmful in these patients. The impact of anticoagulation peri-operatively (in coronary revascularisation) or post-operatively (to prevent venous thromboembolism after joint replacement) may therefore be relevant, and this could be worth studying in future research.

Post-operative pulmonary infections are common, and IPF patients may be more susceptible to these as a result of immunosuppressant medications such as prednisolone and azathioprine, which were commonly used prior to the publication of the PANTHER trial (164). There is evidence that prophylactic antibiotic treatment can result in reduced mortality in IPF (272) and it may be that infectious complications explain part of the raised mortality in this study. There is further evidence that infections can contribute to acute exacerbations (273), and information on cause of death would have been useful to explore this further.

Finally, it is known that abnormal gastro-oesophageal reflux is common in IPF, and evidence suggests the use of proton-pump inhibitors to treat reflux can reduce exacerbation rates (56). It is possible that recumbent and sedated patients with IPF are particularly susceptible to post-operative reflux which may contribute to risk of pulmonary complications, particularly acute exacerbations.

It is notable that the odds ratios for increased mortality associated with lobectomy were less than for other surgery. Lobectomy patients tended to have higher co-morbidity scores, almost certainly related to the presence of underlying cancer, and it might be that this is the primary determinant of survival rather than IPF. An alternative explanation could be that patient selection for surgery is more stringent in view of the poor prognosis due to

the underlying cancer, and therefore IPF and non-IPF groups may be more closely matched, with only 'healthier' IPF patients being offered surgery.

7.4.5 – Comparison to other data

While there is extensive evidence for acute exacerbations and increased mortality in those with ILD following lobectomy, particularly from Japan (136, 260-262, 267, 274, 275), there is less evidence for other procedures. Focussing on acute exacerbations, Ghatol *et al* reported a small case series of four patients, including one who had exacerbations following both total knee replacement and coronary artery bypass grafting, surviving the first but dying after the second (263). The other three had exacerbations following surgical lung biopsy: two of the three did not survive. An accompanying systematic review in the same manuscript did not identify any other reports following non-pulmonary surgery. Basavaraj *et al* presented a case report of an acute exacerbation of previously undiagnosed IPF in a patient undergoing total hip replacement, who also died in-hospital as a result (230). Finally, in a retrospective review of acute exacerbations from South Korea, Song *et al* identified 16 (out of 90) exacerbations that occurred following procedures: 11 after pulmonary surgery, three after spinal surgery, one after bronchoalveolar lavage, and one after trans-arterial chemoembolization of hepatocellular carcinoma (60).

A comprehensive study by Choi *et al* focussed on overall post-operative morbidity in patients with ILD (276). The authors reviewed 336 patients with ILD undergoing major surgery in South Korea from 2005-2010, identifying post-operative pulmonary complications in 37 cases (11%), including acute exacerbations in 11 cases and deaths in 10 cases (3%). Of those that died, six had IPF, of which four had pulmonary surgery, one had emergency repair of a gastric perforation, and one had an elective prostatectomy. The most common complication other than acute exacerbations was pneumonia, which was classified as severe in four patients and the cause of death in three.

7.4.6 – Clinical Implications

It is clear from this study that patients with IPF clinical syndrome are likely to have a higher risk of dying following surgery than their contemporaries without pulmonary fibrosis. While higher mortality for patients with chronic lung disease is perhaps unsurprising, this study provides some useful figures to the patient and clinician considering major surgical intervention.

As this is an observational study, it is important to consider that patients undergoing surgery in the dataset will generally have been pre-selected fitter ones, and stated percentages should not apply to all those considering the listed procedures. For example, while lung function data would be helpful, it is less likely that patients with severely impaired transfer factor will have undergone elective knee replacements in the current dataset. Clearly individual factors such as pulmonary function tests, appearances on computed tomography of the chest, and co-morbidities (and medications) not covered by the updated Charlson score must be taken into account when advising patients. On the other hand, for those patients being considered for surgery without a clear contraindication, these data may provide a useful guide to risk.

Clinicians may need assistance in communicating these risks to patients, as while the relative risks are high, absolute risks remain low. Individual circumstances, for example the burden of pain due to uncontrolled arthritis, will undoubtedly be important in helping patients decide whether to undergo surgery or not. Prospective clinical registries of IPF patients undergoing surgery, as called for by Ghatol *et al* (263), may be a way to better understand the factors that contribute to increased risk and how these might be modified.

7.4.7 – Summary of chapter

This chapter has explored the risk of in-hospital mortality following major surgical procedures in patients with IPF, using a large secondary care

database from the United States. Mortality was higher for all procedures compared to the general population, including both pulmonary and non-pulmonary surgery, and the risk was highest for more specifically-defined IPF.

These findings may prove useful to clinicians and patients with IPF considering major elective surgery, and expand on the data in the previous two chapters considering the impact of IPF or ILD on the risk of surgical intervention.

Chapter 8 : Conclusions and recommendations for further research

In this chapter, I will summarise the key findings of the preceding chapters, before considering areas for future research and outstanding issues in IPF epidemiology.

8.1 – Summary of thesis

Following an overview of the relevant background to this thesis in Chapter 1, Chapters 2 and 3 investigated the current mortality and incidence from idiopathic pulmonary fibrosis (IPF) worldwide, by thorough analysis of international mortality statistics and systematic review of the literature to identify relevant epidemiological studies. In Chapter 2, I demonstrated worldwide variation in mortality from IPF-clinical syndrome, with increasing rates in most countries, most notably in the UK but less so in the United States: overall, however, rates seem to be coalescing worldwide. Variation may reflect true differences in incidence, contrasting approaches to diagnosis, or disparities in clinical coding, while increasing mortality rates may reflect either a true increase in incidence (potentially due to fewer deaths from competing causes, for example, cardiovascular disease) or greater awareness and diagnosis of milder disease. I also showed that IPF is often not listed on death certificates as a cause of death, and therefore mortality statistics are likely to underestimate disease incidence: nevertheless, it was estimated that the current number of deaths from IPF is likely to be somewhere between 30,000-65,000 per year in Europe.

In Chapter 3, I extracted data on incidence and mortality from IPF from over 30 studies from countries across five continents. A conservative estimate of IPF incidence of 3-9 per 100,000 was determined for Europe and North America, with a lower incidence noted for South America and Asia: this may relate to studies capturing fewer cases, for example where insurance datasets do not include milder disease. Overall though, the incidence of IPF is comparable to several higher profile conditions, such as testicular and cervical cancers.

Chapter 4 of this thesis moved on to consider issues of aetiology, and the theory that recent major surgery might be a trigger for the development of IPF. Using a case-control study within UK primary care data, I showed that there was no association between coronary artery bypass grafting or joint

replacement within the previous five years and onset of IPF. The impact of surgical intervention in patients with IPF continued throughout the rest of the thesis: firstly the role of diagnostic surgical lung biopsy in suspected interstitial lung disease (ILD), and secondly the role of major elective surgery in established IPF.

The risks of surgical lung biopsy in the United States were explored in Chapter 5. I estimated that around 12,000 biopsies were being undertaken to diagnose ILD each year in the US, with some variation between regions. The key findings were in-hospital mortality of just under 2% for elective surgery, but up to 16% for urgent and emergency surgery, with higher mortality in older males with co-morbidities. Similar risk factors were identified in a second study from the UK, as reported in Chapter 6, where additional information was available following hospital discharge: in this study, I estimated in-hospital, 30-day and 90-day mortality figures at 1.7%, 2.4% and 3.9% respectively. Re-admissions and ultimate cause of death were most commonly due to the underlying ILD. In contrast to the US, there were increasing numbers of biopsies performed in England, perhaps in part due to increasing incidence of ILD, although a relatively low proportion of IPF was likely to be biopsied (~4.5%), perhaps reflecting a more cautious attitude to surgery in the UK.

Finally, in Chapter 7, the risks of elective surgery were shown to be higher for those with IPF (and highest for most specifically-coded disease) than the general population. This increased risk of in-hospital mortality was shown for both pulmonary surgery (lobectomy), non-pulmonary thoracic surgery (coronary artery bypass grafting), and non-pulmonary non-thoracic surgery (hip and knee replacement), as well as for coronary angioplasty.

8.2 – Major clinical implications

There are a number of clinical implications to this work, which have been described in individual chapters. In summary, there appears to be an increasing incidence of IPF in most regions worldwide, and this needs taking into account when planning healthcare services, particularly in an era of constrained finances and new and emerging targeted therapies for IPF. It also raises questions with regards to aetiology: does this reflect an increasing risk exposure (for example, environmental contributions or related to changing lifestyles) or is it simply the result of increased detection in an ageing population?

Secondly, the risks of surgical lung biopsy need explaining to patients with ILD who are considering a tissue diagnosis. Key questions include the likelihood of the biopsy result altering clinical management, the likely empirical treatment options without a lung biopsy, and the individual patient factors that might impact on surgical risk. Data from the studies in this thesis provide a useful starting point for these discussions, and suggest that clinicians should think carefully about biopsies in the non-elective situation, and also in older males with multiple co-morbidities. Alternative less-invasive diagnostic tests for ILD are also needed.

Finally, the role of major surgery was considered in two different studies from the UK and the US: while surgery was reassuringly not associated with onset of IPF, it did appear to influence mortality in established IPF, and this data will again provide useful guidance for surgeons considering elective procedures in people with this disease. The higher mortality for those with IPF undergoing less invasive procedures (such as knee replacement and coronary angioplasty) leads one to consider why this might be, and whether there could be a target for intervention: this is beyond the scope of this thesis, but further research in this field would be of interest.

8.3 – Suggestions for further research

As outlined in Chapter 3, there have been an increasing number of epidemiological studies of IPF incidence since the turn of the century, with improvements in study quality due to the use of large datasets and careful case selection and verification. However, there are still areas where further research is needed.

First, there is a need for incidence studies from under-represented areas of the World, such as China, India, Russia and Brazil, all heavily-populated countries that are likely to have large numbers of patients with IPF. The challenges of epidemiological studies of IPF in these countries have been recognised (277), but greater awareness of IPF and increased availability of imaging in rural areas will hopefully increase diagnostic ability and allow more reliable estimates. Other areas of the World such as Eastern Europe and the Middle East are likely to have physicians with an interest in ILD in major centres, and could potentially contribute incidence data if the appropriate systems were in place to capture diagnoses. Encouraging more countries to include IPF within their mortality statistics would be a reasonably straightforward way to add to the global picture on the burden of ILD, accepting potential limitations due to diagnostic uncertainties within some developing countries.

Following on from this, updated studies are needed from other countries that have already provided incidence data on IPF, to reflect contemporaneous clinical codes and the most recent diagnostic guidance. This would ensure cases truly represent what is currently labelled IPF in the clinical setting. Clinical validation is a valuable means of strengthening the reliability of a database study, and the use of local information technology systems should enhance the role and comprehensiveness of both national clinical datasets and disease-specific registries. Recent studies from Japan (87), Italy (278) and Canada (264) have been published since the completion of the systematic review in this thesis: all offer useful insights that complement and enhance previous work from these countries. An updated version of the mortality

study in Chapter 2 would be useful in a few years to assess continued trends over time. It is worth emphasising the importance of studies learning from the challenges of previous efforts, with the adoption where possible of measures proposed in Section 3.4.6 to enhance comparability between regions.

The value of assessing incidence in other countries lies partly in raising awareness of the impact of the disease, but also in generating new aetiological theories that might explain its distribution, such as whether a certain country has more cases of IPF due to a certain occupational exposure. Mortality trends over time might also be correlated with historical changes in certain risk factors, for example increasing national and international interest in the effects of air pollution on respiratory health may enhance the ability to consider the impact of changing urbanisation, motor vehicle use and presence of heavy industry on IPF incidence rates. Other smaller-scale aetiological theories that merit further research include further exploration of the link between clotting pathways and IPF: proposed local work investigating the associations between both haematological conditions and use of non-steroidal anti-inflammatory drugs and other anti-platelet agents and the onset of IPF is likely to be of interest.

The likely interaction between genetic predisposition and trigger factors means that studies of other causes of ILD besides IPF may be productive and yield transferable theories: why do some people with rheumatoid arthritis, for example, develop pulmonary fibrosis but not others? Incidence and mortality studies of other types of ILD – including non-specific or unclassified fibrosis – may also shed light on whether recent guidelines have affected diagnosis rates, and caused diagnostic transfer between less and more specific disease categorisations. To complement this, studies comparing the work of multidisciplinary teams may reveal how diagnostic approaches are changing in the era of anti-fibrotic therapy: are clinicians choosing to pragmatically label people more readily as having IPF, or do strict trial criteria mean there is an increasing cohort with unclassifiable disease?

On the issue of diagnostic approaches, it is clear from the work in this thesis that surgical lung biopsy can have unacceptably high mortality in certain population groups. In other situations however, it can remain an important diagnostic tool. Further research needs to consider the value of this procedure, and whether alternative approaches (for example, new techniques such as cryobiopsy, enhanced imaging modalities or use of biomarkers) can negate the need for biopsy. Local case series remain useful in terms of highlighting individual patient characteristics suggestive of adverse outcomes, but selection bias will continue to be an issue, and multicentre studies and trials will be most valuable in determining which patient groups are most likely to benefit from undergoing lung biopsy. It may be that enhanced anaesthetic and surgical techniques will be able to reduce the morbidity and mortality risk of intervention. However, if it can be shown that reliable diagnosis can be achieved non-invasively, this is likely to be the preferred option. Qualitative research on the views of patients and clinicians on acceptable risk profiles may add to the wider picture here. A linked consideration relates to whether anti-fibrotic medications will be licenced in future for 'non-idiopathic' disease, for example CTD-ILD and asbestosis: in these situations, it may be that empirical therapy is trialled early based on CT findings and histological confirmation is deemed unnecessary.

Finally, while this thesis has suggested that people with IPF have a higher mortality after major surgery, the reasons for this are unclear and need further exploration. Ghatol *et al* call for a registry of patients with IPF undergoing surgery (263): while this proposal would need careful consideration to ensure appropriate details were included, this could be an initial means to identify patient, surgical and anaesthetic characteristics associated with adverse outcomes. Potentially this might reveal factors that make surgical risk unacceptable, for example, lung function below a certain level, or a certain type of anaesthesia. Additional research could explore the nature of any morbidity (including the contribution of acute exacerbations, infections or cardiovascular events) which might allow personalised risk

profiles and targeting of those patients most likely to suffer these complications.

A limitation of any registry looking at IPF patients undergoing surgery would be low numbers, and multicentre registries would likely be needed. A possible alternative could be a linked database, such as the UK Hospital Episodes Statistics database combined with primary care data and Office of National Statistics mortality data, although this would likely lack some helpful clinical information. If it is confirmed that less invasive procedures contribute to higher mortality, then reasons for this would need to be proposed and elucidated, depending on any trends seen. For example, both coronary angioplasty and joint replacements require a period of anticoagulation peri-operatively: if this were postulated as a contributing factor to post-operative acute exacerbations, then alternative regimens might need trialling in these patients. Clearly supplementary evidence with additional clinical information is required to explore this further.

8.4 –Conclusions

In conclusion, this thesis has explored three major areas: the incidence and mortality of IPF worldwide, the safety of diagnostic surgical lung biopsy, and the impact of major surgery on IPF. Findings include increasing mortality from IPF worldwide and a conservative global incidence estimate of 3-9 per 100,000, in-hospital mortality of under 2% for elective surgical lung biopsies but higher for non-elective cases, those with increasing age, and those with co-morbidities, and an increased mortality for patients with IPF undergoing major elective surgery.

Key strengths of this work are the international comparative approach, particularly between the UK and the USA, and the use of large representative datasets to identify cases. The main limitation of these datasets relates to whether identified cases truly have IPF: this mirrors clinical practice where diagnostic criteria have changed over the years, and it is likely that a greater acceptance of international consensus diagnostic criteria, the higher profile of IPF research and widespread licencing of anti-fibrotic agents will lead to more consistent and reliable diagnostic labels for future studies.

A greater awareness of the burden of IPF will help specialists plan services and ultimately improve care for their patients. Variation between regions may shed light on aetiological risk factors, and further studies are needed here to determine the impact of possible environmental factors on disease burden. Accurate diagnosis of IPF can be challenging: current data on the risk of surgical lung biopsy will firstly help clinicians and patients weighing up the benefits of the procedure, and secondly may re-invigorate the drive for reliable non-invasive diagnostic tests. Finally, the work on post-surgical mortality suggests a number of further areas for research that will help IPF patients who might require surgical intervention during the course of their illness.

Overall, it is hoped that this thesis will contribute to some of the key questions asked by someone newly-diagnosed with IPF: Why have I got this

disease? Are you sure that it is IPF? And how is it likely to affect my life? Addressing these questions may in turn lead to advances in management options, with the eventual aim of improving the patient experience for those diagnosed with this serious disease.

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2016;11(2):e0147072. PubMed PMID: 26841042. Pubmed Central PMCID: PMC4740484. Epub 2016/02/04.

Appendices

Appendix A: Data sources for international mortality study (Chapter 2)

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.

Appendix B: Search strategy and data extraction tool for systematic review (Chapter 3)

OvidSP search strategy

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 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 retained]

Above strategy designed in conduction with Jane Maltby (medical librarian), Greenfield Medical Library, Queens Medical Centre, University of Nottingham, Nottingham, UK.

Data extraction tool

Data extraction – Systematic review of IPF incidence and mortality

Incidence ☐ Mortality ☐ Both ☐

Reviewer			
Lead author		**Year of paper**	
Journal			
Full paper ☐	Abstract only ☐		

Details of study					
Country / region		Years studied			
Source of data	Registry ☐	Database ☐	Case-finding ☐	Questionnaire ☐	Other ☐
	Details:				
Condition(s) studied	IPF ☐	ILD ☐	ILD with % IPF ☐	Other ☐.....	
Case definition					
Age of cases					
Exclusions					

Incidence of IPF	*crude*	*age-standardised (if available)*	**Mortality from IPF**	*crude*	*age-standardised (if available)*
- Overall			- Overall		
- Male			- Male		
- Female			- Female		
If age-standardised rates included, to which population?					

	Population definition		**Case definition**	
Study Quality	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 C: Read codes used with THIN case-control study (Chapter 4)

Read codes for exclusions from THIN dataset

Exclusion codes – alternative diagnoses

14G1.00	H/O: rheumatoid arthritis
14GC.00	History of connective tissue disease
2G27.00	O/E-hands-rheumatoid spindling
38DZ000	Disease activity score 28 joint in rheumatoid arthritis
43F1.00	Rheumatoid factor positive
66H..12	Rheumatism monitoring
66H..13	Rheumatoid arthrit. monitoring
66HB000	Rheumatoid arthritis annual review
7P20300	Delivery of rehabilitation for rheumatoid arthritis
9hR..00	Exception reporting: rheumatoid arthritis quality indicators
9hR0.00	Except rheumatoid arthritis quality indicator: pt unsuitable
9hR1.00	Except rheumatoid arthritis qual indicator: informed dissent
9mM..00	Rheumatoid arthritis monitoring invitation
9mM0.00	Rheumatoid arthritis monitoring invitation first letter
9mM1.00	Rheumatoid arthritis monitoring invitation second letter
9mM2.00	Rheumatoid arthritis monitoring invitation third letter
9mM3.00	Rheumatoid arthritis monitoring verbal invitation
9mM4.00	Rheumatoid arthritis monitoring telephone invitation
A521.00	Varicella pneumonitis
AD04.00	Toxoplasma pneumonitis
AD5..00	Sarcoidosis of lung
AD51.00	Sarcoidosis of lymph nodes
AD52.00	Sarcoidosis of lung with sarcoidosis of lymph nodes
AD53.00	Sarcoidosis of skin
AD54.00	Sarcoidosis of inferior turbinates
AD55.00	Sarcoid arthropathy
Cyu0600	[X]Sarcoidosis of other and combined sites
F013.00	Meningitis due to sarcoidosis
F326300	Multiple cranial nerve palsies in sarcoidosis
F371.00	Polyneuropathy in collagen vascular disease
F371000	Polyneuropathy in disseminated lupus erythematosus
F371200	Polyneuropathy in rheumatoid arthritis
F371z00	Polyneuropathy in collagen vascular disease NOS
F374900	Polyneuropathy in sarcoidosis
F396100	Myopathy due to disseminated lupus erythematosus
F396400	Myopathy due to rheumatoid arthritis
F396500	Myopathy due to sarcoidosis
F396600	Myopathy due to scleroderma
F4D3300	Eyelid discoid lupus erythematosus
G558300	Sarcoid heart disease
G5y7.00	Sarcoid myocarditis
G5y8.00	Rheumatoid myocarditis
G5yA.00	Rheumatoid carditis
H263.00	Pneumonitis, unspecified
H35..00	Extrinsic allergic alveolitis
H35..11	Hypersensitivity pneumonitis
H350.00	Farmers' lung
H351.00	Bagassosis
H352.00	Bird-fancier's lung
H353.00	Suberosis (cork-handlers' lung)
H354.00	Malt workers' lung

H355.00	Mushroom workers' lung
H356.00	Maple bark strippers' lung
H357.00	"Ventilation" pneumonitis
H35y.00	Other allergic alveolitis
H35yz00	Other allergic alveolitis NOS
H35z.00	Allergic alveolitis and pneumonitis NOS
H35z000	Allergic extrinsic alveolitis NOS
H35z100	Hypersensitivity pneumonitis NOS
H35zz00	Allergic alveolitis and pneumonitis NOS
H4...00	Lung disease due to external agents
H4...11	Pneumoconioses
H4...12	Occupational lung disease
H40..00	Coal workers' pneumoconiosis
H41..00	Asbestosis
H410.00	Pleural plaque disease due to asbestosis
H410.11	Asbestos-induced pleural plaque
H41z.00	Asbestosis NOS
H42..00	Silica and silicate pneumoconiosis
H420.00	Talc pneumoconiosis
H421.00	Simple silicosis
H422.00	Complicated silicosis
H423.00	Massive silicotic fibrosis
H42z.00	Silica pneumoconiosis NOS
H43..00	Pneumoconiosis due to other inorganic dust
H430.00	Aluminosis of lung
H431.00	Bauxite fibrosis of lung
H432.00	Berylliosis
H433.00	Graphite fibrosis of lung
H434.00	Siderosis
H435.00	Stannosis
H43z.00	Pneumoconiosis due to inorganic dust NOS
H44..00	Pneumopathy due to inhalation of other dust
H45..00	Pneumoconiosis NOS
H450.00	Pneumoconiosis associated with tuberculosis
H46..00	Respiratory disease due to chemical fumes and vapours
H48..00	Progressive massive fibrosis
H4y..00	Other specified lung diseases due to external agent
H4y0.00	Acute pulmonary radiation disease
H4y1.00	Chronic pulmonary radiation disease
H4y1000	Chronic pulmonary fibrosis following radiation
H4y1z00	Chronic pulmonary radiation disease NOS
H4y2.00	Drug-induced interstitial lung disorders
H4y2000	Acute drug-induced interstitial lung disorders
H4y2100	Chronic drug-induced interstitial lung disorders
H4yz.00	External agent causing respiratory conditions NOS
H4z..00	Lung disease due to external agents NOS
H560.00	Pulmonary alveolar proteinosis
H561.00	Idiopathic pulmonary haemosiderosis
H562.00	Pulmonary alveolar microlithiasis
H564.00	Bronchiolitis obliterans organising pneumonia
H564.11	Cryptogenic organising pneumonia
H57..00	Lung involvement in diseases EC
H570.00	Rheumatoid lung
H571.00	Rheumatic pneumonia
H572.00	Lung disease with systemic sclerosis
H57y.00	Lung disease with diseases EC
H57y000	Pulmonary amyloidosis

H57y100	Lung disease with polymyositis
H57y200	Pulmonary sarcoidosis
H57y400	Lung disease with systemic lupus erythematosus
H58y500	Respiratory bronchiolitis associated interstitial lung dis
H58y600	Interstitial lung disease due to collagen vascular disease
H58y700	Interstitial lung disease due to connective tissue disease
Hyu4.00 [	X]Lung diseases due to external agents
Hyu4000	[X]Pneumoconiosis due to other dust containing silica
Hyu4100	[X]Pneumoconiosis due to other specified inorganic dusts
Hyu4300	[X]Hypersensitivity pneumonitis due to other organic dusts
Hyu4800	[X]Chronic+other pulmonary manifestations due to radiation
Hyu4900	[X]Respiratory conditions/other specified external agents
Hyu4A00	[X]Respiratory conditions due to unspecified external agent
J63A.00	Hepatic granulomas in sarcoidosis
K01x400	Nephrotic syndrome in systemic lupus erythematosus
K01x411	Lupus nephritis
M154.00	Lupus erythematosus
M154000	Lupus erythematosus chronicus
M154100	Discoid lupus erythematosus
M154200	Lupus erythematosus migrans
M154300	Lupus erythematosus nodularis
M154400	Lupus erythematosus profundus
M154500	Lupus erythematosus tumidus
M154600	Lupus erythematosus unguium mutilans
M154700	Subacute cutaneous lupus erythematosus
M154z00	Lupus erythematosus NOS
M210.00	Circumscribed scleroderma
M210000	Unspecified circumscribed scleroderma
M210400	Linear scleroderma
M210z00	Circumscribed scleroderma NOS
Myu7800	[X]Other local lupus erythematosus
N....00	Musculoskeletal and connective tissue diseases
N....11	Connective tissue diseases
N00..00	Diffuse diseases of connective tissue
N00..11	Collagen diseases
N000.00	Systemic lupus erythematosus
N000000	Disseminated lupus erythematosus
N000300	Systemic lupus erythematosus with organ or sys involv
N000400	Systemic lupus erythematosus with pericarditis
N000500	Neonatal lupus erythematosus
N000z00	Systemic lupus erythematosus NOS
N001.00	Scleroderma
N001.11	Acrosclerosis
N001.12	Systemic sclerosis
N001000	Progressive systemic sclerosis
N001100	CREST syndrome
N003.00	Dermatomyositis
N003.11	Poikilodermatomyositis
N003000	Juvenile dermatomyositis
N003100	Dermatopolymyositis in neoplastic disease
N003X00	Dermatopolymyositis, unspecified
N004.00	Polymyositis
N00y.00	Other specified diffuse collagen diseases
N00z.00	Collagen disease NOS
N04..00	Rheumatoid arthritis and other inflammatory polyarthropathy
N040.00	Rheumatoid arthritis
N040000	Rheumatoid arthritis of cervical spine

N040100	Other rheumatoid arthritis of spine
N040200	Rheumatoid arthritis of shoulder
N040300	Rheumatoid arthritis of sternoclavicular joint
N040400	Rheumatoid arthritis of acromioclavicular joint
N040500	Rheumatoid arthritis of elbow
N040600	Rheumatoid arthritis of distal radio-ulnar joint
N040700	Rheumatoid arthritis of wrist
N040800	Rheumatoid arthritis of MCP joint
N040900	Rheumatoid arthritis of PIP joint of finger
N040A00	Rheumatoid arthritis of DIP joint of finger
N040B00	Rheumatoid arthritis of hip
N040C00	Rheumatoid arthritis of sacro-iliac joint
N040D00	Rheumatoid arthritis of knee
N040E00	Rheumatoid arthritis of tibio-fibular joint
N040F00	Rheumatoid arthritis of ankle
N040G00	Rheumatoid arthritis of subtalar joint
N040H00	Rheumatoid arthritis of talonavicular joint
N040J00	Rheumatoid arthritis of other tarsal joint
N040K00	Rheumatoid arthritis of 1st MTP joint
N040L00	Rheumatoid arthritis of lesser MTP joint
N040M00	Rheumatoid arthritis of IP joint of toe
N040N00	Rheumatoid vasculitis
N040P00	Seronegative rheumatoid arthritis
N040Q00	Rheumatoid bursitis
N040R00	Rheumatoid nodule
N040S00	Rheumatoid arthritis - multiple joint
N040T00	Flare of rheumatoid arthritis
N042.00	Other rheumatoid arthropathy + visceral/systemic involvement
N042000	Rheumatic carditis
N042100	Rheumatoid lung disease
N042200	Rheumatoid nodule
N042z00	Rheumatoid arthropathy + visceral/systemic involvement NOS
N043.00	Juvenile rheumatoid arthritis - Still's disease
N043000	Juvenile rheumatoid arthropathy unspecified
N043100	Acute polyarticular juvenile rheumatoid arthritis
N043200	Pauciarticular juvenile rheumatoid arthritis
N043300	Monarticular juvenile rheumatoid arthritis
N043z00	Juvenile rheumatoid arthritis NOS
N044.00	Chronic post-rheumatic arthropathy
N044.12	Nodular fibrositis of chronic rheumatic disease
N045500	Juvenile rheumatoid arthritis
N047.00	Seropositive errosive rheumatoid arthritis
N04X.00	Seropositive rheumatoid arthritis, unspecified
N04y000	Rheumatoid lung
N04y011	Caplan's syndrome
N04y012	Fibrosing alveolitis associated with rheumatoid arthritis
N233200	Myositis in sarcoidosis
Nyu1000	[X]Rheumatoid arthritis+involvement/other organs or systems
Nyu1100	[X]Other seropositive rheumatoid arthritis
Nyu1200	[X]Other specified rheumatoid arthritis
Nyu1G00	[X]Seropositive rheumatoid arthritis, unspecified
Nyu4.00	[X]Systemic connective tissue disorders
Nyu4300	[X]Other forms of systemic lupus erythematosus
Nyu4400	[X]Other dermatomyositis
Nyu4500	[X]Other forms of systemic sclerosis
Nyu4700	[X]Other systemic diseases of connective tissue
Nyu4800	[X]Dermato(poly)myositis in neoplastic disease CE

Nyu4C00	[X]Systemic disorders/connective tissue in other diseases CE
Nyu4E00	[X]Dermatopolymyositis, unspecified
Nyu4F00	[X]Mixed connective tissue disease
Nyu8900	[X]Myositis in sarcoidosis classified elsewhere
Nz...00	Musculoskeletal and connective tissue diseases NOS
Q471100	Scleroderma in newborn

Use of culprit drugs

1st column is THIN 'drugcode', 2nd column is 'BNF code'

Amiodarone

81066979	00.00.00.00	amiodarone 20mg/5ml oral suspension
81070979	00.00.00.00	amiodarone 200mg/5ml oral suspension
81076979	00.00.00.00	amiodarone 100mg/5ml oral solution
85026998	02.03.02.01	amiodarone 25mg/5ml oral suspension
85651998	02.03.02.00	amiodarone 150mg/3ml solution for injection ampoules
88043997	02.03.02.00	amiodarone hcl 200mg tablets
88043998	02.03.02.00	amiodarone hcl 100mg tablets
90656998	02.03.02.00	amiodarone hcl 100mg tablets
90975998	02.03.02.00	amiodarone 300mg/10ml solution for injection
96933989	02.03.02.00	amiodarone 200mg tablets
96933990	02.03.02.00	amiodarone 100mg tablets
96950996	02.03.02.00	amiodarone 50mg/ml injection
96950997	02.03.02.00	amiodarone 200mg tablets
96950998	02.03.02.00	amiodarone 100mg tablets
96972989	02.03.02.00	amiodarone 200mg tablets
97011989	02.03.02.00	amiodarone 200mg tablets
97085989	02.03.02.00	amiodarone 200mg tablets
97848989	02.03.02.00	amiodarone 200mg tablets
97986989	02.03.02.00	amiodarone 200mg tablets
97986990	02.03.02.00	amiodarone 100mg tablets
98343989	02.03.02.00	amiodarone 200mg tablets
98343990	02.03.02.00	amiodarone 100mg tablets
99811996	02.03.02.00	amiodarone hcl 150mg/3ml inj
99811997	02.03.02.00	amiodarone hcl 200mg tablets
99811998	02.03.02.00	amiodarone hcl 100mg tablets
99872989	02.03.02.00	amiodarone 200mg tablets
99872990	02.03.02.00	amiodarone 100mg tablets

Methotrexate

64115979	00.00.00.00	methotrexate 25mg/3ml solution for injection
78442979	08.01.03.00	methotrexate 50mg/2ml solution for injection
81490998	10.01.03.00	methotrexate 27.5mg/0.55ml inj
81491998	10.01.03.00	methotrexate 22.5mg/0.45ml inj
81492998	10.01.03.00	methotrexate 17.5mg/0.35ml inj
81493998	10.01.03.00	methotrexate 12.5mg/0.25ml inj
81495998	10.01.03.00	methotrexate 22.5mg/0.45ml solution for injection
81496998	10.01.03.00	methotrexate 17.5mg/0.35ml solution for injection
81498998	10.01.03.00	methotrexate 12.5mg/0.25ml solution for injection
81638998	10.01.03.00	methotrexate 30mg/1.5ml solution for injection
81640998	10.01.03.00	methotrexate 25mg/1.25ml solution for injection
81642998	10.01.03.00	methotrexate 20mg/1ml solution for injection

81815998	10.01.03.00	methotrexate 30mg/0.6ml inj
81816998	10.01.03.00	methotrexate 30mg/0.6ml solution for injection
82840998	10.01.03.00	methotrexate 25mg/0.5ml inj
82841998	10.01.03.00	methotrexate 20mg/0.4ml inj
82842998	10.01.03.00	methotrexate 15mg/0.3ml inj
82843998	10.01.03.00	methotrexate 10mg/0.2ml inj
82844998	10.01.03.00	methotrexate 7.5mg/0.15ml inj
82845998	10.01.03.00	methotrexate 25mg/0.5ml solution for injection
82846998	10.01.03.00	methotrexate 20mg/0.4ml solution for injection
82847998	10.01.03.00	methotrexate 15mg/0.3ml solution for injection
82848998	10.01.03.00	methotrexate 10mg/0.2ml solution for injection
82849998	10.01.03.00	methotrexate 7.5mg/0.15ml solution for injection
84438998	08.01.03.00	methotrexate 10mg/5ml oral solution
84439998	08.01.03.00	methotrexate 10mg/5ml oral suspension
85097998	08.01.03.00	methotrexate 1g/40ml solution for injection vials
85100998	08.01.03.00	methotrexate 7.5mg/5ml oral suspension
85639998	10.01.03.00	methotrexate 7.5mg/0.75ml pfs
85640998	10.01.03.00	methotrexate 10mg/1ml pfs
85641998	10.01.03.00	methotrexate 15mg/1.5ml pfs
85642998	10.01.03.00	methotrexate 20mg/2ml p/f syr
85643998	10.01.03.00	methotrexate 25mg/2.5ml syrng
85644998	10.01.03.00	methotrexate 7.5mg/0.75ml solution for injection
85645998	10.01.03.00	methotrexate 10mg/1ml solution for injection
85646998	10.01.03.00	methotrexate 15mg/1.5ml solution for injection
85648998	10.01.03.00	methotrexate 20mg/2ml solution for injection
85650998	10.01.03.00	methotrexate 25mg/2.5ml solution for injection
85737998	08.01.03.00	methotrexate 5g/50ml solution for infusion vials
85738998	08.01.03.00	methotrexate 1g/10ml solution for injection vials
85776998	23.00.00.00	methotrexate oral solution
85777998	08.01.03.00	methotrexate 12.5mg/5ml oral suspension
86327998	08.01.03.00	methotrexate 2.5mg/5ml oral suspension
86339998	08.01.03.00	methotrexate 5mg/0.2ml solution for injection
86342998	08.01.03.00	methotrexate 22.5mg/0.9ml solution for injection
86343998	08.01.03.00	methotrexate 15mg/0.6ml solution for injection
86344998	08.01.03.00	methotrexate 12.5mg/0.5ml solution for injection
86345998	08.01.03.00	methotrexate 10mg/0.4ml solution for injection
86427998	08.01.03.00	methotrexate 17.5mg/0.7ml solution for injection
86434998	08.01.03.00	methotrexate 20mg/0.8ml solution for injection
86435998	08.01.03.00	methotrexate 25mg/1ml solution for injection
86436998	08.01.03.00	methotrexate 500mg/20ml solution for injection vials
86437998	08.01.03.00	methotrexate 50mg/2ml injection
86438998	08.01.03.00	methotrexate 7.5mg/0.3ml solution for injection
86439998	08.01.03.00	methotrexate 30mg/1.2ml solution for injection
86440998	08.01.03.00	methotrexate 27.5mg/1.1ml solution for injection
92488997	08.01.03.00	methotrexate sodium 2.5mg tablet
92488998	08.01.03.00	methotrexate sodium 25mg/ml injection
92639979	08.01.03.00	methotrexate 5g/200ml solution for infusion vials
92650979	08.01.03.00	methotrexate 200mg/8ml solution for injection vials
92655979	08.01.03.00	methotrexate 50mg/2ml solution for injection vials
93074990	08.01.03.00	methotrexate 2.5mg tablets
95867996	08.01.03.00	methotrexate 5mg/2ml solution for injection vials
95867997	08.01.03.00	methotrexate 10mg tablets
95867998	08.01.03.00	methotrexate 2.5mg tablets
95868996	08.01.03.00	methotrexate 50mg/3ml injection
95868997	08.01.03.00	methotrexate 100mg/ml injection
95868998	08.01.03.00	methotrexate 25mg/ml injection
95869997	08.01.03.00	methotrexate 10mg tablets

95869998	08.01.03.00	methotrexate 2.5mg tablets
96279990	08.01.03.00	methotrexate 2.5mg tablets
96752989	08.01.03.00	methotrexate 10mg tablets
96752990	08.01.03.00	methotrexate 2.5mg tablets
96820988	08.01.03.00	methotrexate 5mg/2ml solution for injection vials
98013988	08.01.03.00	methotrexate 100mg/ml injection
98958988	08.01.03.00	methotrexate sodium 2.5mg tablet
98959989	08.01.03.00	methotrexate 10mg tablets
98959990	08.01.03.00	methotrexate 2.5mg tablets
99956998	08.01.03.00	methotrexate 5mg/2ml solution for injection vials

Nitrofurantoin

66739979	00.00.00.00	nitrofurantoin 5mg/5ml oral suspension
66741979	00.00.00.00	nitrofurantoin 5mg/5ml oral solution
66818979	00.00.00.00	nitrofurantoin 25mg/5ml oral solution
90032979	05.01.13.00	nitrofurantoin 25mg/5ml oral suspension
93911979	05.01.13.00	nitrofurantoin 25mg/5ml oral suspension sugar free
93918979	05.01.13.00	nitrofurantoin 50mg tablets
95008990	05.01.13.00	nitrofurantoin 100mg tablets
95009990	05.01.13.00	nitrofurantoin 50mg tablets
95200990	05.01.13.00	nitrofurantoin 25mg/5ml oral suspension sugar free
95714997	05.01.13.00	nitrofurantoin 100mg tablets
95715996	05.01.13.00	nitrofurantoin 100mg modified-release capsules
95715997	05.01.13.00	nitrofurantoin 25mg/5ml oral suspension
95715998	05.01.13.00	nitrofurantoin 100mg capsules
95716996	05.01.13.00	nitrofurantoin 50mg capsules
95716997	05.01.13.00	nitrofurantoin 100mg tablets
95716998	05.01.13.00	nitrofurantoin 50mg tablets
96722992	05.01.13.00	nitrofurantoin 25 mg tab
97677998	05.01.13.00	nitrofurantoin 100mg m/r caps
97980989	05.01.13.00	nitrofurantoin 100mg tablets
97980990	05.01.13.00	nitrofurantoin 50mg tablets
99454997	05.01.13.00	nitrofurantoin 50mg capsules
99454998	05.01.13.00	nitrofurantoin 100mg capsules
99609997	05.01.13.00	nitrofurantoin 100mg tablets
99609998	05.01.13.00	nitrofurantoin 50mg tablets

Read codes for major surgical procedures

Coronary artery bypass grafting

792..11	Coronary artery bypass graft operations
7920.00	Saphenous vein graft replacement of coronary artery
7920.11	Saphenous vein graft bypass of coronary artery
7920000	Saphenous vein graft replacement of one coronary artery
7920100	Saphenous vein graft replacement of two coronary arteries
7920200	Saphenous vein graft replacement of three coronary arteries
7920300	Saphenous vein graft replacement of four+ coronary arteries
7920y00	Saphenous vein graft replacement of coronary artery OS
7920z00	Saphenous vein graft replacement coronary artery NOS
7921.00	Other autograft replacement of coronary artery
7921.11	Other autograft bypass of coronary artery
7921000	Autograft replacement of one coronary artery NEC
7921100	Autograft replacement of two coronary arteries NEC
7921200	Autograft replacement of three coronary arteries NEC

7921300	Autograft replacement of four of more coronary arteries NEC
7921y00	Other autograft replacement of coronary artery OS
7921z00	Other autograft replacement of coronary artery NOS
7922.00	Allograft replacement of coronary artery
7922.11	Allograft bypass of coronary artery
7922000	Allograft replacement of one coronary artery
7922100	Allograft replacement of two coronary arteries
7922200	Allograft replacement of three coronary arteries
7922300	Allograft replacement of four or more coronary arteries
7922y00	Other specified allograft replacement of coronary artery
7922z00	Allograft replacement of coronary artery NOS
7923.00	Prosthetic replacement of coronary artery
7923.11	Prosthetic bypass of coronary artery
7923000	Prosthetic replacement of one coronary artery
7923100	Prosthetic replacement of two coronary arteries
7923200	Prosthetic replacement of three coronary arteries
7923300	Prosthetic replacement of four or more coronary arteries
7923y00	Other specified prosthetic replacement of coronary artery
7923z00	Prosthetic replacement of coronary artery NOS
7924.00	Revision of bypass for coronary artery
7924000	Revision of bypass for one coronary artery
7924100	Revision of bypass for two coronary arteries
7924200	Revision of bypass for three coronary arteries
7924300	Revision of bypass for four or more coronary arteries
7924400	Revision of connection of thoracic artery to coronary artery
7924500	Revision of implantation of thoracic artery into heart
7924y00	Other specified revision of bypass for coronary artery
7924z00	Revision of bypass for coronary artery NOS
7925.00	Connection of mammary artery to coronary artery
7925.11	Creation of bypass from mammary artery to coronary artery
7925000	Double anastomosis of mammary arteries to coronary arteries
7925011	LIMA sequential anastomosis
7925012	RIMA sequential anastomosis
7925100	Double implant of mammary arteries into coronary arteries
7925200	Single anast mammary art to left ant descend coronary art
7925300	Single anastomosis of mammary artery to coronary artery NEC
7925311	LIMA single anastomosis
7925312	RIMA single anastomosis
7925400	Single implantation of mammary artery into coronary artery
7925y00	Connection of mammary artery to coronary artery OS
7925z00	Connection of mammary artery to coronary artery NOS
7926.00	Connection of other thoracic artery to coronary artery
7926000	Double anastom thoracic arteries to coronary arteries NEC
7926100	Double implant thoracic arteries into coronary arteries NEC
7926200	Single anastomosis of thoracic artery to coronary artery NEC
7926300	Single implantation thoracic artery into coronary artery NEC
7926y00	Connection of other thoracic artery to coronary artery OS
7926z00	Connection of other thoracic artery to coronary artery NOS
7927.00	Other open operations on coronary artery
792C.00	Other replacement of coronary artery
792C000	Replacement of coronary arteries using multiple methods
792Cy00	Other specified replacement of coronary artery
792Cz00	Replacement of coronary artery NOS
792D.00	Other bypass of coronary artery
792Dy00	Other specified other bypass of coronary artery
792Dz00	Other bypass of coronary artery NOS

Hip replacement

7K20.00	Total prosthetic replacement of hip joint using cement
7K20.11	Arthroplasty of hip joint using cement
7K20.12	Aufranc total replacement of hip joint using cement
7K20.13	Charnley total replacement of hip joint using cement
7K20.14	Exeter total replacement of hip joint using cement
7K20.15	Farrer total replacement of hip joint using cement
7K20.16	Freeman total replacement of hip joint using cement
7K20.17	Furlong total replacement of hip joint using cement
7K20.18	Howse total replacement of hip joint using cement
7K20.19	Ilch total replacement of hip joint using cement
7K20.1A	McKee total replacement of hip joint using cement
7K20.1B	Monk total replacement of hip joint using cement
7K20.1C	Muller total replacement of hip joint using cement
7K20.1D	Pretoria total replacement of hip joint using cement
7K20.1E	Stanmore total replacement of hip joint using cement
7K20.1F	Turner total replacement of hip joint using cement
7K20.1G	THR - Total prosthetic replacement of hip joint using cement
7K20000	Primary cemented total hip replacement
7K20011	Charnley cemented total hip replacement
7K20100	Conversion to cemented total hip replacement
7K20200	Revision cemented total hip replacement
7K20300	Primary hybrid total replacement of hip joint NEC
7K20400	Conversion to hybrid total hip replacement NEC
7K20500	Revision of hybrid total hip replacement NEC
7K20600	Conver from hybrid total prosth hip joint replace NEC
7K20700	Revision one component total prosth replace hip joint cem
7K20x00	Conversion from cemented total hip replacement
7K20x11	Removal prev cemented total prosthetic replacement hip joint
7K20y00	Total prosthetic replacement of hip joint using cement OS
7K20z00	Total prosthetic replacement of hip joint using cement NOS
7K21.00	Total prosthetic replacement of hip joint not using cement
7K21.11	Freeman total replacement of hip joint not using cement
7K21.12	Furlong total replacement of hip joint not using cement
7K21.13	Lord total replacement of hip joint not using cement
7K21.14	Madreporique total replacement of hip joint not using cement
7K21.15	Monk total replacement of hip joint not using cement
7K21.16	Ring total replacement of hip joint not using cement
7K21.17	THR - Total prosthetic replacement hip joint without cement
7K21000	Primary uncemented total hip replacement
7K21100	Conversion to uncemented total hip replacement
7K21200	Revision uncemented total hip replacement
7K21300	Revision one component tot prosth replace hip joint not cem
7K21x00	Conversion from uncemented total hip replacement
7K21y00	Total prosthetic replacement hip joint not using cement OS
7K21z00	Total prosthetic replacement hip joint not using cement NOS
7K22.00	Other total prosthetic replacement of hip joint
7K22.11	Other arthroplasty of hip joint
7K22.12	THR - Other total prosthetic replacement of hip joint
7K22000	Primary total prosthetic replacement of hip joint NEC
7K22011	Primary hybrid total replacement of hip joint NEC
7K22100	Conversion to total prosthetic replacement of hip joint NEC
7K22112	Conversion to hybrid total hip replacement NEC
7K22200	Revision of total prosthetic replacement of hip joint NEC

7K22211	Revision of hybrid total hip replacement NEC
7K22300	Attention to total hip replacement NEC
7K22400	Revision one component total prosthet replace hip joint NEC
7K22500	Closed reduction dislocated total prosthet replace hip joint
7K22x00	Conversion from prev total pros replace hip joint NEC
7K22x12	Conver from hybrid total prosth hip joint replace NEC
7K22y00	Other specified total prosthetic replacement of hip joint
7K22z00	Total prosthetic replacement of hip joint NOS

Knee replacement

7K30.00	Total prosthetic replacement of knee joint using cement
7K30.11	Anametric total replacement of knee joint using cement
7K30.12	Arthroplasty of knee joint using cement
7K30.13	Attenborough total replacement of knee joint using cement
7K30.14	Autophor arthroplasty of knee joint using cement
7K30.15	Cavendish total replacement of knee joint using cement
7K30.16	Charnley total replacement of knee joint using cement
7K30.17	Deane total replacement of knee joint using cement
7K30.18	Denham total replacement of knee joint using cement
7K30.19	Freeman total replacement of knee joint using cement
7K30.1A	Geomedic total replacement of knee joint using cement
7K30.1B	Geometric total replacement of knee joint using cement
7K30.1C	Guepar hinge replacement of knee joint using cement
7K30.1D	Gunston total replacement of knee joint using cement
7K30.1E	Herbert total replacement of knee joint using cement
7K30.1F	Ilch total replacement of knee joint using cement
7K30.1G	Irving total replacement of knee joint using cement
7K30.1H	Liverpool total replacement of knee joint using cement
7K30.1I	Manchester total replacement of knee joint using cement
7K30.1J	Marmor total replacement of knee joint using cement
7K30.1K	McKee arthroplasty of knee joint using cement
7K30.1L	Melbourne total replacement of knee joint using cement
7K30.1M	Platt arthroplasty of knee joint using cement
7K30.1N	Polycentric total replacement of knee joint using cement
7K30.1O	Pretoria arthroplasty of knee joint using cement
7K30.1P	Sheehan total replacement of knee joint using cement
7K30.1Q	Shiers total replacement of knee joint using cement
7K30.1R	Stanmore total replacement of knee joint using cement
7K30.1S	Swanson total replacement of knee joint using cement
7K30.1T	Uci total replacement of knee joint using cement
7K30.1U	Wallidus hinge arthroplasty of knee joint using cement
7K30.1V	TKR -Total prosthetic replacement of knee joint using cement
7K30000	Primary cemented total knee replacement
7K30100	Conversion to cemented total knee replacement
7K30200	Revision cemented total knee replacement
7K30300	Revision one component total prosth replace knee joint cem
7K30x00	Conversion from cemented total knee replacement
7K30y00	Total prosthetic replacement of knee joint using cement OS
7K30z00	Total prosthetic replacement of knee joint using cement NOS
7K31.00	Total prosthetic replacement of knee joint not using cement
7K31.11	Arthroplasty of knee joint not using cement
7K31.12	TKR - Total prosthetic replacement knee joint without cement
7K31000	Primary uncemented total knee replacement
7K31100	Conversion to uncemented total knee replacement
7K31200	Revision uncemented total knee replacement

7K31300	Revis one compon total prosth replace knee joint not cement
7K31x00	Conversion from uncemented total knee replacement
7K31x11	Removal previous uncemented total prosthet replacement knee
7K31y00	Total prosthetic replacement knee joint not using cement OS
7K31z00	Total prosthetic replacement knee joint not using cement NOS
7K32.00	Other total prosthetic replacement of knee joint
7K32.12	TKR - Other total prosthetic replacement of knee joint
7K32000	Primary total knee replacement NEC
7K32011	Primary hybrid total knee replacement NEC
7K32100	Conversion to total knee replacement NEC
7K32112	Conversion to hybrid total knee replacement NEC
7K32200	Revision of total knee replacement NEC
7K32211	Revision hybrid total knee replacement NEC
7K32300	Revis one component total prosthetic replace knee joint NEC
7K32400	Attention to total knee replacement NEC
7K32411	Attention to hybrid total knee replacement NEC
7K32500	Arthrolysis of total prosthetic replacement of knee joint
7K32600	Prosthetic arthroplasty of the patellofemoral joint
7K32x00	Conversion from total knee replacement NEC
7K32x12	Conversion from hybrid total knee replacement NEC
7K32y00	Other total prosthetic replacement of knee joint OS
7K32z00	Other total prosthetic replacement of knee joint NOS
7K37.00	Cemented unicompartmental knee replacement
7K37000	Primary cemented unicompartmental knee replacement
7K37100	Conversion to cemented unicompartmental knee replacement
7K37200	Revision cemented unicompartmental knee replacement
7K37x00	Conversion from cemented unicompartmental knee replacement
7K38.00	Uncemented unicompartmental knee replacement
7K38000	Primary uncemented unicompartmental knee replacement
7K38100	Conversion to uncemented unicompartmental knee replacement
7K38200	Revision uncemented unicompartmental knee replacement
7K38x00	Conversion from uncemented unicompartmental knee replacement
7K39.00	Hybrid unicompartmental knee replacement
7K39000	Primary hybrid unicompartmental knee replacement
7K39100	Conversion to hybrid unicompartmental knee replacement
7K39200	Revision hybrid unicompartmental knee replacement
7K39x00	Conversion from hybrid unicompartmental knee replacement
7K3A.00	Unicompartmental knee replacement NOS
7K6c.00	Hybrid prosthetic replacement hip joint cemented acetab comp
7K6c000	Pri hybrid prosth replacement hip jo cemented acetab comp
7K6c100	Conver hybrid prosthetic replacement hip joint cem ace comp
7K6c200	Revis hybrid prosth replace hip joint cement acetabular comp
7K6cx00	Conversion prev hyb prosth replace hip joint cem acetab comp
7K6cy00	OS hybrid prosthetic replacement hip jo cement acetabul comp
7K6cz00	Hybrid prosthetic replacement hip jo cemented aceta comp NOS
7K6d.00	Hybrid prosthetic replace hip joint cemented femoral compon
7K6d000	Primary hybrid prosthetic replace hip jo cemented femo comp
7K6d100	Conver hybrid prosthetic replacement hip jo cement fem comp
7K6d200	Revis hybrid prosthetic replacement hip jo cemented fem comp
7K6dx00	Conv prev hybrid prosth replace hip jo cement femoral comp
7K6dy00	OS hybrid prosthetic replacement hip jo cement femoral comp
7K6dz00	Hybrid prosthetic replace hip jo cemented femoral compon NOS
7K6e.00	Hybrid prosthetic replacement of hip joint using cement
7K6e000	Primary hybrid prosthetic replacement hip joint cement NEC
7K6e100	Conversion hybrid prosthetic replacement hip jo cement NEC
7K6e200	Revision hybrid prosthetic replacement hip joint cement NEC
7K6e300	Attention hybrid prosthetic replacement hip joint cement NEC

7K6ex00	Conver previous hybrid prosthetic replace hip joint cem NEC
7K6ey00	OS hybrid prosthetic replacement of hip joint using cement
7K6ez00	Hybrid prosthetic replacement of hip joint using cement NOS
7K6q.00	Hybrid prosthetic replacement of knee joint using cement
7K6q000	Primar hybrid prosthetic replacement knee joint using cement
7K6q100	Conver hybrid prosthetic replacement knee joint using cement
7K6q200	Revis hybrid prosthetic replacement knee joint using cement
7K6q300	Atten hybrid prosthetic replacement knee joint using cement
7K6qx00	Conver from prev hyb prosth replace of knee joint us cement
7K6qy00	OS hybrid prosthetic replacement of knee joint using cement
7K6qz00	Hybrid prosthetic replacement of knee joint using cement NOS

Read codes for smoking

Smoking Read codes

1st column is Read code. 2nd column is description. 3rd column is interpretation of status: Current, Ex, Never, Unknown. Unclear interpretations classified as unknown during analysis.

137..00	Tobacco consumption	Current or Ex
137..11	Smoker - amount smoked	Current
1371.00	Never smoked tobacco	Never
1371.11	Non-smoker	Never or Ex
1372.00	Trivial smoker - < 1 cig/day	Current
1372.11	Occasional smoker	Current
1373.00	Light smoker - 1-9 cigs/day	Current
1374.00	Moderate smoker - 10-19 cigs/d	Current
1375.00	Heavy smoker - 20-39 cigs/day	Current
1376.00	Very heavy smoker - 40+cigs/d	Current
1377.00	Ex-trivial smoker (<1/day)	Ex
1378.00	Ex-light smoker (1-9/day)	Ex
1379.00	Ex-moderate smoker (10-19/day)	Ex
137A.00	Ex-heavy smoker (20-39/day)	Ex
137B.00	Ex-very heavy smoker (40+/day)	Ex
137C.00	Keeps trying to stop smoking	Current
137D.00	Admitted tobacco cons untrue ?	Unknown
137E.00	Tobacco consumption unknown	Unknown
137F.00	Ex-smoker - amount unknown	Ex
137G.00	Trying to give up smoking	Current
137H.00	Pipe smoker	Current
137J.00	Cigar smoker	Current
137j.00	Ex-cigarette smoker	Ex
137K.00	Stopped smoking	Ex
137L.00	Current non-smoker	Never or Ex
137M.00	Rolls own cigarettes	Current
137N.00	Ex pipe smoker	Ex
137O.00	Ex cigar smoker	Ex
137P.00	Cigarette smoker	Current
137P.11	Smoker	Current
137Q.00	Smoking started	Current
137Q.11	Smoking restarted	Current
137R.00	Current smoker	Current
137S.00	Ex smoker	Ex

137T.00	Date ceased smoking	Ex
137V.00	Smoking reduced	Current
137X.00	Cigarette consumption	Current or Ex
137Y.00	Cigar consumption	Current or Ex
137Z.00	Tobacco consumption NOS	Current or Ex
137a.00	Pipe tobacco consumption	Current or Ex
137b.00	Ready to stop smoking	Current
137c.00	Thinking about stopping smoking	Current
137d.00	Not interested in stopping smoking	Current
137e.00	Smoking restarted	Current
137f.00	Reason for restarting smoking	Current
137g.00	Cigarette pack-years	Unknown
137h.00	Minutes from waking to first tobacco consumption	Current
13p..00	Smoking cessation milestones	Current or Ex
13p0.00	Negotiated date for cessation of smoking	Current
13p1.00	Smoking status at 4 weeks	Unknown
13p2.00	Smoking status between 4 and 52 weeks	Current or Ex
13p3.00	Smoking status at 52 weeks	Current or Ex
13p4.00	Smoking free weeks	Current or Ex
13p5.00	Smoking cessation programme start date	Current
13p6.00	Carbon monoxide reading at 4 weeks	Unknown
4I90.00	Expired carbon monoxide concentration	Unknown
6791.00	Health ed. - smoking	Current
67A3.00	Pregnancy smoking advice	Current
67H1.00	Lifestyle advice regarding smoking	Current
745H.00	Smoking cessation therapy	Unknown
745H000	Nicotine replacement therapy using nicotine patches	Current
745H100	Nicotine replacement therapy using nicotine gum	Current
745H200	Nicotine replacement therapy using nicotine inhalator	Current
745H300	Nicotine replacement therapy using nicotine lozenges	Current
745H400	Smoking cessation drug therapy	Current
745Hy00	Other specified smoking cessation therapy	Current
745Hz00	Smoking cessation therapy NOS	Unknown
8B2B.00	Nicotine replacement therapy	Current
8B3Y.00	Over the counter nicotine replacement therapy	Current
8B3f.00	Nicotine replacement therapy provided free	Current
8BP3.00	Nicotine replacement therapy provided by community pharmacist	Current
8CAL.00	Smoking cessation advice	Current
8CAg.00	Smoking cessation advice provided by community pharmacist	Current
8H7i.00	Referral to smoking cessation advisor	Current
8HTK.00	Referral to stop-smoking clinic	Current
8I2I.00	Nicotine replacement therapy contraindicated	Current
8I39.00	Nicotine replacement therapy refused	Current
9N2k.00	Seen by smoking cessation advisor	Unknown
9N4M.00	DNA - Did not attend smoking cessation clinic	Unknown
9OO..00	Anti-smoking monitoring admin.	Unknown
9OO..11	Stop smoking clinic admin.	Unknown
9OO..12	Stop smoking monitoring admin.	Unknown
9OO1.00	Attends stop smoking monitor.	Unknown
9OO2.00	Refuses stop smoking monitor	Unknown
9OO3.00	Stop smoking monitor default	Unknown
9OO4.00	Stop smoking monitor 1st letter	Unknown
9OO5.00	Stop smoking monitor 2nd letter	Unknown
9OO6.00	Stop smoking monitor 3rd letter	Unknown
9OO7.00	Stop smoking monitor verb.inv.	Current

9OO8.00	Stop smoking monitor phone inv	Current
9OO9.00	Stop smoking monitoring delete	Unknown
9OOA.00	Stop smoking monitor. check done	Unknown
9OOZ.00	Stop smoking monitor admin.NOS	Unknown
E023.00	Nicotine withdrawal	Unknown
E251.00	Tobacco dependence	Current
E251100	Tobacco dependence, continuous	Current
E251300	Tobacco dependence in remission	Ex
E251z00	Tobacco dependence NOS	Current
ZG23300	Advice on smoking	Current
ZRBm200	Fagerstrom test for nicotine dependence	Current
ZRBm211	FTND - Fagerstrom test for nicotine dependence	Current
ZRaM.00	Motives for smoking scale	Current
ZRaM.11	MFS - Motives for smoking scale	Current
ZRao.00	Occasions for smoking scale	Current
ZRh4.00	Reasons for smoking scale	Current
ZRh4.11	RFS - Reasons for smoking scale	Current
ZV11600	[V]Personal history of tobacco abuse	Current or Ex
ZV4K000	[V]Tobacco use	Current or Ex
ZV6D800	[V]Tobacco abuse counselling	Current

Appendix D: ICD-9-CM codes used with NIS studies (Chapters 5 & 7)

ICD-9-CM codes for exclusions from surgical lung biopsy study

Diagnostic codes suggesting lung cancer

162.2 Malignant neoplasm of lung: main bronchus
162.3 Malignant neoplasm of lung: upper lobe, bronchus or lung
162.4 Malignant neoplasm of lung: middle lobe, bronchus or lung
162.5 Malignant neoplasm of lung: lower lobe, bronchus or lung
162.8 Malignant neoplasm of lung: other parts of bronchus or lung
162.9 Malignant neoplasm of lung: bronchus and lung, unspecified

163 Malignant neoplasm of pleura
165 Malignant neoplasm of other and ill-defined sites within the respiratory system and intrathoracic organs

212.3 Benign neoplasm of bronchus and lung
212.4 Benign neoplasm of pleura
212.9 Benign neoplasm of respiratory and intrathoracic organs: site unspecified

Procedural codes suggesting lung cancer

32.30 Thoracoscopic segmental resection of lung
32.29 Other and unspecified segmental resection of lung
32.41 Thoracoscopic lobectomy of lung
32.49 Other lobectomy of lung
32.50 Thoracoscopic pneumonectomy
32.59 Other and unspecified pneumonectomy

ICD-9-CM codes for complications from surgical lung biopsy study

451.11 Iatrogenic pulmonary embolism
427.5 Cardiorespiratory arrest
481 Pneumonia (pneumococcal)
482 Other bacterial pneumonia
485 Bronchopneumonia, organism unspecified
486 Pneumonia, organism unspecified
510 Empyema
511.1 Pleural effusion
511.9 Unspecified pleural effusion
512.1 Post-operative pneumothorax
518.0 Pulmonary collapse / atelectasis
518.4 Post-operative pulmonary oedema
518.5 Respiratory insufficiency following surgery
518.7 Transfusion associated acute lung injury
570 Acute liver failure
584 Acute kidney injury
799.1 Respiratory arrest

997.02 Post-operative stroke
997.3 Respiratory complications, including ventilator associated pneumonia (997.31 after 2008) and Mendelson's syndrome (chemical / aspiration pneumonitis) (997.39 after 2008)
998.0 Post-operative shock
998.1 Haemorrhage of haematoma or seroma complicating a procedure
998.2 Accidental puncture or laceration during a procedure
998.3 Disruption of wound
998.4 Foreign body accidentally left during procedure
998.5 Post-operative infection
998.6 Persistent post-operative fistula
998.7 Acute reaction to foreign substance accidentally left during procedure
998.81 Surgical emphysema
998.83 Non-healing surgical wound
998.89 Other specified complications
998.9 Unspecified complication of procedure, not elsewhere classified

E8700 Accidental cut, puncture, perforation or haemorrhage during surgical operation
E8710 Foreign object left in body during surgical operation
E8720 Failure of sterile precautions during surgical operation
E8740 Mechanical failure of instrument during surgical operation
E8762 Failure in suture and ligature during surgical operation
E8763 Misplaced endotracheal tube during surgical operation
E8765 Performance of inappropriate operation

31.1 Temporary tracheostomy
96.72 Ventilator dependence (Continuous invasive mechanical ventilation for 96 consecutive hours or more)

ICD-9-CM codes for procedures from post-surgical mortality study

Coronary artery bypass grafting

36.10 Aortocoronary bypass for heart revascularization, not otherwise specified
36.11 (Aorto)coronary bypass of one coronary artery
36.12 (Aorto)coronary bypass of two coronary arteries
36.13 (Aorto)coronary bypass of three coronary arteries
36.14 (Aorto)coronary bypass of four or more coronary arteries
36.15 Single internal mammary-coronary artery bypass
36.16 Double internal mammary-coronary artery bypass
36.17 Abdominal - coronary artery bypass
36.19 Other bypass anastomosis for heart revascularization

Not including:
35.00 Closed heart valvotomy, unspecified valve
35.01 Closed heart valvotomy, aortic valve
35.02 Closed heart valvotomy, mitral valve

35.03 Closed heart valvotomy, pulmonary valve
35.04 Closed heart valvotomy, tricuspid valve

35.10 Open heart valvuloplasty without replacement, unspecified valve
35.11 Open heart valvuloplasty of aortic valve without replacement
35.12 Open heart valvuloplasty of mitral valve without replacement
35.13 Open heart valvuloplasty of pulmonary valve without replacement
35.14 Open heart valvuloplasty of tricuspid valve without replacement

35.20 Replacement of unspecified heart valve
35.21 Replacement of aortic valve with tissue graft
35.22 Other replacement of aortic valve
35.23 Replacement of mitral valve with tissue graft
35.24 Other replacement of mitral valve
35.25 Replacement of pulmonary valve with tissue graft
35.26 Repair of pulmonary valve with replacement
35.27 Replacement of tricuspid valve with tissue graft
35.28 Other replacement of tricuspid valve

Coronary angioplasty

00.66 Percutaneous transluminal coronary angioplasty [PTCA] or coronary atherectomy
36.09 Other removal of coronary artery obstruction - Coronary angioplasty NOS
36.01, 36.02, 36.05 – previously applied codes for this prior to 2005, now deleted.
See http://www.cdc.gov/nchs/data/icd/icd-9-cm_fy14_cnvtbl_final.pdf for details of conversion between updated ICD-9-CM codes, accessed June 2016

Hip replacement
81.51 Total hip replacement
81.52 Partial hip replacement
81.53 Revision of hip replacement, not otherwise specified

Knee replacement
81.54 Total knee replacement
81.55 Revision of knee replacement, not otherwise specified

Lobectomy
32.41 Thoracoscopic lobectomy of lung
32.49 Other lobectomy of lung
32.4 Lobectomy of lung – old code prior to 2007

Appendix E: Codes and additional data for HES study (Chapter 6)

Codes for exclusions

OPCS-4 Procedural codes suggesting resection for lung cancer

E54.1 Total pneumonectomy
E54.2 Bilobectomy of lung
E54.3 Lobectomy of lung
E54.4 Segmentectomy of lung NEC
E54.5 Partial lobectomy of lung NEC

ICD-10 codes suggesting lung cancer

C34.0 Malignant neoplasm: main bronchus
C34.1 Malignant neoplasm: upper lobe, bronchus or lung
C34.2 Malignant neoplasm: middle lobe, bronchus or lung
C34.3 Malignant neoplasm: lower lobe, bronchus or lung
C34.8 Malignant neoplasm: overlapping lesion of bronchus and lung
C34.9 Malignant neoplasm: bronchus or lung unspecified
C45.0 Mesothelioma of pleura
C78.0 Secondary malignant neoplasm of lung

ICD-10 codes for complications

E42.3 Temporary tracheostomy
I26 Pulmonary embolism
J13 Streptococcal pneumonia
J14 Haemophilus pneumonia
J15 Other bacterial pneumonia
J18 Pneumonia, organism unspecified
J22 Unspecified acute lower respiratory tract infection
J80 Acute respiratory distress syndrome
J86.0 Pyothorax with fistula
J86.9 Pyothorax without fistula
J90 Pleural effusion
J93.8 Other pneumothorax
J93.9 Pneumothorax unspecified
J94.2 Haemothorax
J95.1 Acute pulmonary insufficiency following thoracic surgery
J95.3 Chronic pulmonary insufficiency following thoracic surgery
J95.4 Mendelson's syndrome (chemical / aspiration pneumonitis)
J95.8 Other post-procedural respiratory disorders
J95.9 Post-procedural respiratory disorders, unspecified
J96.0 Acute respiratory failure
J98.1 Pulmonary collapse
R09.2 Respiratory arrest
Z99.1 Dependence on respirator (ventilator)

I21 Acute myocardial infarction
I46.0 Cardiac arrest with successful resuscitation
I46.1 Sudden cardiac death
I46.9 Cardiac arrest, unspecified
I47 Paroxysmal tachycardia
I48.3 Typical atrial flutter
I48.4 Atypical atrial flutter
I48.9 Atrial fibrillation and atrial flutter unspecified
I63 Cerebral infarction (ie stroke)
K25.0 Acute gastric ulcer, with haemorrhage
K25.1 Acute gastric ulcer, with perforation
K25.2 Acute gastric ulcer, with haemorrhage and perforation
K26.0 Acute duodenal ulcer, with haemorrhage
K26.1 Acute duodenal ulcer, with perforation
K26.2 Acute duodenal ulcer, with haemorrhage and perforation
K27.0 Acute peptic ulcer, with haemorrhage
K27.1 Acute peptic ulcer, with perforation
K27.2 Acute peptic ulcer, with haemorrhage and perforation
K28.0 Acute gastrojejunal ulcer, with haemorrhage
K28.1 Acute gastrojejunal ulcer, with perforation
K28.2 Acute gastrojejunal c ulcer, with haemorrhage and perforation
K72.0 Acute and subacute hepatic failure
N17 Acute kidney injury
N99.0 Post-procedural renal failure
T81.0 Haemorrhage and haematoma complicating a procedure, not elsewhere classified
T81.1 Shock during or resulting from a procedure, not elsewhere classified
T81.2 Accidental puncture or laceration during a procedure, not elsewhere classified
T81.3 Disruption of operation wound, not elsewhere classified
T81.4 Infection following a procedure, not elsewhere classified
T81.5 Foreign body accidentally left in body cavity or operation wound following a procedure
T81.6 Acute reaction to foreign substance accidentally left during a procedure
T81.7 Vascular complications following a procedure, not elsewhere classified
T81.8 Other complications of procedure, not elsewhere classified
T81.9 Unspecified complication of procedure

Plus
OPCS-4 code Y71.4 - Failed minimal access approach converted to open

Codes selected pragmatically: while streptococcal pneumonia would be an unusual cause of *hospital-acquired* pneumonia, its code might easily be used by coders to define this condition.

List of Thoracic Surgical Centres in England

There is no clear definitive universal data source for the number of thoracic surgical centres in England, as there are discrepancies between terminology: one National Health Service trust may run two hospitals, which may be counted as either one or two centres. The following list of centres was compiled for the raw estimate of average numbers of procedures per centre.

Southwest
Bristol Royal Infirmary
Derriford, Plymouth
Royal Devon and Exeter

London
Barts and London Chest
Royal Brompton & Harefield
Imperial - Hammersmith
UCL
Guys
Kings
St George's

Southeast
Southampton General
John Radcliffe, Oxford

East of England
Norwich and Norfolk
Papworth, Cambridge
Essex Cardiothoracic Centre

East Midlands
Nottingham City Hospital
Glenfield, Leicester

West Midlands
Heart of England, Birmingham
New Cross, Wolverhampton
University Hospital Coventry and Warwick
Royal Stoke, Stoke-on-Trent

Yorkshire and the Humber
Northern General, Sheffield
St James's, Leeds
Castle Hill, Hull

Northwest
Liverpool Heart and Chest
UHSM, Manchester
Victoria Hospital, Blackpool

Northeast
Freeman, Newcastle
James Cook, Middlesborough