A descriptive epidemiological study of Interstitial Lung Disease in the United Kingdom general population

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Dekan

“I've come loaded with statistics, for I've noticed that a man can't prove anything without statistics.”

-Mark Twain
(1835 - 1910)

“Not everything that can be counted counts; and not everything that counts can be counted.”

-George H. Gallup
(1901-1984)

“Whether epidemiology alone can, in strict logic, ever prove causality, even in this modern sense, may be questioned, but the same must also be said of laboratory experiments on animals.”

-Sir Richard Doll
(1912-2005)

“It remains an astonishing, disturbing fact that in America – a nation where nearly every new drug is subjected to rigorous scrutiny as a potential carcinogen, and even the bare hint of a substance’s link to cancer ignites a firestorm of public hysteria and media anxiety – one of the most potent and common carcinogens known to humans can be freely bought and sold at every corner store for a few dollars.”

-Siddharta Mukherjee
in The Emperor of all Maladies. A Biography of Cancer

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List of abbreviations

AIP	acute interstitial pneumonia
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
BCDSP	Boston Collaborative Drug Surveillance Program
BMI	body mass index
BOOP	bronchiolitis obliterans organizing pneumonia
BTS	British Thoracic Society
CFA	cryptogenic fibrosing alveolitis
CI	confidence interval
CL	confidence limit(s)
COP	cryptogenic organizing pneumonia
COPD	chronic obstructive pulmonary disease
CRP	clinico-radio-pathologic
CTD	connective tissue disease
DIP	desquamative interstitial pneumonia
DLCO	diffusing capacity of the lung for carbon monoxide
DM	diabetes mellitus
DPLD	diffuse parenchymal lung disease
DRAD	drug-/radiation-induced
EAA	extrinsic allergic alveolitis
ECHO	echocardiography
ERS	European Respiratory Society
FVC	forced vital capacity
GDP	gross domestic product

GERD	gastro-esophogeal reflux disease
GIP	giant cell interstitial pneumonia
GPRD	General Practice Research Database
HP	hypersensitivity pneumonia
HRCT	high resolution computed tomography
ICD	International Classification of Diseases
IFA	idiopathic fibrosing alveolitis
IIP	idiopathic interstitial pneumonia
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IIP	idiopathic interstitial pneumonia
ISAC	Independent Scientific Advisory Committee
LAM	lymphangioleiomyomatosis
LIP	lymphocytic interstitial pneumonia
MHRA	Medicines and Healthcare Products Regulatory Agency
NEC	not elsewhere classified
NHS	National Health Services
NOS	not otherwise specified
NSIP	non-specific interstitial pneumonia
ODIS	associated with other diseases
OPCS	Office of Population Censuses and Surveys
PAH	pulmonary arterial hypertension
PAP	pulmonary alveolar proteinosis
PFT	pulmonary function test
PH	pulmonary hypertension
RA	rheumatoid arthritis

RBILD	respiratory bronchiolitis interstitial lung disease
READ	non-abbreviation, medical coding system developed by UK GP, James “Read”
SSc	systemic sclerosis, scleroderma
SLB	surgical lung biopsy
SLE	systemic lupus erythematosus
SS	Sjörgen’s syndrome, sicca
TB	tuberculosis
TBBx	transbronchial biospy
TLC	total lung capacity
UK	United Kingdom
VAMP	Value Added Medical Products
WG	Wegener’s granulomatosis

Summary

Interstitial lung disease (ILD) is a heterogeneous group of parenchymal lung disorders having varied histopathologies. Although histologically different, the ILDs have rather similar clinical presentations consisting of increasing dyspnea, a restrictive lung function, impaired gas exchange, and widespread shadowing on chest radiography. Approximately two-thirds of ILD cases have no known etiology. The remaining one-third is either associated with connective tissue disease (CTD) or caused by various environmental or occupational exposures including inhalation of asbestos or other inorganic particles, inhalation of inorganic agents, certain drugs and radiation therapy. It is widely accepted that prevention, improved prognosis and quality of healthcare are dependent on a better understanding of disease epidemiology, and it is to this end that the present research contributes.

This doctoral research project makes use of a large and well-validated primary care database to investigate the frequency of ILD, the incidence of comorbidity after diagnosis, and characteristics of ILD patients at diagnosis compared to a general population control group. For many ILD subgroups an increase in incidence density and prevalence over time was observed, however it is uncertain to what extent secular trends played a role in these findings. Rates for all-cause mortality and comorbidities varied greatly across ILD subgroups, as did patient characteristics at diagnosis. This research project also delved deeper into specific epidemiological topics relating to certain ILD subgroups within the more broadly-classified, non-idiopathic ILD disease category.

1 Introduction

1.1 Burden of respiratory disease in the global context

Respiratory disease is one of the leading causes of mortality worldwide. The number of deaths attributed to respiratory disease is expected to climb even further until 2020, in particular from tuberculosis (TB), chronic obstructive pulmonary disease (COPD), and lung cancer. The predicted numbers are staggering: In 2020, of 68 million deaths worldwide, 11.9 million will have been attributed to respiratory disease (4.7 million from COPD, 2.5 million from pneumonia, 2.4 million from TB and 2.3 from lung cancer). In terms of worldwide incidence, prevalence, mortality, and health care costs, respiratory disease ranks second after cardiovascular disease [Alberg AJ et al. 2007, Loddenkemper R et al. 2003].

Respiratory disease imposes a tremendous burden on healthcare budgets. In the European Union alone, with annual direct costs (i.e. costs paid directly for healthcare services) totalling approximately €47.3 billion and assuming a total annual expenditure on healthcare of approximately €800 billion (estimated 9% of gross domestic product (GDP)), the direct cost of respiratory disease accounts for approximately 6% of the total healthcare budget [Rabe KF et al. 2007]. For the predominant respiratory diseases, namely, asthma, pneumonia, TB, and COPD total annual direct and indirect costs (i.e. the value of lost productivity from time off work due to illness) are estimated at €17.7, €10.1 and €2.1 €38.7 billion, respectively [Rees J 2005, Loddenkemper R et al. 2003].

From the healthcare regulatory perspective, interstitial lung disese (ILD) is classified as an “orphan disease”, that is, a disease affecting less than one in 2,000 people worldwide [Loddenkemper R et al. 2003].

No precise data are available on the total cost of ILD at the population level, however individual costs are estimated to be high, since most patients will eventually become incapable of working (i.e. due to dyspnea on exertion), and require continued home oxygen therapy. Others will require lung transplantation or continued palliative care. [Loddenkemper R et al. 2003].

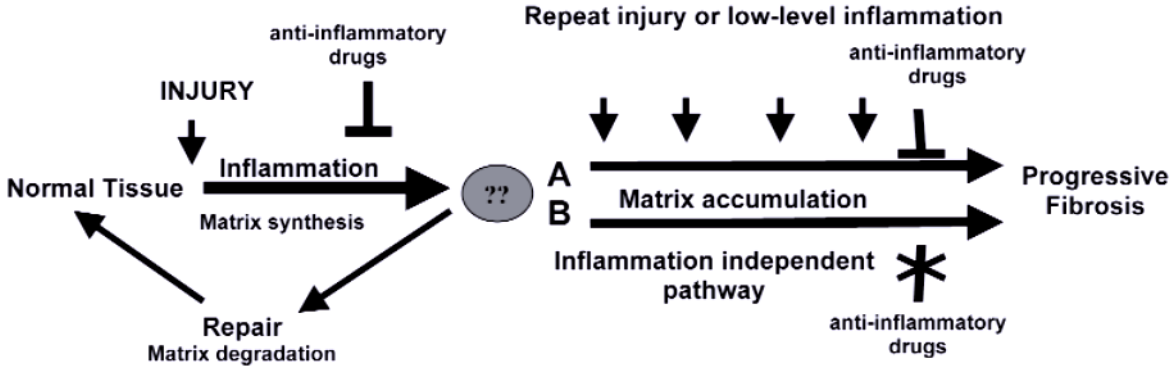
1.2 Evolving paradigms of ILD pathogenesis and disease classification

ILD is also known as diffuse parenchymal lung disease (DPLD) and refers to a large group of acute and chronic pulmonary diseases characterized by damage to the lung parenchyma, with varying patterns of inflammation and/or fibrosis [ATS/ERS 2002, Leslie KO 2006]. Although the pulmonary interstitium (i.e. the space between the epithelial and basement membranes) is the primary site of the parenchymal damage, these diseases also frequently affect the airspaces, peripheral airways, vasculature, and corresponding epithelial and endothelial surfaces [Cushley MJ et al. 1999]. Furthermore, despite being numerous and histopathologically diverse, the physiologic, radiographic, and clinical manifestations of the ILDs are often quite similar, that is, a restrictive (as opposed to obstructive) lung function and impaired gas exchange, widespread shadowing of the lungs on chest X-ray, and increasing shortness of breath or dyspnea, respectively.

The older model of pathogenesis was a universal one. It maintained that all ILDs are characterized by inflammation of the lung interstitium, and that chronic inflammation causes irreversible fibrosis [Crystal RG 1981]. Presence of inflammation was proven by research on alveolitis conducted during the mid-1970s and early 1980s following the introduction of a new medical procedure called bronchoalveolar lavage (BAL) [Chapman HA 2004]. Later, with the introduction of high resolution computed tomography (HRCT), the presence of ground glass opacities was found to be consistent with edema and/or inflammation, features viewed as 'less fibrotic' occurring in very stages of the disease. This was the rationale behind treating these patients with high-dose of anti-inflammatory drugs such as dexamethasone. However, as clinicians became confronted with the fact that many forms of ILD are recalcitrant to corticosteroid treatment, a new hypothesis of disease pathogenesis emerged, namely that fibrosis itself could arise and progress in the absence of inflammation.

A visual description of the pathways (shown as A and B) from normal lung tissue to fibrosis progression is shown Figure 1.1 below.

Figure 1.1 **Pathways from normal lung tissue to fibrosis** [taken and adapted from Gauldie J. et al. 2002]



Adapted from Gauldie J et al., Resp Res. 2001 Epub Sep26

Some types of ILD are characterized by marked inflammation (e.g. bronchiolitis obliterans organising pneumonia (BOOP), or bacterial pneumonia) with presence of stimulated matrix synthesis, however, after treatment a return to normal lung tissue is observed. In this type of disease, lung matrix remodelling does not occur and lung function is restored to baseline levels (as exhibited at the left-hand side of figure 1.1). However, some forms of ILD are characterized by repeated injury (e.g. hypersensitivity pneumonitis) or continuous low-level-inflammation (e.g. chronic forms of bird-fancier's disease), which can lead to scarring and progressive fibrosis with serious functional impairment (as exhibited by pathway A in Figure 1.1) [Gauldie J et al. 2002]. Treatment with corticosteroids can improve pulmonary function, but a return to normal lung function is not observed. And still other forms of ILD exhibit an abnormal, out-of-control repair process with progression to fibrosis. This progression to fibrosis is believed to be the underlying mechanism present in the idiopathic

interstitial pneumonias (IIPs) and is characterized by the absence of inflammation (as exhibited by pathway B in Figure 1.1) (e.g. IPF, acute interstitial pneumonia (AIP), cryptogenic organising pneumonia (COP)) [Gauldie J et al. 2002]. Drugs with strong anti-inflammatory properties (e.g. dexamethasone) have minimal to no influence on progressive functional impairment which eventually leads to respiratory failure. In spite of their clinical distinctions (IPF, AIP, COP, etc.), these disorders are characteristic of matrix remodelling and share a common paradigm of disease progression: Provisional matrices formed in the context of injury emitting signals to activate inflammatory response and epithelial cells, provoking ingrowth and/or expansion of connective tissue that lead to permanent matrix reordering [Chapman HA 2004, Kolb J & Gauldie J 2011].

With this addition to the paradigm of fibrosis pathogenesis – the possibility of progressive fibrosis in the absence of chronic inflammation – a new histological classification was proposed by Katzenstein et al. (see Figure 1.2), comprised of four distinct major forms of idiopathic interstitial pneumonia having well-defined histological patterns [Katzenstein AA & Myers JL 1998]. The failure to recognize these different patterns has often given rise to clinical diversity observed in patients with these conditions [Katzenstein AA & Myers JL 1998]. This classification scheme put forth the patterns usual interstitial pneumonia (UIP) and desquamative interstitial pneumonia (DIP) from Liebow's original classification and included two 'new' entities, namely acute interstitial pneumonia (AIP) [Katzenstein AA et al. 1986] and non-specific interstitial pneumonia (NSIP) [Katzenstein AA & Fiorelli RF 1994].

Figure 1.2 Evolution of histological classification of ILD

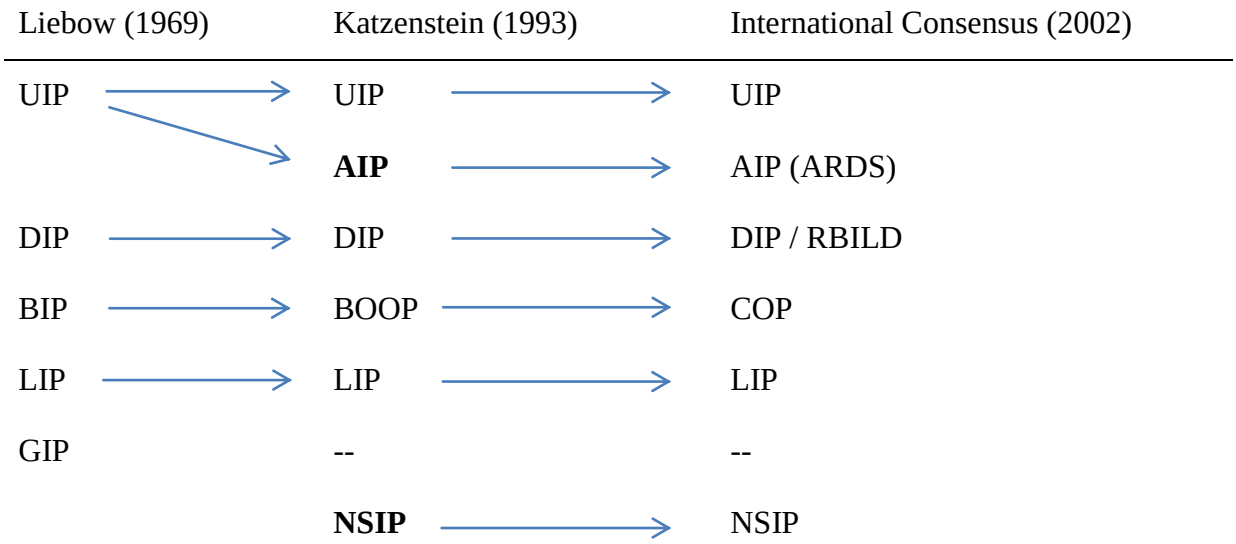
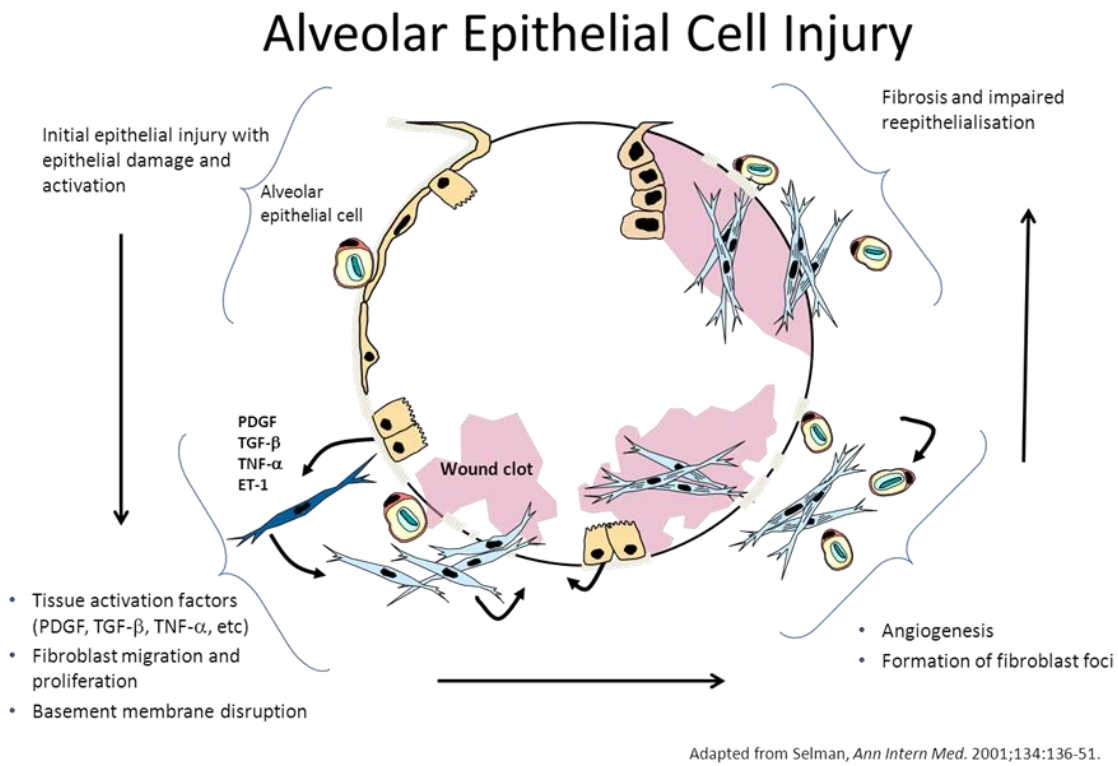


Figure 1.2: comparison with the older (or Liebow's) and newer (or Katzenstein's) classification of idiopathic interstitial pneumonia. UIP: usual interstitial pneumonia, NSIP: non-specific interstitial pneumonia, DIP: desquamative interstitial pneumonia, RBILD: respiratory bronchiolitis interstitial pneumonia, AIP: acute interstitial pneumonia, BIP: bronchiolitis obliterans interstitial pneumonia, BOOP: bronchiolitis obliterans organising pneumonia, COP: cryptogenic organising pneumonia, LIP: lymphoid interstitial pneumonia, GIP: giant cell interstitial pneumonia, HP: interstitial pneumonia, IPF: idiopathic pulmonary fibrosis, HBV: Hepstein barr virus

The next dilemma awaiting to be solved was whether or not the pathological characteristics of these different histological patterns could explain a pathway that leads to lung fibrosis. The diagnostic clue to UIP is the presence of a patchy, non-uniform, and variable distribution of interstitial changes, the appearance of which can be readily appreciated at low magnification [Katzenstein AA & Myers JL 1998]. Histological variation from one low-magnification field to another is characteristic, with alternating zones of interstitial fibrosis, inflammation, honeycombing, and normal lung tissue. Honeycombing is a manifestation of scarring and architectural restructuring that follows lung injury of a variety of causes, and is not specific to UIP. Another facet of the histological variability of UIP is appreciated when the nature of the fibrosis is

examined. Although most of the fibrotic zones are composed of “old”, relatively acellular collagen bundles, small aggregates of actively proliferating myofibroblasts and fibroblasts are consistently identifiable [Katzenstein AA & Myers JL 1998]. These aggregates, termed “fibroblast foci”, are characterized by spindle-shaped cells (see Figure 1.3) which are usually arranged with their long axes parallel to the long axes of the alveolar septa. [Selman et al. 2001] Fibroblast foci are widely scattered and can be found in inflamed, fibrotic, and honeycombed areas. Although fibroblast foci are not pathognomonic of UIP, they are necessary for the diagnosis [Katzenstein AA & Myers JL 1998, Du Bois R & King TE 2007]. They indicate that the fibrotic process is active rather than representing the residue of a process that once occurred, but is now inactive. The presence of fibroblast foci in some places, and of scarring with collagen deposition or honeycomb changes in others, exhibits temporal heterogeneity, a feature that is central to diagnosing UIP and distinguishing it from other IIPs [Katzenstein AA & Myers JL 1998].

Figure 1.3 **Depiction of alveolar epithelial cell injury** [taken and adapted from Selman et al. 2001]

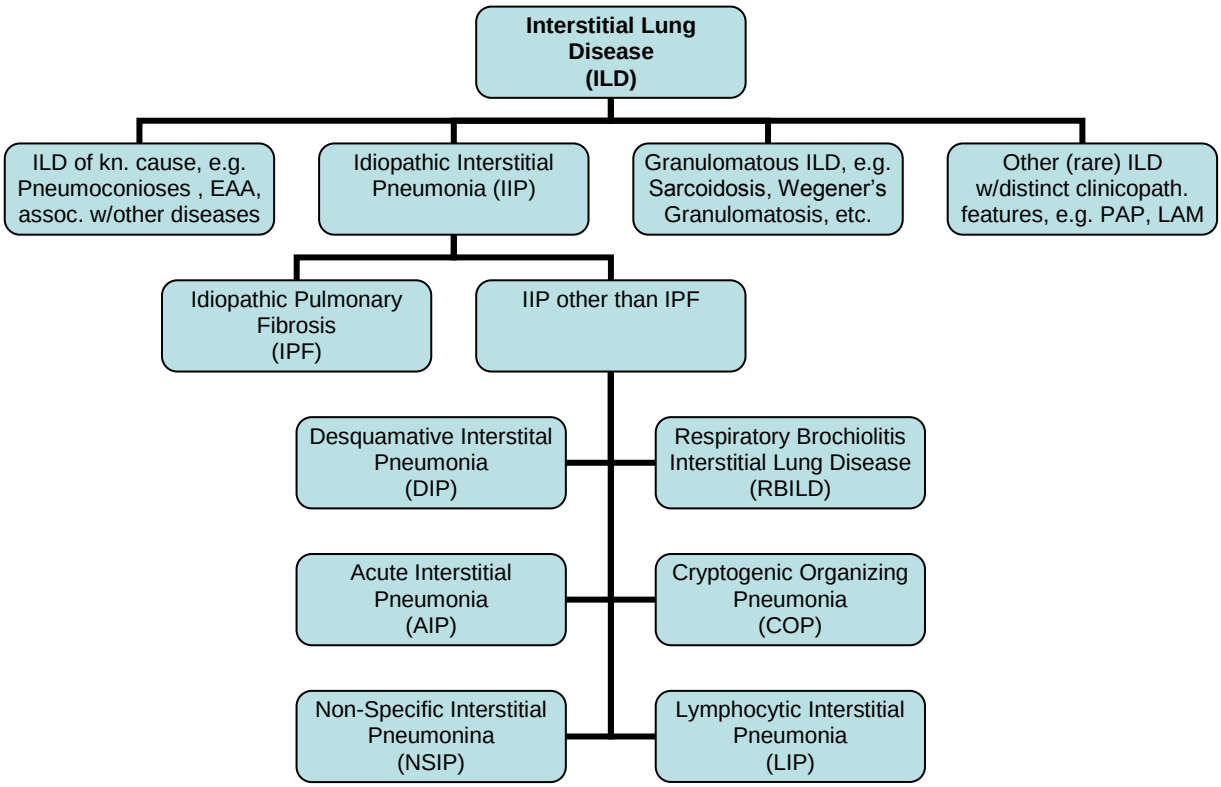


NSIP is characterised by the presence of varying degrees of inflammation and fibrosis within alveolar walls, but it lacks more specific changes that would indicate a diagnosis of UIP, DIP, or AIP. As further explained by Katzenstein & Fiorelli, NSIP comprises "…a fairly sizable group of idiopathic interstitial pneumonias (that) cannot be pigeon-holed into one of the three main groups, and we have termed these lesions nonspecific interstitial pneumonia or fibrosis." [Katzenstein AA & Fiorelli RF 1994]. The new hypothesis relating to the absence of inflammation in the progression of lung fibrosis and this new pathologic classification have been well-received by specialists because the histopathology of different types of lung fibrosis is clearly

defined and provides a basis for research on antifibrotic therapeutics, instead of anti-inflammatory agents [Du Bois R & King TE 2007].

With the general acceptance of these distinct histological patterns together with the changing nature of the pathophysiologic model during the final three decades of the last millennium, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) put forth in the years 2000-2002 joint consensus statements that defined classification, diagnosis, and management of ILD [ATS/ERS 2002, ATS 2000]. These guidelines classify the ILDs based on clinical, radiologic, and pathologic findings into four main categories: (1) ILD of known cause (e.g. environmental exposure, drug exposure, association with a connective tissue disease (CTD), etc.), (2) granulomatous ILD (i.e. sarcoidosis, Wegener's Granulomatosis), (3) extremely rare ILD with well-defined clinico-pathologic features (e.g. pulmonary alveolar proteinosis (PAP), eosinophilic pneumonia, lymphangioleiomyomatosis (LAM), etc.), and (4) idiopathic interstitial pneumonia (IIP) (see Figure 1.4). The latter is further subdivided into seven distinct clinico-pathologic disease entities, the causes of which are unknown by definition. In the order of relative frequency, they are: idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonitis (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonitis (AIP), respiratory bronchiolitis-interstitial disease (RBILD), desquamative interstitial pneumonia (DIP), and lymphoid interstitial pneumonia (LIP) (Figure 1.4).

Figure 1.4 **Classification of ILD, taken and adapted from ATS/ERS consensus statements** [taken and adapted from ATS/ERS 2002]



2 Aims of this dissertation

Large-scale epidemiological investigations of the full spectrum of ILD are few and far between. In fact, until very recently, the only true population-based study, conducted over 20 years ago, encompassed a relatively small US population of approximately half a million inhabitants, and was restricted to a two-year study period [Coultas DB et al. 1994]. Over the last decade, however, there have been some population-based investigations, mainly in the form of questionnaires to chest specialists, specialty clinic registries or database studies exploring only the most commonly-occurring ILD entities such as IPF.

Updated, epidemiological data describing ILD disease frequency, natural history, and survivorship are essential for public health planning, such as the prediction of health care resource use and the justification for health education programs. Furthermore, current data would greatly enhance our understanding of presumed risk factors for ILD, disease classification, and the natural history and treatment of ILD. Most importantly, the careful evaluation of descriptive epidemiologic findings would better define the breadth and burden of ILD in the general population, may yield important clues about the etiology of the idiopathic subgroups, and would hopefully guide researchers and health care practitioners in their approaches to developing treatments and caring for ILD patients.

Therefore, it is the aim of this dissertation to report the following epidemiological investigations of ILD using data from the general population: (1) To describe the demographic and clinical characteristics of patients with a first-time diagnosis of ILD, and to compare these characteristics to a cohort of non-ILD control subjects; (2) To calculate incidence and prevalence of ILD subgroups (to the extent possible) using the currently-accepted classification paradigm; (3) To determine absolute and relative rates of all-cause mortality in different ILD subgroups; (4) To determine the relative risk of certain comorbidities after a first-time diagnosis of ILD; (5) To explore in more depth certain epidemiological topics pertaining to the subgroup of ILD classified as being of known cause or associated with other conditions. These topics are are handled as manuscripts (either in press or submitted and under review by various biomendical journals) in Section 8 of this dissertation.

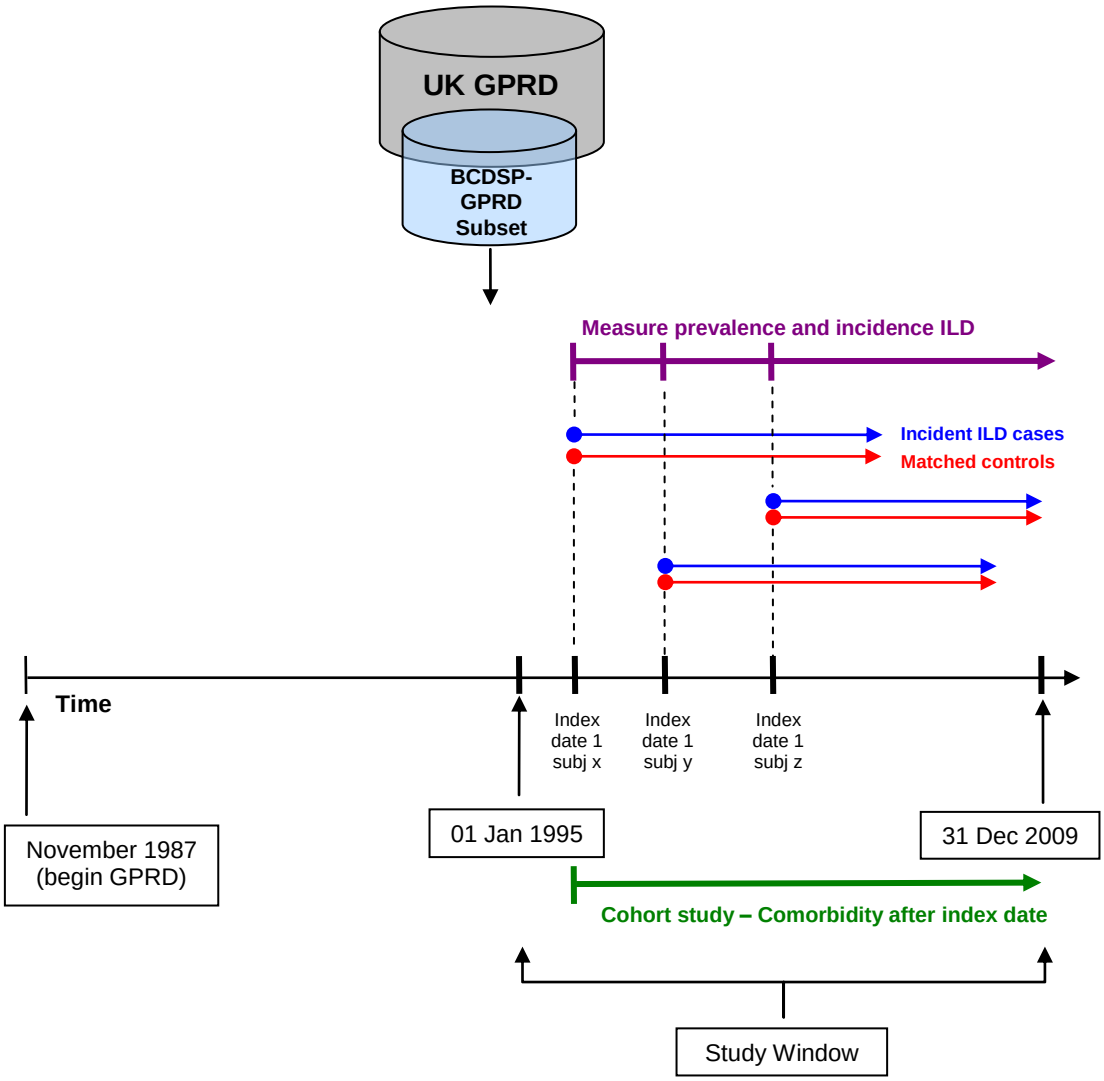
3 Methods

3.1 Data source

This U.K. General Practice Research Database (GPRD) is a large and well-validated database that was established in June 1987. It is the largest of its kind, and has been used for numerous disease epidemiology and drug safety studies [Wood L & Martinez C 2004, Jick H 1997, Garcia-Rodriguez L & Perez Gutthann 1998]. About 450 general practices throughout the UK participate in the GPRD, which contains some 5 million active patients, and a total of approximately 13 million patients who are representative of the overall UK population with regard to age, sex, geographic distribution and annual turnover rate. All patient information stored in the database is strictly anonymous. The general practitioners (GPs) participating in the GPRD have been trained to record relevant medical information in a standardized and coded manner using office computers. Medical diagnoses are coded in the form of 'Read' codes. In addition, information on patient demographics, some laboratory data, and virtually all drug prescriptions are also recorded by the GPs. Prescriptions are generated directly on the computer, containing not only the name of the drug prescribed, but also the route of administration, dosage, and number of doses dispensed on each prescription, which are recorded as so-called 'Multilex' codes. Hospital discharge and referral letters, as well as death certificates, can be reviewed as a means of validating diagnoses recorded in the computer record. In addition, it is also possible to contact GPs and patients indirectly through the GPRD-group at MHRA to pose follow-up questions or submit questionnaires [Wood L & Martinez C 2004, Jick H 1997, Garcia-Rodriguez L & Perez Gutthann 1998]. The recorded

information on drug exposure and on outpatient diagnoses in the GPRD has been validated in numerous publications and proven to be of high quality [Jick H et al. 1991, Jick H et al. 1992, Jick SS et al. 2003]. The data for the present study was extracted from the large subset of GPRD data currently being used by the Boston Collaborative Drug Surveillance Program (BCDSP) and its associates (i.e. including the Basel Pharmacoepidemiology Unit directed by Prof. Christoph Meier).

Figure 3.1 Study design



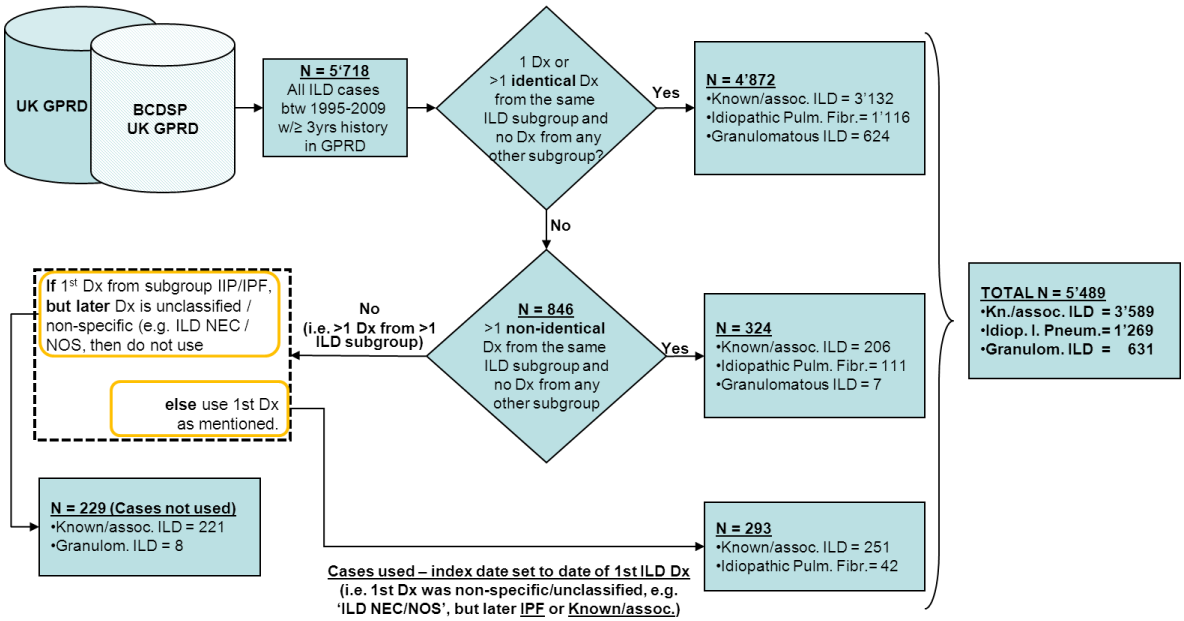
3.2 Timeframes and approval

The analyses took place between January 2010 and December 2011 and included GPRD data between January 1995 and the end of 2009. This dissertation is based on two protocols (Protocol Nos. 10-021-R and 10-145) submitted to and approved by the Independent Scientific Advisory Committee (ISAC) of the U.K. Medicines and Healthcare products Regulatory Agency (MHRA).

3.3 Study population

The study population consisted of all patients with 3 or more years of recorded history in the GPRD who had a first-time diagnosis of an ILD (see diagnosis codes in Appendix 1) between January 1995 and the end of 2009. The date of first-time diagnosis of an ILD is subsequently referred to as 'index date.' A comparison/control group of ILD-free subjects was matched 1:1 to the ILD cohort on age (i.e. year of birth), gender, general practice, calendar time (i.e. index date assignment as per matched case), and number of years of recorded history in the database. The inclusion criterion of a minimum of 3 years of medical history was applied in order to increase the likelihood of including incident (rather than prevalent) ILD subjects in the study. Each ILD case and matched control was categorized by ILD subgroup (as per the ATS/ERS classification scheme Figure 1 above: ILD of known cause or associated w/other diseases, idiopathic interstitial pneumonia, granulomatous ILD, or other forms of ILD) based on diagnosis codes as well as an algorithm developed to handle cases having more than one ILD diagnosis code (see Figure 3.2 below).

Figure 3.2 ILD case-selection algorithm and resulting sample sizes



BCDSP = Boston Collaborative Drug Surveillance Program
Dx = diagnosis, NEC = not elsewhere classified, NOS = not otherwise specified

3.4 Prevalence of ILD

The prevalence of ILD was estimated for three 5-year periods (1995-1999, 2000-2004, and 2005-2009). Prevalent cases in each period included existing cases (i.e. those diagnosed with ILD in a previous period and still alive and present in the database during the applicable period) and newly diagnosed ILD cases during the applicable period. The denominator was defined as the number of patients in the GPRD with any activity during the applicable period. Estimates for period prevalence were stratified by age group (in 10-yr bands) and gender, and a 95% confidence interval for each estimate was calculated.

3.5 Incidence of ILD

The incidence rate of ILD was calculated for three 5-year periods (1995-1999, 2000-2004, and 2005-2009). Incident cases were defined as newly diagnosed ILD patients during the applicable period. The denominator for each period was defined as the total person time (in years) of all GPRD subjects who had at least 3 years of recorded medical history. Rates of incidence density were stratified by age group (10-yr age bands) and gender, and a 95% confidence interval was calculated for each rate.

3.6 All-cause mortality

All-cause mortality rates were calculated for three 5-year periods (1995-1999, 2000-2004, and 2005-2009) for the ILD cohorts. The numerators for these rates were the number of deaths in a given period divided by the total number of patients in the GPRD with any activity during the applicable period. Rates of all-cause mortality were stratified by age group (10-yr age bands) and gender, and 95% confidence intervals were calculated for all rates.

3.7 Characteristics of ILD cases and controls

The ILD and non-ILD cohorts are described statistically in terms of various characteristics at or prior to the index date. Variables include body mass index, smoking status, smoking amount, alcohol consumption status, quantity of alcohol consumption, no. of general practice visits, no. and type of drug prescriptions, and for a small proportion of subjects, level of blood glucose prior to index date. Odds ratios and 95% confidence intervals were determined using conditional logistic regression.

3.8 Comorbidity after index date

As per protocol, a variety of disease diagnoses were investigated post index date. For certain commonly occurring diagnoses, patients were not excluded from the analysis on the basis of having had such a diagnosis prior to index date. These diagnoses included pneumonia, respiratory (non-pneumonia) infections, pneumothorax, and bone fracture. For the cardiovascular disease diagnoses, in which greater interest was placed on whether or not they were truly incident after index date, patients having already had such a diagnosis in their medical history were excluded from the analysis. These outcomes included pulmonary embolism, deep vein thrombosis, myocardial infarction, congestive heart failure, ischemic heart disease, cerebrovascular events, and pulmonary hypertension. Survival time was calculated as the number of days from index date until either first diagnosis of an event (i.e. outcome of interest as aforementioned), recorded medical history terminates, death, or study period ends. In order to account for the matched design in the analysis, crude and adjusted hazard ratios (i.e. rate ratios) for the comparison of event rates in the ILD vs. non-ILD cohorts were determined using stratified Cox proportional hazards regression.

4 Results

4.1 Prevalence of ILD

4.1.1 Idiopathic Interstitial Pneumonia (IIP)

4.1.1.1 Idiopathic Pulmonary Fibrosis (IPF)

The estimated prevalence of IPF more than doubled from the period 1995-1999 (7.2 per 100'000 inhabitants) to the period 2000-2004 (15.2 per 100'000). No further increase was noted during the period 2005-2009. In all time periods, the overall gender-specific prevalence of IPF was approximately twice as high for males versus females. The highest overall age-specific estimates were observed in those 80-89 years of age for the periods 2000-2004 and 2005-2009 (64.4 and 66.7 per 100'000 inhabitants, respectively). Table 4.1.1.1 below shows overall and age-/gender-specific 5-year period prevalence estimates with 95% confidence limits.

Table 4.1.1.1 IPF: 5-yr prevalence estimates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
30 - 39	**Male**	**1.6**	0.2	3.1	**4.0**	2.0	5.9	**3.5**	1.8	5.2
	Female	**0.3**	0.0	0.9	**2.4**	0.9	4.0	**2.9**	1.3	4.4
	Overall	**1.0**	0.2	1.7	**3.2**	2.0	4.4	**3.2**	2.0	4.3
40 - 49	**Male**	**4.5**	2.2	6.8	**10.3**	7.1	13.6	**7.5**	4.9	10.2
	Female	**0.3**	0.0	0.8	**4.0**	2.0	5.9	**6.2**	3.9	8.6
	Overall	**2.2**	1.1	3.3	**7.0**	5.2	8.9	**6.9**	5.1	8.6
50 - 59	**Male**	**16.3**	12.2	20.5	**30.9**	25.7	36.1	**41.4**	35.2	47.6
	Female	**6.4**	4.1	8.7	**19.0**	15.2	22.8	**23.4**	19.0	27.8
	Overall	**10.8**	8.6	13.1	**24.5**	21.4	27.7	**31.9**	28.2	35.7
60 - 69	**Male**	**41.6**	35.1	48.2	**82.0**	74.0	90.0	**82.3**	74.5	90.2
	Female	**17.0**	13.2	20.8	**32.6**	27.9	37.2	**38.9**	33.8	44.0
	Overall	**28.1**	24.5	31.7	**55.5**	51.1	60.0	**59.4**	54.8	64.0
70 - 79	**Male**	**57.2**	49.3	65.0	**97.2**	88.5	105.9	**81.5**	74.1	88.8
	Female	**24.5**	19.7	29.2	**54.8**	48.7	61.0	**46.9**	41.5	52.3
	Overall	**39.5**	35.0	43.9	**74.8**	69.6	80.1	**63.5**	59.0	68.0

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
80 - 89	**Male**	**18.8**	14.4	23.2	**48.1**	41.7	54.5	**45.9**	40.2	51.5
	Female	**16.8**	12.9	20.6	**34.4**	29.3	39.5	**27.4**	23.2	31.7
	Overall	**17.7**	14.8	20.6	**40.9**	36.8	45.0	**36.4**	32.9	39.9
90+	**Male**	**1.9**	0.5	3.2	**1.7**	0.5	2.9	**1.6**	0.5	2.7
	Female	**2.1**	0.7	3.5	**4.7**	2.8	6.6	**3.8**	2.1	5.5
	Overall	**2.0**	1.0	3.0	**3.3**	2.1	4.4	**2.7**	1.7	3.8
OVERALL	**MALE**	**9.9**	9.1	10.8	**19.8**	18.8	20.9	**19.0**	18.0	20.0
	FEMALE	**4.9**	4.3	5.4	**11.0**	10.3	11.8	**10.8**	10.1	11.5
	----------	**7.2**	6.7	7.7	**15.2**	14.5	15.8	**14.7**	14.1	15.4

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All prevalence estimates and 95% CLs are per 100'000 inhabitants.

4.1.2 Granulomatous ILD

4.1.2.1 Sarcoidosis

The estimated 5-year period prevalence of sarcoidosis increased more than 5-fold from the period 1995-1999 (1.4 per 100'000 inhabitants) to the period 2005-2009 (7.5 per 100'000 inhabitants). No prevalent cases of sarcoidosis were found in those younger than 20 years of age. The highest overall age-specific estimates were found in those 50-59 years of age during the periods 2000-2004 and 2005-2009, 18.3 per 100'000 during, and 37.5 per 100'000, respectively). In all age categories below 60 years, the estimated prevalence of sarcoidosis was higher in males than in females. Thereafter, the prevalence is generally higher in females than in males. Table 4.1.2.1 below shows overall and age-/gender-specific 5-year period prevalence estimates with 95% confidence limits.

Table 4.1.2.1 Sarcoidosis: 5-yr prevalence estimates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
30 - 39	**Male**	**8.5**	5.2	11.7	**11.1**	7.9	14.4	**5.2**	3.1	7.3
	Female	**1.6**	0.2	3.0	**4.6**	2.6	6.7	**3.1**	1.5	4.7
	Overall	**5.0**	3.2	6.7	**7.9**	5.9	9.8	**4.2**	2.8	5.5
40 - 49	**Male**	**9.7**	6.3	13.0	**25.9**	20.7	31.1	**26.3**	21.3	31.2
	Female	**2.3**	0.8	3.8	**9.5**	6.5	12.5	**18.3**	14.2	22.3
	Overall	**5.7**	3.9	7.4	**17.3**	14.4	20.2	**22.2**	19.0	25.3
50 - 59	**Male**	**4.6**	2.4	6.8	**23.2**	18.7	27.7	**51.1**	44.2	58.0
	Female	**6.4**	4.1	8.7	**14.1**	10.9	17.4	**25.3**	20.8	29.9
	Overall	**5.6**	4.0	7.2	**18.3**	15.6	21.0	**37.5**	33.5	41.6
60 - 69	**Male**	**3.2**	1.4	5.0	**7.6**	5.2	10.1	**22.9**	18.8	27.0
	Female	**3.1**	1.5	4.7	**12.2**	9.3	15.0	**23.9**	19.9	27.9
	Overall	**3.2**	1.9	4.4	**10.1**	8.2	12.0	**23.4**	20.5	26.3
70 - 79	**Male**	**0.0**	0.0	0.0	**4.3**	2.4	6.1	**13.7**	10.7	16.8
	Female	**0.5**	0.0	1.1	**13.3**	10.2	16.3	**23.5**	19.7	27.3
	Overall	**0.3**	0.0	0.6	**9.0**	7.2	10.8	**18.8**	16.4	21.3
80 - 89	**Male**	**1.3**	0.2	2.5	**1.5**	0.4	2.7	**2.7**	1.3	4.1
	Female	**0.0**	0.0	0.0	**4.0**	2.2	5.8	**10.6**	7.9	13.2
	Overall	**0.6**	0.1	1.2	**2.8**	1.8	3.9	**6.7**	5.2	8.3
90+	**Male**	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**2.1**	0.9	3.3
	Overall	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**1.1**	0.4	1.7
OVERALL	**MALE**	**2.0**	1.6	2.3	**4.7**	4.2	5.2	**7.7**	7.1	8.3
	FEMALE	**1.0**	0.7	1.2	**4.0**	3.5	4.4	**7.2**	6.6	7.8
	----------	**1.4**	1.2	1.7	**4.3**	4.0	4.7	**7.5**	7.0	7.9

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All prevalence estimates and 95% CLs are per 100'000 inhabitants.

4.1.2.2 Wegener's Granulomatosis

The estimated 5-year period prevalence of Wegener's Granulomatosis increased more than 3-fold from the period 2000-2004 to 2005-2009 (from 1.7 to 5.8 per 100'000 inhabitants, respectively). Overall gender-specific estimates indicate that prevalence is roughly equal in males and females. For all three time periods the

highest overall age-specific prevalence estimates were found in those 60-89 years of age. Table 4.1.2.2 below shows overall and age-/gender-specific 5-year period prevalence estimates with 95% confidence intervals.

Table 4.1.2.2 WG: 5-yr prevalence estimates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
10 - 19	**Male**	**1.1**	0.0	2.1	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Female	**0.6**	0.0	1.3	**1.1**	0.1	2.1	**1.1**	0.1	2.0
	Overall	**0.8**	0.2	1.5	**0.5**	0.1	1.0	**0.5**	0.1	1.0
20 - 29	**Male**	**0.0**	0.0	0.0	**3.7**	2.0	5.5	**2.9**	1.4	4.4
	Female	**3.5**	1.5	5.6	**5.4**	3.2	7.5	**3.0**	1.5	4.5
	Overall	**1.8**	0.8	2.8	**4.5**	3.1	5.9	**3.0**	1.9	4.0
30 - 39	**Male**	**0.0**	0.0	0.0	**1.5**	0.3	2.7	**3.1**	1.5	4.7
	Female	**1.6**	0.2	3.0	**3.9**	2.0	5.8	**4.2**	2.3	6.1
	Overall	**0.8**	0.1	1.5	**2.7**	1.6	3.8	**3.6**	2.4	4.8
40 - 49	**Male**	**1.5**	0.2	2.8	**3.0**	1.2	4.8	**6.6**	4.1	9.0
	Female	**2.8**	1.2	4.5	**4.2**	2.2	6.2	**7.2**	4.6	9.7
	Overall	**2.2**	1.1	3.3	**3.6**	2.3	5.0	**6.9**	5.1	8.6
50 - 59	**Male**	**6.8**	4.1	9.5	**6.4**	4.0	8.7	**7.8**	5.1	10.4
	Female	**3.1**	1.5	4.7	**13.1**	10.0	16.3	**13.4**	10.1	16.8
	Overall	**4.7**	3.3	6.2	**10.0**	8.0	12.0	**10.8**	8.6	12.9
60 - 69	**Male**	**6.4**	3.9	9.0	**15.9**	12.4	19.4	**25.0**	20.7	29.4
	Female	**5.5**	3.4	7.7	**8.4**	6.0	10.7	**23.0**	19.1	26.9
	Overall	**5.9**	4.3	7.6	**11.8**	9.8	13.9	**24.0**	21.1	26.9
70 - 79	**Male**	**9.6**	6.4	12.9	**14.8**	11.4	18.3	**17.9**	14.5	21.4
	Female	**5.5**	3.3	7.8	**10.4**	7.7	13.0	**14.7**	11.7	17.7
	Overall	**7.4**	5.5	9.3	**12.5**	10.3	14.6	**16.3**	14.0	18.5
80 - 89	**Male**	**0.5**	0.0	1.3	**5.7**	3.5	7.9	**10.1**	7.5	12.8
	Female	**0.5**	0.0	1.1	**8.2**	5.7	10.7	**16.7**	13.4	20.0
	Overall	**0.5**	0.0	1.0	**7.0**	5.3	8.7	**13.5**	11.4	15.6
90+	**Male**	**0.0**	0.0	0.0	**0.4**	0.0	1.0	**3.6**	2.0	5.3
	Female	**0.0**	0.0	0.0	**0.4**	0.0	0.9	**4.9**	3.0	6.8
	Overall	**0.0**	0.0	0.0	**0.4**	0.0	0.8	**4.3**	3.0	5.6
OVERALL	**MALE**	**1.8**	1.4	2.2	**3.7**	3.2	4.2	**5.5**	4.9	6.0
	FEMALE	**1.6**	1.3	2.0	**3.8**	3.3	4.2	**6.1**	5.6	6.7
	---------	**1.7**	1.5	2.0	**3.7**	3.4	4.1	**5.8**	5.4	6.2

L=Lower, **U**=Upper, **CL**=Confidence Limit; * All prevalence estimates and 95% CLs are per 100'000 inhabitants.

4.1.3 ILD of known cause or associated with other diseases

4.1.3.1 Extrinsic Allergic Alveolitis (EAA)

The overall estimated 5-year period prevalence of EAA increased significantly from one measurement period to the next, with an almost three-fold increase from the period 1995-1999 to 2004-2009 (3.3 to 9.4 per 100'000 inhabitants). Overall gender-specific estimates were similar in males and females in all time periods. No prevalent cases were found in those under 10 years of age. Age-specific estimates generally increased in those 50 years and older from one time period to the next. Table 4.1.3.1 below shows overall and age-/gender-specific 5-year period prevalence estimates with 95% confidence intervals.

Table 4.1.3.1 EAA: 5-yr prevalence estimates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
20 - 29	**Male**	**0.3**	0.0	0.9	**2.2**	0.8	3.5	**3.9**	2.2	5.6
	Female	**0.9**	0.0	1.9	**1.8**	0.6	3.0	**1.6**	0.5	2.7
	Overall	**0.6**	0.0	1.2	**2.0**	1.1	2.9	**2.8**	1.7	3.8
30 - 39	**Male**	**9.1**	5.7	12.5	**4.0**	2.0	5.9	**2.8**	1.3	4.4
	Female	**5.0**	2.6	7.5	**3.9**	2.0	5.8	**2.4**	1.0	3.8
	Overall	**7.0**	5.0	9.1	**3.9**	2.6	5.3	**2.6**	1.6	3.7
40 - 49	**Male**	**13.6**	9.6	17.6	**27.2**	21.9	32.6	**14.4**	10.7	18.0
	Female	**8.2**	5.4	11.0	**10.0**	6.9	13.1	**9.5**	6.6	12.4
	Overall	**10.7**	8.3	13.1	**18.2**	15.2	21.2	**11.9**	9.5	14.2
50 - 59	**Male**	**13.3**	9.6	17.1	**20.0**	15.8	24.2	**26.4**	21.5	31.4
	Female	**7.9**	5.3	10.5	**21.6**	17.5	25.6	**18.6**	14.7	22.6
	Overall	**10.4**	8.2	12.6	**20.9**	17.9	23.8	**22.3**	19.2	25.4
60 - 69	**Male**	**11.0**	7.6	14.4	**23.3**	19.1	27.6	**28.7**	24.1	33.4
	Female	**8.2**	5.5	10.8	**28.6**	24.2	32.9	**39.2**	34.1	44.3
	Overall	**9.5**	7.4	11.6	**26.1**	23.1	29.2	**34.3**	30.8	37.7
70 - 79	**Male**	**7.1**	4.3	9.8	**26.4**	21.9	31.0	**34.1**	29.3	38.9
	Female	**5.8**	3.5	8.1	**22.7**	18.7	26.7	**37.0**	32.2	41.8
	Overall	**6.4**	4.6	8.1	**24.5**	21.5	27.5	**35.6**	32.2	39.0

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
80 - 89	**Male**	**1.3**	0.2	2.5	**7.7**	5.2	10.3	**22.4**	18.4	26.3
	Female	**4.4**	2.4	6.4	**11.0**	8.1	13.9	**15.8**	12.6	19.1
	Overall	**3.0**	1.8	4.2	**9.4**	7.5	11.4	**19.0**	16.5	21.5
90+	**Male**	**1.1**	0.0	2.1	**0.0**	0.0	0.0	**4.2**	2.4	6.0
	Female	**0.0**	0.0	0.0	**1.2**	0.2	2.1	**5.1**	3.2	7.1
	Overall	**0.5**	0.0	1.0	**0.6**	0.1	1.1	**4.7**	3.4	6.0
OVERALL	**MALE**	**3.8**	3.3	4.4	**7.7**	7.0	8.3	**9.6**	8.9	10.3
	FEMALE	**2.8**	2.3	3.2	**7.2**	6.6	7.8	**9.2**	8.6	9.9
	----------	**3.3**	2.9	3.6	**7.4**	7.0	7.9	**9.4**	8.9	9.9

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All prevalence estimates and 95% CLs are per 100'000 inhabitants.

4.1.3.2 Pneumoconioses

The overall estimated 5-year period prevalence of the pneumoconioses increased significantly from one time period to the next, with an approximate six-fold increase observed from the period 1995-1999 to 2004-2009 (8.2 to 48.2 per 100'000 inhabitants). With respect to overall gender-specific estimates, prevalence in males was approximately 10-15 times higher in males than in females in each period. Overall age-specific estimates were highest in those aged 70-79 during the periods 2000-2004 and 2005-2009 (115.1 and 219.2 per 100'000 inhabitants, respectively). Table 4.1.3.2 below shows overall and age-/gender-specific 5-year period prevalence estimates with 95% confidence intervals.

Table 4.1.3.2 Pneumoconioses: 5-yr prevalence estimates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
10 - 19	**Male**	**0.3**	0.0	0.8	**2.3**	0.9	3.7	**2.5**	1.1	3.9
	Female	**0.3**	0.0	0.8	**1.7**	0.5	3.0	**1.1**	0.1	2.0
	Overall	**0.3**	0.0	0.7	**2.0**	1.1	3.0	**1.8**	1.0	2.7
20 - 29	**Male**	**3.5**	1.5	5.4	**6.8**	4.4	9.2	**4.1**	2.3	5.8
	Female	**0.0**	0.0	0.0	**2.0**	0.7	3.3	**3.6**	1.9	5.3
	Overall	**1.8**	0.8	2.8	**4.4**	3.1	5.8	**3.9**	2.6	5.1
30 - 39	**Male**	**2.0**	0.4	3.5	**9.1**	6.2	12.1	**18.5**	14.6	22.5
	Female	**3.8**	1.6	5.9	**3.7**	1.8	5.5	**5.1**	3.0	7.1
	Overall	**2.9**	1.6	4.2	**6.4**	4.7	8.1	**11.8**	9.6	14.0
40 - 49	**Male**	**9.7**	6.3	13.0	**18.0**	13.6	22.3	**14.4**	10.7	18.0
	Female	**0.8**	0.0	1.6	**4.5**	2.4	6.6	**13.9**	10.4	17.4
	Overall	**4.9**	3.2	6.5	**10.9**	8.6	13.3	**14.1**	11.6	16.6
50 - 59	**Male**	**33.8**	27.8	39.7	**70.0**	62.2	77.8	**41.2**	35.0	47.4
	Female	**1.5**	0.4	2.7	**5.7**	3.6	7.8	**11.7**	8.6	14.8
	Overall	**16.0**	13.2	18.7	**35.5**	31.7	39.3	**25.6**	22.3	29.0
60 - 69	**Male**	**88.6**	79.0	98.1	**193.3**	181.1	205.6	**176.1**	164.6	187.5
	Female	**2.2**	0.8	3.6	**10.6**	8.0	13.3	**22.0**	18.1	25.8
	Overall	**41.2**	36.8	45.6	**95.4**	89.6	101.3	**94.9**	89.1	100.6
70 - 79	**Male**	**81.8**	72.3	91.2	**227.2**	213.9	240.5	**424.5**	407.7	441.3
	Female	**3.1**	1.4	4.8	**15.1**	11.8	18.3	**30.4**	26.1	34.7
	Overall	**39.2**	34.8	43.7	**115.1**	108.6	121.6	**219.2**	210.9	227.6
80 - 89	**Male**	**17.5**	13.2	21.7	**154.1**	142.7	165.6	**387.1**	370.7	403.4
	Female	**3.3**	1.6	5.0	**8.6**	6.0	11.2	**26.7**	22.6	30.9
	Overall	**9.8**	7.7	12.0	**77.8**	72.2	83.4	**201.7**	193.4	209.9
90+	**Male**	**0.5**	0.0	1.3	**20.1**	16.0	24.2	**137.9**	127.6	148.2
	Female	**0.0**	0.0	0.0	**3.9**	2.2	5.6	**17.1**	13.6	20.6
	Overall	**0.2**	0.0	0.6	**11.6**	9.5	13.8	**75.7**	70.4	81.0
OVERALL	**MALE**	**16.6**	15.5	17.7	**50.7**	49.0	52.4	**90.5**	88.3	92.7
	FEMALE	**1.0**	0.8	1.3	**3.9**	3.5	4.4	**9.2**	8.6	9.9
	----------	**8.2**	7.7	8.8	**26.0**	25.2	26.9	**48.2**	47.1	49.3

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All prevalence estimates and 95% CLs are per 100'000 inhabitants.

4.1.3.3 Drug-/radiation induced ILD (DRAD-ILD)

The overall estimated 5-year period prevalence of drug/radiation-induced ILD increased significantly from one time period to the next, with an approximate five-fold increase observed from the period 1995-1999 to 2004-2009 (0.4 to 2.1 per 100'000 inhabitants respectively). With respect to overall gender-specific estimates, prevalence was higher in females than in males in all time period. No prevalent cases were found in those under the age of 20 years, and the highest overall age-specific estimates were observed in those aged 70-79. Table 4.1.2.2 below shows overall and age-/gender-specific 5-year period prevalence estimates with 95% confidence intervals.

Table 4.1.3.3 DRAD-ILD: 5-yr. prevalence estimates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
30 - 39	**Male**	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.7**	0.0	1.4
	Female	**1.6**	0.2	3.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Overall	**0.8**	0.1	1.5	**0.0**	0.0	0.0	**0.3**	0.0	0.7
40 - 49	**Male**	**0.3**	0.0	0.9	**0.8**	0.0	1.7	**0.0**	0.0	0.0
	Female	**0.8**	0.0	1.6	**2.5**	0.9	4.0	**2.1**	0.7	3.4
	Overall	**0.6**	0.0	1.1	**1.7**	0.8	2.6	**1.1**	0.4	1.8
50 - 59	**Male**	**0.3**	0.0	0.8	**1.1**	0.1	2.1	**2.9**	1.3	4.6
	Female	**1.3**	0.3	2.4	**2.9**	1.5	4.4	**3.2**	1.6	4.9
	Overall	**0.9**	0.2	1.5	**2.1**	1.2	3.0	**3.1**	1.9	4.3
60 - 69	**Male**	**1.3**	0.2	2.5	**3.6**	1.9	5.3	**3.1**	1.6	4.6
	Female	**1.8**	0.5	3.0	**4.0**	2.4	5.6	**4.9**	3.1	6.7
	Overall	**1.6**	0.7	2.4	**3.8**	2.7	5.0	**4.0**	2.8	5.2
70 - 79	**Male**	**0.6**	0.0	1.4	**5.9**	3.8	8.0	**6.4**	4.4	8.5
	Female	**3.1**	1.4	4.8	**5.8**	3.8	7.8	**11.4**	8.7	14.0
	Overall	**1.9**	1.0	2.9	**5.9**	4.4	7.3	**9.0**	7.3	10.7
80 - 89	**Male**	**1.1**	0.0	2.1	**3.5**	1.8	5.3	**6.0**	3.9	8.0
	Female	**0.0**	0.0	0.0	**4.6**	2.7	6.5	**10.0**	7.5	12.6
	Overall	**0.5**	0.0	1.0	**4.1**	2.8	5.4	**8.1**	6.4	9.7

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
90+	**Male**	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**2.4**	1.1	3.8
	Female	**0.0**	0.0	0.0	**0.2**	0.0	0.6	**3.0**	1.6	4.5
	Overall	**0.0**	0.0	0.0	**0.1**	0.0	0.3	**2.7**	1.7	3.8
OVERALL	**MALE**	**0.3**	0.1	0.4	**1.1**	0.9	1.4	**1.6**	1.3	1.9
	FEMALE	**0.6**	0.4	0.8	**1.4**	1.1	1.7	**2.5**	2.2	2.9
	----------	**0.4**	0.3	0.5	**1.3**	1.1	1.5	**2.1**	1.8	2.3

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All prevalence estimates and 95% CLs are per 100'000 inhabitants.

4.1.3.4 ILD associated with other diseases (ILD-ODIS)

The overall and gender-specific overall estimated 5-year period prevalence of ILD associated with other diseases remained relatively stable over time. No prevalent cases were found in those younger than 10 years of age, and the highest age-specific estimates were observed in those 70-79 years of age. Except for those aged 80 and over, a general decrease in 5-year period prevalence was observed from 2000-2004 to 2005-2009. Table 4.1.3.4 below shows overall and age-/gender-specific 5-year period prevalence estimates with 95% confidence intervals.

Table 4.1.3.4 ILD-ODIS: 5-yr prevalence estimates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
20 - 29	**Male**	**1.4**	0.2	2.7	**0.0**	0.0	0.0	**1.0**	0.1	1.8
	Female	**1.2**	0.0	2.3	**1.6**	0.4	2.7	**0.0**	0.0	0.0
	Overall	**1.3**	0.5	2.2	**0.8**	0.2	1.3	**0.5**	0.1	0.9
30 - 39	**Male**	**1.3**	0.0	2.6	**1.7**	0.4	3.0	**0.0**	0.0	0.0
	Female	**2.2**	0.6	3.8	**2.4**	0.9	4.0	**1.1**	0.1	2.1
	Overall	**1.8**	0.7	2.8	**2.1**	1.1	3.1	**0.5**	0.1	1.0
40 - 49	**Male**	**2.7**	0.9	4.5	**2.2**	0.7	3.7	**1.5**	0.3	2.6
	Female	**6.4**	3.9	8.9	**14.2**	10.5	17.9	**8.1**	5.4	10.8
	Overall	**4.7**	3.1	6.3	**8.5**	6.4	10.5	**4.9**	3.4	6.3
50 - 59	**Male**	**13.9**	10.1	17.7	**7.7**	5.1	10.3	**3.9**	2.0	5.8
	Female	**16.7**	13.0	20.5	**16.9**	13.3	20.4	**13.4**	10.1	16.8
	Overall	**15.5**	12.8	18.2	**12.6**	10.4	14.9	**8.9**	6.9	10.9

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
60 - 69	**Male**	**35.2**	29.1	41.2	**28.3**	23.7	33.0	**16.9**	13.3	20.4
	Female	**22.1**	17.8	26.4	**30.5**	26.0	35.0	**23.9**	19.9	27.9
	Overall	**28.0**	24.4	31.6	**29.5**	26.2	32.7	**20.6**	17.9	23.3
70 - 79	**Male**	**45.6**	38.5	52.6	**47.6**	41.5	53.7	**30.1**	25.6	34.6
	Female	**30.3**	25.0	35.5	**29.2**	24.7	33.8	**24.5**	20.6	28.4
	Overall	**37.3**	33.0	41.6	**37.9**	34.2	41.6	**27.2**	24.2	30.1
80 - 89	**Male**	**11.8**	8.3	15.3	**17.4**	13.6	21.3	**25.8**	21.6	30.0
	Female	**14.0**	10.4	17.5	**25.2**	20.8	29.6	**25.0**	21.0	29.1
	Overall	**13.0**	10.5	15.5	**21.5**	18.6	24.4	**25.4**	22.5	28.3
90+	**Male**	**0.8**	0.0	1.7	**1.7**	0.5	2.9	**9.3**	6.6	12.0
	Female	**2.1**	0.7	3.5	**4.5**	2.7	6.3	**12.2**	9.2	15.1
	Overall	**1.5**	0.6	2.3	**3.2**	2.1	4.3	**10.8**	8.8	12.8
OVERALL	**MALE**	**7.9**	7.1	8.6	**7.8**	7.2	8.5	**6.6**	6.0	7.2
	FEMALE	**6.7**	6.1	7.4	**8.8**	8.1	9.5	**7.7**	7.1	8.3
	----------	**7.3**	6.8	7.8	**8.3**	7.9	8.8	**7.2**	6.7	7.6

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All prevalence estimates and 95% CLs are per 100'000 inhabitants.

4.2 Incidence of ILD

4.2.1 Idiopathic Interstitial Pneumonia (IIP)

4.2.1.1 Idiopathic Pulmonary Fibrosis (IPF)

The overall 5-year incidence of IPF increased from the period 1995-1999 to 2000-2004 (3.5 to 4.3 per 100'000 person-years, respectively) and then decreased during the period 2005-2009. The overall gender-specific rates show an approximate 2:1 ratio of males versus females. No incident cases of IPF were observed for those under the age of 20 years, and the highest age-specific rates can be found in those aged 70-79. Table 4.2.1.1 below shows overall and age-/gender-specific 5-year incidence rates with 95% confidence limits.

Table 4.2.1.1 IPF: 5-yr incidence rates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
30-39	**Male**	**0.3**	0.0	2.5	**0.8**	0.3	2.4	**0.2**	0.0	1.7
	Female	**0.3**	0.0	2.4	**0.3**	0.0	1.9	**0.2**	0.0	1.8
	Overall	**0.3**	0.1	1.4	**0.5**	0.2	1.4	**0.2**	0.1	1.0
40-49	**Male**	**1.3**	0.5	3.6	**1.8**	0.8	3.9	**0.5**	0.1	2.2
	Female	**0.3**	0.0	2.0	**1.4**	0.6	3.3	**0.8**	0.3	2.5
	Overall	**0.8**	0.3	1.8	**1.6**	0.9	2.8	**0.7**	0.3	1.6
50-59	**Male**	**6.6**	4.4	10.1	**6.2**	4.2	9.2	**3.9**	2.3	6.5
	Female	**2.9**	1.6	5.1	**3.2**	1.9	5.3	**1.0**	0.4	2.6
	Overall	**4.6**	3.3	6.4	**4.6**	3.4	6.3	**2.4**	1.5	3.7
60-69	**Male**	**19.3**	15.2	24.6	**20.9**	17.2	25.6	**11.1**	8.5	14.7
	Female	**6.9**	4.8	9.9	**8.2**	6.1	11.0	**3.9**	2.5	6.0
	Overall	**12.5**	10.2	15.2	**14.1**	11.9	16.6	**7.3**	5.8	9.2
70-79	**Male**	**31.1**	25.6	37.7	**28.4**	24.0	33.7	**17.0**	13.8	20.9
	Female	**12.2**	9.2	16.2	**15.4**	12.4	19.2	**6.8**	5.0	9.4
	Overall	**20.8**	17.7	24.4	**21.5**	18.8	24.6	**11.7**	9.8	13.9
80-89	**Male**	**10.6**	7.7	14.7	**21.3**	17.3	26.1	**12.1**	9.4	15.6
	Female	**8.6**	6.2	12.0	**11.2**	8.6	14.7	**7.6**	5.6	10.3
	Overall	**9.5**	7.6	12.0	**16.0**	13.6	18.8	**9.8**	8.1	11.9
90+	**Male**	**1.1**	0.4	3.0	**1.3**	0.6	3.0	**0.4**	0.1	1.8
	Female	**1.2**	0.5	2.9	**1.6**	0.8	3.2	**1.0**	0.4	2.5
	Overall	**1.2**	0.6	2.3	**1.5**	0.9	2.5	**0.7**	0.4	1.6
OVERALL	**MALE**	**4.9**	4.3	5.6	**5.8**	5.3	6.5	**3.4**	3.0	3.8
	FEMALE	**2.4**	2.0	2.8	**3.0**	2.6	3.5	**1.6**	1.3	1.9
	----------	**3.5**	3.2	3.9	**4.3**	4.0	4.7	**2.4**	2.2	2.7

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All prevalence estimates and 95% CLs are per 100'000 inhabitants.

4.2.2 Granulomatous ILD

4.2.2.1 Sarcoidosis

The overall 5-year incidence of sarcoidosis increased from the period 1995-1999 to 2000-2004 (0.6 to 1.0 per 100'000 person-years, respectively) and thereafter remained stable from 2000-2004 to 2005-2009. No incident cases were observed in those younger than 20 years or those aged 90 years and older. In all three periods,

the highest overall age-specific incidence rates were found in those aged 40-49, with a greater than two-fold increase in this age band between the periods 1995-1999 to 2000-2004 (2.6 to 6.1 per 100'000 person-years, respectively). Table 4.2.2.1 below shows overall and age-/gender-specific 5-year incidence rates with 95% confidence limits.

Table 4.2.2.1 Sarcoidosis: 5-yr incidence rates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
20 - 29	**Male**	**0.6**	0.2	2.5	**0.7**	0.2	2.1	**0.4**	0.1	1.7
	Female	**0.3**	0.0	2.2	**0.2**	0.0	1.7	**0.2**	0.0	1.6
	Overall	**0.5**	0.2	1.4	**0.5**	0.2	1.2	**0.3**	0.1	1.0
30 - 39	**Male**	**2.8**	1.4	5.6	**2.3**	1.2	4.5	**3.4**	2.0	5.7
	Female	**0.7**	0.2	2.8	**2.6**	1.4	4.9	**2.2**	1.2	4.3
	Overall	**1.7**	0.9	3.2	**2.5**	1.6	3.9	**2.8**	1.9	4.2
40 - 49	**Male**	**4.7**	2.8	7.9	**7.6**	5.2	11.2	**7.1**	4.9	10.5
	Female	**0.9**	0.3	2.7	**4.7**	2.9	7.5	**2.9**	1.6	5.3
	Overall	**2.6**	1.6	4.2	**6.1**	4.5	8.3	**5.0**	3.6	6.9
50 - 59	**Male**	**1.5**	0.6	3.6	**2.7**	1.5	4.9	**5.2**	3.3	8.2
	Female	**2.7**	1.5	4.8	**3.2**	1.9	5.3	**4.2**	2.6	6.8
	Overall	**2.1**	1.3	3.5	**3.0**	2.0	4.4	**4.7**	3.4	6.5
60 - 69	**Male**	**1.8**	0.8	3.9	**1.9**	1.0	3.7	**2.0**	1.0	3.8
	Female	**1.4**	0.6	3.2	**3.3**	2.1	5.3	**2.7**	1.6	4.6
	Overall	**1.6**	0.9	2.8	**2.7**	1.8	3.9	**2.4**	1.6	3.6
70 - 79	**Male**	**0.0**	0.0	0.0	**0.4**	0.1	1.7	**0.8**	0.3	2.1
	Female	**0.5**	0.1	2.0	**2.1**	1.2	3.8	**0.9**	0.4	2.1
	Overall	**0.3**	0.1	1.1	**1.3**	0.8	2.3	**0.8**	0.4	1.6
80 - 89	**Male**	**0.3**	0.0	2.0	**0.2**	0.0	1.6	**0.0**	0.0	0.0
	Female	**0.0**	0.0	0.0	**0.6**	0.2	1.9	**0.4**	0.1	1.5
	Overall	**0.1**	0.0	0.9	**0.4**	0.2	1.2	**0.2**	0.0	0.8
OVERALL	**MALE**	**0.8**	0.5	1.0	**1.0**	0.8	1.3	**1.1**	0.9	1.4
	FEMALE	**0.4**	0.3	0.7	**1.1**	0.9	1.4	**0.8**	0.6	1.1
	----------	**0.6**	0.5	0.8	**1.0**	0.9	1.2	**1.0**	0.8	1.2

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All incidence rates and 95% CLs are per 100'000 person-years.

4.2.2.2 Wegener's Granulomatosis

Overall 5-year incidence of Wegener's Granulomatosis remained relatively steady across all three time periods (0.7, 0.8, and 0.9 per 100'000 person-years). Overall gender-specific rates were roughly equal for males and females in all periods. During the period 2000-2009, no incident cases were observed in those younger than 10 years of age. Generally, the highest age-specific rates were found in those aged 50-79. Table 4.2.2.2 below shows overall and age-/gender-specific 5-year incidence rates with 95% confidence limits.

Table 4.2.2.2 WG: 5-yr incidence rates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
10 - 19	**Male**	**0.3**	0.0	2.0	**0.4**	0.1	1.8	**0.0**	0.0	0.0
	Female	**0.3**	0.0	2.1	**0.2**	0.0	1.6	**0.7**	0.2	2.2
	Overall	**0.3**	0.1	1.2	**0.3**	0.1	1.0	**0.3**	0.1	1.1
20 - 29	**Male**	**0.0**	0.0	0.0	**0.5**	0.1	1.8	**0.4**	0.1	1.7
	Female	**1.3**	0.5	3.4	**0.5**	0.1	1.9	**0.2**	0.0	1.6
	Overall	**0.6**	0.2	1.7	**0.5**	0.2	1.2	**0.3**	0.1	1.0
30 - 39	**Male**	**0.0**	0.0	0.0	**1.3**	0.5	3.1	**0.5**	0.1	1.9
	Female	**0.7**	0.2	2.8	**1.3**	0.5	3.2	**0.7**	0.2	2.3
	Overall	**0.3**	0.1	1.4	**1.3**	0.7	2.4	**0.6**	0.3	1.5
40 - 49	**Male**	**0.7**	0.2	2.7	**1.2**	0.4	3.1	**1.9**	0.9	4.0
	Female	**0.9**	0.3	2.7	**1.4**	0.6	3.3	**2.4**	1.3	4.6
	Overall	**0.8**	0.3	1.8	**1.3**	0.7	2.5	**2.2**	1.3	3.5
50 - 59	**Male**	**2.1**	1.0	4.4	**3.5**	2.1	5.8	**4.7**	2.9	7.6
	Female	**1.2**	0.5	2.9	**3.6**	2.3	5.9	**4.2**	2.6	6.8
	Overall	**1.6**	0.9	2.8	**3.6**	2.5	5.1	**4.4**	3.2	6.2
60 - 69	**Male**	**2.3**	1.2	4.7	**3.0**	1.8	5.1	**3.5**	2.1	5.7
	Female	**2.6**	1.4	4.7	**0.9**	0.4	2.2	**3.1**	1.9	5.1
	Overall	**2.5**	1.6	3.9	**1.9**	1.2	3.0	**3.3**	2.3	4.7
70 - 79	**Male**	**3.3**	1.9	6.0	**2.2**	1.2	4.0	**1.0**	0.4	2.3
	Female	**3.3**	1.9	5.7	**2.7**	1.6	4.5	**1.6**	0.8	3.0
	Overall	**3.3**	2.2	5.0	**2.4**	1.6	3.6	**1.3**	0.8	2.2

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
80 - 89	**Male**	**0.6**	0.1	2.3	**0.9**	0.3	2.5	**1.2**	0.5	2.7
	Female	**0.2**	0.0	1.7	**0.8**	0.3	2.2	**1.3**	0.6	2.7
	Overall	**0.4**	0.1	1.2	**0.9**	0.4	1.8	**1.2**	0.7	2.1
90+	**Male**	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.2**	0.0	1.6
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Overall	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.1**	0.0	0.8
OVERALL	**MALE**	**0.6**	0.5	0.9	**0.9**	0.7	1.2	**0.9**	0.7	1.1
	FEMALE	**0.7**	0.5	1.0	**0.8**	0.6	1.0	**0.9**	0.7	1.2
	----------	**0.7**	0.5	0.9	**0.8**	0.7	1.0	**0.9**	0.7	1.1

L=Lower, **U**=Upper, **CL**=Confidence Limit;* All incidence rates and 95% CLs are per 100'000 person-years.

4.2.3 ILD of known cause or associated with other diseases

4.2.3.1 Extrinsic Allergic Alveolitis (EAA)

Overall 5-year incidence of EAA remained relatively stable across all three time periods (1.3, 1.3, and 1.1 per 100'000 person-years). Overall gender-specific rates were roughly equal for males and females in all periods. During all periods, no incident cases were observed in those younger than 10 years of age. Generally, the highest age-specific rates were found in those aged 50-79. Table 4.2.3.1 below shows overall and age-/gender-specific 5-year incidence rates with 95% confidence limits.

Table 4.2.3.1 EAA: 5-year incidence rates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
10 - 19	**Male**	**0.3**	0.0	2.0	**0.7**	0.2	2.0	**0.0**	0.0	0.0
	Female	**0.0**	0.0	0.0	**0.5**	0.1	1.8	**0.0**	0.0	0.0
	Overall	**0.1**	0.0	1.0	**0.6**	0.2	1.3	**0.0**	0.0	0.0
20 - 29	**Male**	**0.3**	0.0	2.2	**0.5**	0.1	1.8	**0.2**	0.0	1.5
	Female	**0.3**	0.0	2.2	**0.7**	0.2	2.2	**0.2**	0.0	1.6
	Overall	**0.3**	0.1	1.2	**0.6**	0.2	1.4	**0.2**	0.1	0.9

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
30 - 39	**Male**	**3.1**	1.6	6.0	**1.3**	0.5	3.1	**0.7**	0.2	2.2
	Female	**2.1**	0.9	4.6	**1.3**	0.5	3.2	**0.5**	0.1	2.0
	Overall	**2.6**	1.6	4.3	**1.3**	0.7	2.4	**0.6**	0.3	1.5
40 - 49	**Male**	**5.0**	3.0	8.3	**1.8**	0.8	3.9	**3.0**	1.7	5.5
	Female	**2.6**	1.3	4.9	**1.1**	0.4	2.9	**2.9**	1.6	5.3
	Overall	**3.7**	2.5	5.5	**1.4**	0.8	2.6	**3.0**	2.0	4.5
50 - 59	**Male**	**5.4**	3.4	8.6	**4.0**	2.4	6.5	**4.4**	2.7	7.2
	Female	**3.4**	2.0	5.7	**6.6**	4.7	9.4	**6.7**	4.6	9.8
	Overall	**4.3**	3.0	6.1	**5.4**	4.1	7.2	**5.6**	4.2	7.6
60 - 69	**Male**	**4.7**	2.9	7.6	**6.3**	4.4	9.0	**3.3**	2.0	5.4
	Female	**3.8**	2.3	6.2	**5.6**	3.9	8.0	**4.7**	3.1	7.0
	Overall	**4.2**	3.0	5.9	**5.9**	4.6	7.6	**4.0**	2.9	5.5
70 - 79	**Male**	**4.3**	2.5	7.2	**3.9**	2.4	6.2	**4.1**	2.6	6.2
	Female	**2.5**	1.4	4.7	**2.3**	1.3	4.0	**1.8**	0.9	3.3
	Overall	**3.3**	2.2	5.0	**3.0**	2.1	4.3	**2.8**	2.0	4.1
80 - 89	**Male**	**0.9**	0.3	2.7	**0.7**	0.2	2.1	**1.2**	0.5	2.7
	Female	**1.5**	0.7	3.3	**1.0**	0.4	2.5	**0.6**	0.2	1.7
	Overall	**1.2**	0.6	2.3	**0.9**	0.4	1.8	**0.9**	0.4	1.7
90+	**Male**	**0.3**	0.0	2.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Female	**0.0**	0.0	0.0	**0.2**	0.0	1.4	**0.0**	0.0	0.0
	Overall	**0.1**	0.0	0.9	**0.1**	0.0	0.8	**0.0**	0.0	0.0
OVERALL	**MALE**	**1.6**	1.3	2.0	**1.3**	1.1	1.6	**1.1**	0.9	1.4
	FEMALE	**1.1**	0.9	1.4	**1.3**	1.1	1.7	**1.1**	0.9	1.4
	----------	**1.3**	1.1	1.6	**1.3**	1.2	1.6	**1.1**	0.9	1.3

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All incidence rates and 95% CLs are per 100'000 person-years.

4.2.3.2 Pneumoconioses

Overall 5-year incidence of the Pneumoconioses increased approximately two-fold from the period 1995-1999 to 2000-2004 (3.7 to 7.2 per 100'000 person-years, respectively). For all three periods, overall gender-specific rates were roughly 10-20 times higher in males than in females. Incident cases were found in all age bands, with the highest age-specific rates observed in those aged 50-79. Table 4.2.3.2 below shows overall and age-/gender-specific 5-year incidence rates with 95% confidence limits.

Table 4.2.3.2 Pneumoconioses: 5-year incidence rates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
<10	**Male**	**0.0**	0.0	0.0	**0.6**	0.2	1.9	**0.4**	0.1	1.7
	Female	**0.5**	0.1	1.9	**0.2**	0.0	1.5	**0.0**	0.0	0.0
	Overall	**0.2**	0.1	0.9	**0.4**	0.2	1.1	**0.2**	0.1	0.9
10 - 19	**Male**	**0.3**	0.0	2.0	**0.7**	0.2	2.0	**0.5**	0.1	1.8
	Female	**0.3**	0.0	2.1	**0.7**	0.2	2.1	**0.0**	0.0	0.0
	Overall	**0.3**	0.1	1.2	**0.7**	0.3	1.5	**0.2**	0.1	0.9
20 - 29	**Male**	**1.2**	0.5	3.3	**2.5**	1.4	4.5	**1.7**	0.8	3.4
	Female	**0.0**	0.0	0.0	**0.2**	0.0	1.7	**1.1**	0.5	2.6
	Overall	**0.6**	0.2	1.7	**1.4**	0.8	2.4	**1.4**	0.8	2.4
30 - 39	**Male**	**1.0**	0.3	3.2	**2.1**	1.0	4.2	**2.7**	1.5	4.8
	Female	**1.0**	0.3	3.2	**1.3**	0.5	3.2	**2.5**	1.3	4.6
	Overall	**1.0**	0.5	2.3	**1.7**	1.0	2.9	**2.6**	1.7	3.9
40 - 49	**Male**	**3.3**	1.8	6.2	**6.8**	4.5	10.2	**3.8**	2.3	6.5
	Female	**0.3**	0.0	2.0	**1.9**	0.9	4.1	**1.9**	0.9	3.9
	Overall	**1.7**	0.9	3.1	**4.3**	3.0	6.1	**2.8**	1.9	4.4
50 - 59	**Male**	**16.0**	12.2	21.0	**28.5**	23.7	34.2	**22.6**	18.2	28.1
	Female	**1.0**	0.4	2.6	**2.4**	1.3	4.3	**5.0**	3.2	7.7
	Overall	**7.6**	5.9	9.9	**14.5**	12.1	17.2	**13.3**	11.0	16.2
60 - 69	**Male**	**39.5**	33.4	46.8	**61.1**	54.4	68.7	**71.6**	64.3	79.8
	Female	**1.2**	0.5	2.9	**4.3**	2.8	6.4	**4.9**	3.3	7.2
	Overall	**18.4**	15.5	21.7	**30.6**	27.3	34.2	**36.3**	32.7	40.3
70 - 79	**Male**	**38.1**	31.9	45.4	**62.5**	55.7	70.1	**67.7**	61.0	75.2
	Female	**1.3**	0.5	3.1	**4.0**	2.6	6.1	**4.6**	3.1	6.7
	Overall	**18.0**	15.2	21.4	**31.4**	28.1	35.1	**34.7**	31.3	38.3
80 - 89	**Male**	**7.5**	5.1	11.0	**26.1**	21.7	31.4	**35.6**	30.7	41.2
	Female	**1.0**	0.4	2.6	**2.9**	1.7	4.9	**3.5**	2.3	5.5
	Overall	**4.0**	2.8	5.7	**13.9**	11.7	16.5	**19.0**	16.5	21.9
90+	**Male**	**0.3**	0.0	2.0	**0.4**	0.1	1.8	**1.1**	0.5	2.6
	Female	**0.0**	0.0	0.0	**0.2**	0.0	1.4	**0.6**	0.2	1.9
	Overall	**0.1**	0.0	0.9	**0.3**	0.1	1.0	**0.9**	0.4	1.7
OVERALL	**MALE**	**7.5**	6.7	8.3	**13.8**	12.9	14.7	**15.1**	14.2	16.1
	FEMALE	**0.4**	0.3	0.7	**1.3**	1.0	1.6	**1.6**	1.4	2.0
	----------	**3.7**	3.3	4.1	**7.2**	6.7	7.6	**8.1**	7.6	8.6

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All incidence rates and 95% CLs are per 100'000 person-years.

4.2.3.3 Drug-/radiation-induced ILD (DRAD-ILD)

The overall 5-year incidence of drug/radiation-induced ILD increased steadily from the period 1995-1999 to 2005-2009 (0.2 to 0.5 per 100'000 person-years, respectively). In all periods, overall gender-specific rates were roughly equal in males and females. No incident cases were observed in those younger than 20 years or those aged 90 years and older. In all three periods, the highest overall age-specific incidence rates were found in those aged 60-79. Table 4.2.3.3 below shows overall and age-/gender-specific 5-year incidence rates with 95% confidence limits.

Table 4.2.3.3 DRAD- ILD: 5-year incidence rates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
30 - 39	**Male**	**0.0**	0.0	0.0	**0.3**	0.0	1.8	**0.0**	0.0	0.0
	Female	**0.7**	0.2	2.8	**0.0**	0.0	0.0	**0.5**	0.1	2.0
	Overall	**0.3**	0.1	1.4	**0.1**	0.0	0.9	**0.2**	0.1	1.0
40 - 49	**Male**	**0.3**	0.0	2.4	**0.0**	0.0	0.0	**0.5**	0.1	2.2
	Female	**0.3**	0.0	2.0	**0.8**	0.3	2.6	**0.0**	0.0	0.0
	Overall	**0.3**	0.1	1.2	**0.4**	0.1	1.3	**0.3**	0.1	1.1
50 - 59	**Male**	**0.3**	0.0	2.1	**0.2**	0.0	1.8	**1.4**	0.6	3.3
	Female	**1.0**	0.4	2.6	**0.4**	0.1	1.7	**1.5**	0.7	3.3
	Overall	**0.7**	0.3	1.6	**0.3**	0.1	1.1	**1.4**	0.8	2.6
60 - 69	**Male**	**1.2**	0.4	3.1	**2.4**	1.3	4.3	**1.5**	0.7	3.2
	Female	**0.9**	0.4	2.5	**1.3**	0.6	2.7	**2.9**	1.8	4.8
	Overall	**1.0**	0.5	2.1	**1.8**	1.1	2.9	**2.3**	1.5	3.4
70 - 79	**Male**	**0.3**	0.0	2.2	**2.6**	1.5	4.6	**1.5**	0.8	3.1
	Female	**1.5**	0.7	3.4	**1.9**	1.0	3.5	**1.4**	0.7	2.8
	Overall	**1.0**	0.5	2.0	**2.2**	1.5	3.4	**1.5**	0.9	2.4
80 - 89	**Male**	**0.6**	0.1	2.3	**0.9**	0.3	2.5	**0.8**	0.3	2.1
	Female	**0.0**	0.0	0.0	**1.0**	0.4	2.5	**0.9**	0.4	2.2
	Overall	**0.3**	0.1	1.1	**1.0**	0.5	1.9	**0.9**	0.4	1.7
OVERALL	**MALE**	**0.2**	0.1	0.4	**0.5**	0.3	0.7	**0.4**	0.3	0.6
	FEMALE	**0.3**	0.2	0.5	**0.4**	0.3	0.6	**0.5**	0.4	0.7
	----------	**0.2**	0.2	0.4	**0.4**	0.3	0.6	**0.5**	0.4	0.6

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All incidence rates and 95% CLs are per 100'000 person-years.

4.2.3.4 ILD associated with other diseases (ILD-ODIS)

The overall 5-year incidence of ILD associated with other diseases decreased four-fold from the period 1995-1999 to 2005-2009 (2.8 to 0.7 per 100'000 person-years, respectively). Except in the period 1995-1999, overall gender-specific rates were roughly equal in males and females. No incident cases were observed in those younger than 10 of age and the highest overall age-specific incidence rates were found in those aged 50-79. Table 4.2.3.4 below shows overall and age-/gender-specific 5-year incidence rates with 95% confidence limits.

Table 4.2.3.4 ILD-ODIS: 5-year incidence rates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
20 - 29	**Male**	**0.3**	0.0	2.2	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Female	**0.3**	0.0	2.2	**0.5**	0.1	1.9	**0.0**	0.0	0.0
	Overall	**0.3**	0.1	1.2	**0.2**	0.1	0.9	**0.0**	0.0	0.0
30 - 39	**Male**	**0.3**	0.0	2.5	**0.3**	0.0	1.8	**0.0**	0.0	0.0
	Female	**0.7**	0.2	2.8	**2.1**	1.1	4.2	**0.2**	0.0	1.8
	Overall	**0.5**	0.2	1.6	**1.2**	0.6	2.3	**0.1**	0.0	0.9
40 - 49	**Male**	**0.7**	0.2	2.7	**0.6**	0.1	2.4	**0.5**	0.1	2.2
	Female	**2.3**	1.1	4.6	**2.2**	1.1	4.4	**0.8**	0.3	2.5
	Overall	**1.5**	0.8	2.9	**1.4**	0.8	2.6	**0.7**	0.3	1.6
50 - 59	**Male**	**6.0**	3.9	9.4	**2.0**	1.0	4.0	**1.9**	0.9	4.1
	Female	**6.3**	4.3	9.2	**3.2**	1.9	5.3	**1.2**	0.5	3.0
	Overall	**6.2**	4.6	8.2	**2.6**	1.8	4.0	**1.6**	0.9	2.8
60 - 69	**Male**	**12.0**	8.8	16.3	**5.4**	3.6	8.0	**3.1**	1.8	5.2
	Female	**8.1**	5.8	11.3	**3.7**	2.4	5.8	**2.1**	1.2	3.9
	Overall	**9.8**	7.8	12.3	**4.5**	3.4	6.0	**2.6**	1.7	3.8
70 - 79	**Male**	**19.2**	15.0	24.6	**7.1**	5.1	10.0	**2.9**	1.7	4.8
	Female	**11.7**	8.8	15.6	**4.6**	3.1	6.8	**3.0**	1.9	4.8
	Overall	**15.1**	12.5	18.2	**5.8**	4.4	7.5	**2.9**	2.1	4.2
80 - 89	**Male**	**5.7**	3.7	8.9	**1.4**	0.6	3.1	**2.6**	1.5	4.4
	Female	**5.4**	3.6	8.2	**2.7**	1.6	4.7	**2.0**	1.1	3.7
	Overall	**5.6**	4.1	7.5	**2.1**	1.3	3.3	**2.3**	1.5	3.4

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
90+	**Male**	**0.6**	0.1	2.3	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Female	**1.2**	0.5	2.9	**0.0**	0.0	0.0	**0.2**	0.0	1.5
	Overall	**0.9**	0.4	1.9	**0.0**	0.0	0.0	**0.1**	0.0	0.8
OVERALL	**MALE**	**3.1**	2.7	3.7	**1.2**	1.0	1.5	**0.8**	0.6	1.0
	FEMALE	**2.6**	2.2	3.0	**1.3**	1.1	1.6	**0.7**	0.5	0.9
	----------	**2.8**	2.5	3.2	**1.3**	1.1	1.5	**0.7**	0.6	0.9

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All incidence rates and 95% CLs are per 100'000 person-years.

4.3 All-cause mortality

4.3.1 Idiopathic Interstitial Pneumonia (IIP)

4.3.1.1 Idiopathic Pulmonary Fibrosis (IPF)

Overall 5-year all-cause mortality in IPF patients increased more than two-fold from the period 1995-1999 to 2000-2004 (0.9 to 2.3 per 100'000 inhabitants). Overall gender-specific rates showed all-cause mortality to be more than twice as high in males as in females. No deaths were observed in those under the age of 30 years, and the highest overall age-specific rates were found in those 70-79 years of age. Table 4.3.1.1 below shows overall and age-/gender-specific 5-year mortality rates with 95% confidence limits.

Table 4.3.1.1 IPF: 5-year all-cause mortality rates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
30 - 39	**Male**	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.2**	0.0	0.6
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Overall	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.1**	0.0	0.3
40 - 49	**Male**	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**1.0**	0.0	1.9
	Female	**0.0**	0.0	0.0	**0.2**	0.0	0.7	**0.0**	0.0	0.0
	Overall	**0.0**	0.0	0.0	**0.1**	0.0	0.4	**0.5**	0.0	0.9
50 - 59	**Male**	**0.8**	0.0	1.7	**2.0**	0.7	3.4	**2.9**	1.3	4.6
	Female	**0.2**	0.0	0.7	**0.8**	0.0	1.6	**0.6**	0.0	1.4
	Overall	**0.5**	0.0	1.0	**1.4**	0.6	2.1	**1.7**	0.8	2.6

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
60 - 69	**Male**	**2.1**	0.7	3.6	**11.5**	8.5	14.4	**12.6**	9.6	15.7
	Female	**1.5**	0.4	2.7	**3.0**	1.6	4.4	**3.3**	1.8	4.8
	Overall	**1.8**	0.9	2.7	**6.9**	5.3	8.5	**7.7**	6.1	9.4
70 - 79	**Male**	**9.6**	6.4	12.9	**18.7**	14.9	22.5	**16.0**	12.7	19.3
	Female	**3.1**	1.4	4.8	**7.8**	5.5	10.1	**6.1**	4.1	8.0
	Overall	**6.1**	4.4	7.9	**13.0**	10.8	15.1	**10.8**	9.0	12.7
80 - 89	**Male**	**5.4**	3.0	7.7	**12.6**	9.3	15.8	**9.6**	7.0	12.1
	Female	**4.0**	2.1	5.8	**6.6**	4.3	8.8	**5.3**	3.4	7.1
	Overall	**4.6**	3.1	6.1	**9.4**	7.5	11.4	**7.4**	5.8	8.9
90+	**Male**	**0.5**	0.0	1.3	**1.1**	0.1	2.0	**0.2**	0.0	0.6
	Female	**0.2**	0.0	0.7	**1.2**	0.2	2.1	**1.1**	0.2	2.1
	Overall	**0.4**	0.0	0.8	**1.1**	0.5	1.8	**0.7**	0.2	1.2
OVERALL	**MALE**	**1.3**	1.0	1.6	**3.4**	2.9	3.8	**3.2**	2.8	3.6
	FEMALE	**0.6**	0.4	0.8	**1.4**	1.1	1.7	**1.2**	1.0	1.5
	----------	**0.9**	0.8	1.1	**2.3**	2.1	2.6	**2.2**	1.9	2.4

L=Lower, **U**=Upper, **CL**=Confidence Limit; * All mortality rates and 95% CLs are per 100'000 inhabitants.

4.3.2 Granulomatous ILD

4.3.2.1 Sarcoidosis

Overall 5-year all-cause mortality in sarcoidosis patients was estimated at 0.1 per 100'000 inhabitants during the periods 2000-2004 and 2005-2009. No deaths were observed in those below 30 years or above 90 years of age. Table 4.3.2.1 below shows overall and age- /gender-specific 5-year mortality rates with 95% confidence limits.

Table 4.3.2.1 Sarcoidosis: 5-year all-cause mortality rates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
30 - 39	**Male**	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.2**	0.0	0.6
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Overall	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.1**	0.0	0.3
40 - 49	**Male**	**0.0**	0.0	0.0	**0.5**	0.0	1.3	**0.5**	0.0	1.2
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.5**	0.0	1.1
	Overall	**0.0**	0.0	0.0	**0.3**	0.0	0.6	**0.5**	0.0	0.9

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
50 - 59	**Male**	**0.3**	0.0	0.8	**0.2**	0.0	0.7	**0.2**	0.0	0.7
	Female	**0.0**	0.0	0.0	**0.2**	0.0	0.6	**0.4**	0.0	1.0
	Overall	**0.1**	0.0	0.4	**0.2**	0.0	0.5	**0.3**	0.0	0.7
60 - 69	**Male**	**0.0**	0.0	0.0	**0.2**	0.0	0.6	**1.0**	0.1	1.8
	Female	**0.0**	0.0	0.0	**0.2**	0.0	0.5	**0.5**	0.0	1.1
	Overall	**0.0**	0.0	0.0	**0.2**	0.0	0.4	**0.7**	0.2	1.2
70 - 79	**Male**	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.5**	0.0	1.1
	Female	**0.0**	0.0	0.0	**0.4**	0.0	0.9	**0.3**	0.0	0.8
	Overall	**0.0**	0.0	0.0	**0.2**	0.0	0.5	**0.4**	0.1	0.8
80 - 89	**Male**	**0.0**	0.0	0.0	**0.4**	0.0	1.1	**0.0**	0.0	0.0
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.2**	0.0	0.5
	Overall	**0.0**	0.0	0.0	**0.2**	0.0	0.5	**0.1**	0.0	0.3
OVERALL	**MALE**	**0.0**	0.0	0.1	**0.1**	0.0	0.2	**0.2**	0.1	0.3
	FEMALE	**0.0**	0.0	0.0	**0.1**	0.0	0.1	**0.1**	0.0	0.2
	----------	**0.0**	0.0	0.0	**0.1**	0.0	0.1	**0.1**	0.1	0.2

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All mortality rates and 95% CLs are per 100'000 inhabitants.

4.3.2.2 Wegener's Granulomatosis (WG)

Overall 5-year all-cause mortality in WG patients remained relatively stable across all three time periods (0.1, 0.2, and 0.2 per 100'000 inhabitants). Generally, mortality in males was more frequent than in females and the highest overall age-specific rates were observed in those 70-79 years of age. Table 4.3.2.2 below shows overall and age-/gender-specific 5-year mortality rates with 95% confidence limits.

Table 4.3.2.2 WG: 5-year all-cause mortality rates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
30 - 39	**Male**	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.2**	0.0	0.7
	Overall	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.1**	0.0	0.3
40 - 49	**Male**	**0.0**	0.0	0.0	**0.3**	0.0	0.8	**0.0**	0.0	0.0
	Female	**0.0**	0.0	0.0	**0.2**	0.0	0.7	**0.0**	0.0	0.0
	Overall	**0.0**	0.0	0.0	**0.3**	0.0	0.6	**0.0**	0.0	0.0

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
50 - 59	**Male**	**0.0**	0.0	0.0	**0.7**	0.0	1.5	**1.2**	0.1	2.3
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Overall	**0.0**	0.0	0.0	**0.3**	0.0	0.7	**0.6**	0.1	1.1
60 - 69	**Male**	**0.3**	0.0	0.8	**1.4**	0.4	2.4	**0.2**	0.0	0.6
	Female	**0.2**	0.0	0.7	**0.7**	0.0	1.4	**0.2**	0.0	0.5
	Overall	**0.2**	0.0	0.6	**1.0**	0.4	1.6	**0.2**	0.0	0.4
70 - 79	**Male**	**0.8**	0.0	1.8	**1.2**	0.2	2.2	**1.2**	0.3	2.1
	Female	**0.7**	0.0	1.5	**0.9**	0.1	1.7	**1.3**	0.4	2.2
	Overall	**0.8**	0.2	1.4	**1.1**	0.4	1.7	**1.3**	0.6	1.9
80 - 89	**Male**	**0.3**	0.0	0.8	**0.2**	0.0	0.7	**1.1**	0.2	1.9
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.3**	0.0	0.8
	Overall	**0.1**	0.0	0.4	**0.1**	0.0	0.3	**0.7**	0.2	1.2
90+	**Male**	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.2**	0.0	0.6
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Overall	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.1**	0.0	0.3
OVERALL	**MALE**	**0.1**	0.0	0.2	**0.3**	0.1	0.4	**0.3**	0.2	0.4
	FEMALE	**0.1**	0.0	0.1	**0.1**	0.1	0.2	**0.2**	0.1	0.2
	----------	**0.1**	0.0	0.1	**0.2**	0.1	0.3	**0.2**	0.1	0.3

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All mortality rates and 95% CLs are per 100'000 inhabitants.

4.3.3 ILD of known cause or associated with other diseases

4.3.3.1 Extrinsic Allergic Alveolitis (EAA)

Overall 5-year all-cause mortality in EAA patients increased three-fold from the period 1995-1999 to 2000-2004 (0.1 to 0.3 per 100'000 inhabitants, respectively). No deaths were observed in those under 30 years of age, and the highest age-specific rates were found in those 60-79 year of age. Generally, in all age bands and across all time periods, mortality rates were higher in males than in females. Table 4.3.3.1 below shows overall and age- /gender-specific 5-year mortality rates with 95% confidence limits.

Table 4.3.3.1 EAA: 5-year all-cause mortality rates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
30 - 39	**Male**	**0.0**	0.0	0.0	**0.2**	0.0	0.7	**0.0**	0.0	0.0
	Female	**0.3**	0.0	0.9	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Overall	**0.2**	0.0	0.5	**0.1**	0.0	0.4	**0.0**	0.0	0.0
40 - 49	**Male**	**0.0**	0.0	0.0	**0.5**	0.0	1.3	**0.2**	0.0	0.7
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Overall	**0.0**	0.0	0.0	**0.3**	0.0	0.6	**0.1**	0.0	0.4
50 - 59	**Male**	**0.5**	0.0	1.3	**0.5**	0.0	1.1	**1.0**	0.0	1.9
	Female	**0.0**	0.0	0.0	**0.4**	0.0	0.9	**0.4**	0.0	1.0
	Overall	**0.2**	0.0	0.6	**0.4**	0.0	0.8	**0.7**	0.1	1.2
60 - 69	**Male**	**0.3**	0.0	0.8	**1.2**	0.2	2.2	**1.7**	0.6	2.9
	Female	**0.2**	0.0	0.7	**0.9**	0.1	1.6	**1.2**	0.3	2.1
	Overall	**0.2**	0.0	0.6	**1.0**	0.4	1.6	**1.5**	0.7	2.2
70 - 79	**Male**	**1.1**	0.0	2.2	**1.4**	0.4	2.5	**2.1**	0.9	3.3
	Female	**0.2**	0.0	0.7	**0.7**	0.0	1.4	**0.3**	0.0	0.8
	Overall	**0.6**	0.1	1.2	**1.1**	0.4	1.7	**1.2**	0.6	1.8
80 - 89	**Male**	**0.3**	0.0	0.8	**0.7**	0.0	1.4	**0.4**	0.0	0.9
	Female	**0.0**	0.0	0.0	**1.0**	0.1	1.9	**0.2**	0.0	0.5
	Overall	**0.1**	0.0	0.4	**0.8**	0.3	1.4	**0.3**	0.0	0.6
90+	**Male**	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.2**	0.0	0.6
	Overall	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.1**	0.0	0.3
OVERALL	**MALE**	**0.2**	0.0	0.3	**0.3**	0.2	0.5	**0.4**	0.2	0.5
	FEMALE	**0.0**	0.0	0.1	**0.2**	0.1	0.3	**0.2**	0.1	0.3
	----------	**0.1**	0.0	0.2	**0.3**	0.2	0.4	**0.3**	0.2	0.4

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All mortality rates and 95% CLs are per 100'000 inhabitants.

4.3.3.2 Pneumoconioses

Overall 5-year all-cause mortality of the Pneumoconioses increased more than five-fold from the period 1995-1999 to 2004-2009 (0.4 to 2.2 per 100'000 inhabitants, respectively). No deaths were observed in those below age 30, and the highest overall age-specific rates were found among those 70-79 years of age. In all age bands and across all time periods, rates were much higher in males than in females.

Table 4.3.3.2 below shows overall and age-/gender-specific 5-year mortality rates with 95% confidence limits.

Table 4.3.3.2 Pneumoconioses: 5-year all-cause mortality rates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
20 - 29	**Male**	**0.0**	0.0	0.0	**0.2**	0.0	0.6	**0.0**	0.0	0.0
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Overall	**0.0**	0.0	0.0	**0.1**	0.0	0.3	**0.0**	0.0	0.0
30 - 39	**Male**	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Overall	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
40 - 49	**Male**	**0.0**	0.0	0.0	**0.3**	0.0	0.8	**0.0**	0.0	0.0
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Overall	**0.0**	0.0	0.0	**0.1**	0.0	0.4	**0.0**	0.0	0.0
50 - 59	**Male**	**0.8**	0.0	1.7	**1.8**	0.6	3.1	**2.4**	0.9	3.9
	Female	**0.0**	0.0	0.0	**0.2**	0.0	0.6	**0.0**	0.0	0.0
	Overall	**0.4**	0.0	0.8	**0.9**	0.3	1.6	**1.1**	0.4	1.9
60 - 69	**Male**	**2.1**	0.7	3.6	**8.6**	6.1	11.2	**13.6**	10.4	16.8
	Female	**0.0**	0.0	0.0	**0.5**	0.0	1.1	**0.7**	0.0	1.4
	Overall	**1.0**	0.3	1.6	**4.3**	3.1	5.5	**6.8**	5.2	8.3
70 - 79	**Male**	**6.2**	3.6	8.8	**14.4**	11.1	17.8	**24.0**	20.0	28.0
	Female	**0.0**	0.0	0.0	**0.5**	0.0	1.2	**1.0**	0.2	1.7
	Overall	**2.9**	1.7	4.1	**7.1**	5.5	8.7	**12.0**	10.0	14.0
80 - 89	**Male**	**1.6**	0.3	2.9	**9.7**	6.8	12.6	**14.3**	11.1	17.4
	Female	**0.5**	0.0	1.1	**0.6**	0.0	1.3	**2.0**	0.9	3.2
	Overall	**1.0**	0.3	1.7	**4.9**	3.5	6.3	**8.0**	6.3	9.6
90+	**Male**	**0.0**	0.0	0.0	**0.4**	0.0	1.0	**0.6**	0.0	1.3
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.4**	0.0	0.9
	Overall	**0.0**	0.0	0.0	**0.2**	0.0	0.5	**0.5**	0.1	0.9
OVERALL	**MALE**	**0.8**	0.5	1.0	**2.6**	2.2	3.0	**4.2**	3.7	4.6
	FEMALE	**0.0**	0.0	0.1	**0.1**	0.1	0.2	**0.3**	0.2	0.4
	----------	**0.4**	0.3	0.5	**1.3**	1.1	1.5	**2.2**	1.9	2.4

L=Lower, **U**=Upper, **CL**=Confidence Limit; * All mortality rates and 95% CLs are per 100'000 inhabitants.

4.3.3.3 Drug-/radiation-induced ILD (DRAD-ILD)

Overall 5-year all-cause mortality in drug-/radiation-induced ILD patients increased three-fold from the period 1995-1999 to 2000-2004 (0.1 to 0.3 per 100'000

inhabitants, respectively). No deaths were observed in those under 30 years of age, and the highest age-specific rates were found in those 60-89 years of age. Across all time periods mortality rates in the age group 60-79 were generally higher in males than in females. Table 4.3.3.3 below shows overall and age-/gender-specific 5-year mortality rates with 95% confidence limits.

Table 4.3.3.3 DRAD-ILD: 5-year all-cause mortality rates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
30 - 39	**Male**	**0.0**	0.0	0.0	**0.2**	0.0	0.7	**0.0**	0.0	0.0
	Female	**0.3**	0.0	0.9	**0.0**	0.0	0.0	**0.2**	0.0	0.7
	Overall	**0.2**	0.0	0.5	**0.1**	0.0	0.4	**0.1**	0.0	0.3
40 - 49	**Male**	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.2**	0.0	0.7
	Female	**0.0**	0.0	0.0	**0.2**	0.0	0.7	**0.0**	0.0	0.0
	Overall	**0.0**	0.0	0.0	**0.1**	0.0	0.4	**0.1**	0.0	0.4
50 - 59	**Male**	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.7**	0.0	1.5
	Female	**0.4**	0.0	1.1	**0.2**	0.0	0.6	**0.0**	0.0	0.0
	Overall	**0.2**	0.0	0.6	**0.1**	0.0	0.3	**0.3**	0.0	0.7
60 - 69	**Male**	**0.5**	0.0	1.3	**0.6**	0.0	1.3	**1.9**	0.7	3.1
	Female	**0.2**	0.0	0.7	**0.3**	0.0	0.8	**1.2**	0.3	2.1
	Overall	**0.4**	0.0	0.8	**0.5**	0.1	0.9	**1.6**	0.8	2.3
70 - 79	**Male**	**0.0**	0.0	0.0	**1.0**	0.1	1.9	**1.0**	0.2	1.9
	Female	**0.2**	0.0	0.7	**0.4**	0.0	0.9	**0.5**	0.0	1.0
	Overall	**0.1**	0.0	0.4	**0.7**	0.2	1.2	**0.8**	0.3	1.2
80 - 89	**Male**	**0.3**	0.0	0.8	**0.4**	0.0	1.1	**0.5**	0.0	1.2
	Female	**0.0**	0.0	0.0	**0.6**	0.0	1.3	**1.0**	0.2	1.8
	Overall	**0.1**	0.0	0.4	**0.5**	0.1	1.0	**0.8**	0.3	1.3
OVERALL	**MALE**	**0.1**	0.0	0.1	**0.2**	0.1	0.3	**0.3**	0.2	0.4
	FEMALE	**0.1**	0.0	0.2	**0.1**	0.0	0.2	**0.2**	0.1	0.3
	----------	**0.1**	0.0	0.1	**0.1**	0.1	0.2	**0.3**	0.2	0.3

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All mortality rates and 95% CLs are per 100'000 inhabitants.

4.3.3.4 ILD associated with other diseases (ILD-ODIS)

Overall 5-year all-cause mortality in patients with ILD associated with other diseases remained relatively stable across all three time periods (0.7, 0.7, and 0.6 per 100'000 inhabitants). Generally, mortality in males was more frequent than in females and the highest overall age-specific rates were observed in those 70-89 years of age. No deaths were observed in patients under 40 years of age. Table 4.3.3.4 below shows overall and age-/gender-specific 5-year mortality rates with 95% confidence limits.

Table 4.3.3.4 ILD-ODIS: 5-year all-cause mortality rates* and 95% confidence limits, stratified by age band and gender

Age band	Gender	1995-1999	L95% CL	U95% CL	2000-2004	L95% CL	U95% CL	2005-2009	L95% CL	U95% CL
40 - 49	**Male**	**0.0**	0.0	0.0	**0.5**	0.0	1.3	**0.2**	0.0	0.7
	Female	**0.0**	0.0	0.0	**0.0**	0.0	0.0	**0.2**	0.0	0.7
	Overall	**0.0**	0.0	0.0	**0.3**	0.0	0.6	**0.2**	0.0	0.6
50 - 59	**Male**	**0.8**	0.0	1.7	**0.9**	0.0	1.8	**1.2**	0.1	2.3
	Female	**0.4**	0.0	1.1	**1.0**	0.1	1.8	**1.3**	0.3	2.3
	Overall	**0.6**	0.1	1.1	**0.9**	0.3	1.6	**1.3**	0.5	2.0
60 - 69	**Male**	**1.3**	0.2	2.5	**3.8**	2.1	5.5	**2.7**	1.3	4.1
	Female	**0.9**	0.0	1.8	**1.9**	0.8	3.0	**1.7**	0.7	2.8
	Overall	**1.1**	0.4	1.8	**2.8**	1.8	3.8	**2.2**	1.3	3.1
70 - 79	**Male**	**6.8**	4.1	9.5	**5.9**	3.8	8.0	**3.7**	2.1	5.2
	Female	**2.9**	1.3	4.5	**3.3**	1.8	4.8	**2.4**	1.2	3.6
	Overall	**4.7**	3.1	6.2	**4.5**	3.2	5.8	**3.0**	2.0	4.0
80 - 89	**Male**	**2.4**	0.8	4.0	**1.8**	0.5	3.0	**1.4**	0.4	2.4
	Female	**2.6**	1.0	4.1	**0.8**	0.0	1.6	**2.2**	1.0	3.4
	Overall	**2.5**	1.4	3.6	**1.3**	0.5	2.0	**1.8**	1.1	2.6
90+	**Male**	**0.5**	0.0	1.3	**0.0**	0.0	0.0	**0.0**	0.0	0.0
	Female	**0.9**	0.0	1.8	**0.0**	0.0	0.0	**0.2**	0.0	0.6
	Overall	**0.7**	0.1	1.3	**0.0**	0.0	0.0	**0.1**	0.0	0.3
OVERALL	**MALE**	**0.8**	0.6	1.1	**0.9**	0.7	1.2	**0.7**	0.5	0.9
	FEMALE	**0.5**	0.4	0.7	**0.5**	0.4	0.7	**0.6**	0.4	0.8
	----------	**0.7**	0.5	0.8	**0.7**	0.6	0.9	**0.6**	0.5	0.8

L=Lower, **U**=Upper, **CL**=Confidence Limit
* All mortality rates and 95% CLs are per 100'000 inhabitants.

4.4 Characteristics of ILD cases and controls

4.4.1 Idiopathic Interstitial Pneumonia (IIP)

4.4.1.1 Idiopathic Pulmonary Fibrosis (IPF)

No direct match for the diagnostic term 'IPF' was found in the GPRD. The Read Codes used to identify the present IPF study population were 'Cryptogenic Fibrosing Alveolitis,' Idiopathic Fibrosing Alveolitis,' and 'Idiopathic Fibrosing Alveolitis NOS.' which are the diagnostic terms commonly used in the UK over the last 20-30 years. The use of these terms for IPF is discussed Section 5.0. Using these diagnostic terms, we identified 1269 incident cases of IPF between 1995 and 2009. The mean (SD) age was roughly 73 (10.2) years and 816 (64%) were male. The proportion of ex-smokers was markedly higher among IPF cases compared to controls (36.2% vs. 24.3%), and the raised odds ratio for ex-smokers vs. non-smokers was significant at the 5% level (OR=1.96, 95%CI:1.6 to 2.4). Higher frequencies of practice visits and drug prescriptions prior to index date were statistically significantly associated with a diagnosis of IPF. Further characteristics of IPF cases and their matched controls can be found in Table 4.4.1.1 below.

Table 4.4.1.1 Characteristics of IPF cases and matched controls at/prior to index date

Characteristics		Cases (n=1269) n (%)	Controls (n=1269) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Age in years [mean (sd)]		72.86(10.24)	72.85(10.23)	**----**	----	----
	Min.	29	29	**----**	----	----
	Max.	95	97	**----**	----	----
Gender	Males	816 (64.3)	816 (64.3)	**----**	----	----
	Females	453 (35.7)	453 (35.7)	**----**	----	----
BMI(kg/m2)	18.5 - 24.9 (Ref.)	351 (27.7)	364 (28.7)	**1.00**	----	----
	14.0 - 18.4	16 (1.3)	15 (1.2)	**1.16**	0.57	2.37
	25.0 - 29.9	475 (37.4)	430 (33.9)	**1.15**	0.95	1.41
	30.0 - 39.9	207 (16.3)	152 (12.0)	**1.42**	1.09	1.83
	40.0 - 55.9	6 (0.5)	12 (0.9)	**0.52**	0.19	1.41
	Unknown	214 (16.9)	296 (23.3)	**0.68**	0.53	0.87

Characteristics		Cases (n=1269) n (%)	Controls (n=1269) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Smoking status	Non-smkrs (Ref.)	533 (42.0)	627 (49.4)	**1.00**	----	----
	Curr-smkrs	195 (15.4)	191 (15.1)	**1.23**	0.96	1.57
	Ex-smkrs	459 (36.2)	308 (24.3)	**1.96**	1.60	2.40
	Unknown	82 (6.5)	143 (11.3)	**0.57**	0.41	0.80
Categories of no. of cigarettes smoked/day	0 (Ref.)	109 (8.6)	98 (7.7)	**1.00**	----	----
	1 - 10	147 (11.6)	119 (9.4)	**1.12**	0.77	1.64
	11 - 20	86 (6.8)	63 (5.0)	**1.29**	0.82	2.03
	21+	32 (2.5)	15 (1.2)	**1.88**	0.95	3.69
	Unknown	895 (70.5)	974 (76.8)	**0.82**	0.60	1.11
Last alcohol status prior to index date	None (Ref.)	191 (15.1)	236 (18.6)	**1.00**	----	----
	Current	839 (66.1)	816 (64.3)	**1.39**	1.08	1.78
	Never	214 (16.9)	198 (15.6)	**1.45**	1.08	1.96
	Ex	25 (2.0)	19 (1.5)	**1.85**	0.95	3.60
Categories of alcohol units/week (for last recording prior to index date)	0 (Ref.)	705 (55.6)	717 (56.5)	**1.00**	----	----
	1 - 7	293 (23.1)	297 (23.4)	**1.02**	0.83	1.25
	8 - 14	144 (11.3)	125 (9.9)	**1.19**	0.90	1.56
	15 - 29	87 (6.9)	82 (6.5)	**1.09**	0.78	1.54
	30+	40 (3.2)	48 (3.8)	**0.87**	0.56	1.34
Categories of avg. alcohol units/week (for all recorded alcohol units recorded prior to index date)	0 units/wk (Ref.)	596 (47.0)	635 (50.0)	**1.00**	----	----
	0.01 - 7.99	398 (31.4)	383 (30.2)	**1.15**	0.95	1.40
	8.00 - 14.99	141 (11.1)	120 (9.5)	**1.33**	0.99	1.79
	15.00 - 29.99	100 (7.9)	86 (6.8)	**1.27**	0.92	1.75
	30+	34 (2.7)	45 (3.5)	**0.85**	0.52	1.38
Categories of Hb1Ac level before index date (closest recording prior to index date)	<6.5 (Ref.)	62 (4.9)	42 (3.3)	**1.00**	----	----
	6.5 - 7.4	51 (4.0)	41 (3.2)	**0.85**	0.47	1.53
	7.5 - 8.9	30 (2.4)	30 (2.4)	**0.68**	0.36	1.29
	>=9.0	17 (1.3)	12 (0.9)	**0.95**	0.40	2.26
	Unknown	1109 (87.4)	1144 (90.1)	**0.64**	0.43	0.97
Categories of average level of Hb1Ac before index date	<6.5 (Ref.)	52 (4.1)	43 (3.4)	**1.00**	----	----
	6.5 - 7.4	39 (3.1)	34 (2.7)	**0.93**	0.50	1.73
	7.5 - 8.9	49 (3.9)	37 (2.9)	**1.06**	0.59	1.92
	>=9.0	20 (1.6)	11 (0.9)	**1.52**	0.64	3.62
	Unknown	1109 (87.4)	1144 (90.1)	**0.77**	0.50	1.19
Categories of no. of practice visits prior to the index date based on diagnoses recordings	0 - 29 (Ref.)	306 (24.1)	444 (35.0)	**1.00**	----	----
	30 - 58	345 (27.2)	337 (26.6)	**2.01**	1.57	2.58
	59 - 104	309 (24.3)	281 (22.1)	**2.55**	1.92	3.37
	105+	309 (24.3)	207 (16.3)	**4.31**	3.10	5.99
Categories of no. of practice visits prior to index date based on diagnoses and prescriptions recordings	0 - 54 (Ref.)	268 (21.1)	380 (29.9)	**1.00**	----	----
	55 - 111	322 (25.4)	332 (26.2)	**1.61**	1.26	2.04
	112 - 199	366 (28.8)	309 (24.3)	**2.20**	1.70	2.85
	200+	313 (24.7)	248 (19.5)	**2.86**	2.09	3.91

Characteristics		Cases (n=1269) n (%)	Controls (n=1269) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Categories of no. of practice visits based on diagnoses recordings (falling on separate dates) during 1 year prior to index date (index date visit excluded)	0 - 4 (Ref.)	193 (15.2)	489 (38.5)	**1.00**	----	----
	5 - 10	362 (28.5)	381 (30.0)	**3.65**	2.76	4.83
	11 - 18	377 (29.7)	244 (19.2)	**6.91**	5.09	9.38
	19+	337 (26.6)	155 (12.2)	**12.08**	8.53	17.12
Categories of no. of practice visits based on diagnoses and prescriptions recordings (falling on separate dates) during 1 year prior to index date (index date visit excluded)	0 - 9 (Ref.)	193 (15.2)	405 (31.9)	**1.00**	----	----
	10 - 18	328 (25.8)	366 (28.8)	**2.19**	1.70	2.82
	19 - 28	364 (28.7)	303 (23.9)	**3.20**	2.46	4.16
	29+	384 (30.3)	195 (15.4)	**5.85**	4.36	7.84
Categories of no. of drug prescriptions ever, prior to index date (index date excluded)	0 - 42 (Ref.)	245 (19.3)	327 (25.8)	**1.00**	----	----
	43 - 135	322 (25.4)	334 (26.3)	**1.41**	1.11	1.80
	136 - 323	358 (28.2)	340 (26.8)	**1.66**	1.29	2.12
	324+	344 (27.1)	268 (21.1)	**2.30**	1.72	3.07
Categories of no. of drug prescriptions during 1 year prior to index date (index date excluded)	0 - 7 (Ref.)	194 (15.3)	347 (27.3)	**1.00**	----	----
	8 - 24	322 (25.4)	338 (26.6)	**1.82**	1.43	2.32
	25 - 51	368 (29.0)	322 (25.4)	**2.36**	1.83	3.04
	52+	385 (30.3)	262 (20.6)	**3.31**	2.52	4.35

CL=Confidence Limit

4.4.2 Granulomatous ILD

4.4.2.1 Sarcoidosis

Three hundred and thirty incident cases of sarcoidosis were identified between 1995 and 2009. The mean (SD) age was roughly 52 (13) years and 171 (52%) were male. For those cases and controls where smoking status was available, fewer cases vs. controls were found to be either current or ex-smokers (9.7% vs. 23% and 16.7% vs. 18.8%, respectively). Higher frequencies of practice visits and drug prescriptions prior to index date were statistically significantly associated with a diagnosis of sarcoidosis. Further characteristics of sarcoidosis cases and controls can be found in Table 4.4.2.1 below.

Table 4.4.2.1 Characteristics of Sarcoidosis cases and matched controls at / prior to index date

Characteristics		Cases (n=330) n (%)	Controls (n=330) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Age in years [mean (sd)]		51.55(13.01)	51.55(13.00)	**----**	----	----
	Min.	23	23	**----**	----	----
	Max.	84	84	**----**	----	----
Gender	Males	171 (51.8)	171 (51.8)	**----**	----	----
	Females	159 (48.2)	159 (48.2)	**----**	----	----
BMI(kg/m2)	18.5 - 24.9 (Ref.)	102 (30.9)	90 (27.3)	**1.00**	----	----
	14.0 - 18.4	9 (2.7)	1 (0.3)	**7.62**	0.93	62.06
	25.0 - 29.9	95 (28.8)	90 (27.3)	**0.96**	0.63	1.46
	30.0 - 39.9	71 (21.5)	47 (14.2)	**1.37**	0.83	2.26
	40.0 - 55.9	12 (3.6)	15 (4.5)	**0.65**	0.27	1.56
	Unknown	41 (12.4)	87 (26.4)	**0.36**	0.21	0.61
Smoking status	Non-smkrs (Ref.)	218 (66.1)	154 (46.7)	**1.00**	----	----
	Curr-smkrs	32 (9.7)	76 (23.0)	**0.27**	0.16	0.45
	Ex-smkrs	55 (16.7)	62 (18.8)	**0.63**	0.41	0.97
	Unknown	25 (7.6)	38 (11.5)	**0.43**	0.24	0.77
Categories of no. of cigarettes smoked/day	0 (Ref.)	17 (5.2)	21 (6.4)	**1.00**	----	----
	1 - 10	26 (7.9)	44 (13.3)	**0.69**	0.29	1.64
	11 - 20	13 (3.9)	36 (10.9)	**0.42**	0.16	1.10
	21+	2 (0.6)	8 (2.4)	**0.33**	0.06	1.84
	Unknown	272 (82.4)	221 (67.0)	**1.45**	0.71	2.96
Last alcohol status prior to index date	None (Ref.)	53 (16.1)	70 (21.2)	**1.00**	----	----
	Current	225 (68.2)	216 (65.5)	**1.40**	0.92	2.14
	Never	48 (14.5)	38 (11.5)	**1.78**	0.97	3.26
	Ex	4 (1.2)	6 (1.8)	**0.95**	0.25	3.55
Categories of alcohol units/week (for last recording prior to index date)	0 (Ref.)	175 (53.0)	167 (50.6)	**1.00**	----	----
	1 - 7	89 (27.0)	73 (22.1)	**1.20**	0.80	1.81
	8 - 14	39 (11.8)	52 (15.8)	**0.68**	0.41	1.11
	15 - 29	11 (3.3)	25 (7.6)	**0.43**	0.21	0.90
	30+	16 (4.8)	13 (3.9)	**1.10**	0.51	2.37
Categories of avg. alcohol units/week (for all recorded alcohol units recorded prior to index date)	0 units/wk (Ref.)	157 (47.6)	156 (47.3)	**1.00**	----	----
	0.01 - 7.99	109 (33.0)	88 (26.7)	**1.28**	0.86	1.92
	8.00 - 14.99	36 (10.9)	47 (14.2)	**0.74**	0.44	1.23
	15.00 - 29.99	19 (5.8)	27 (8.2)	**0.69**	0.36	1.32
	30+	9 (2.7)	12 (3.6)	**0.71**	0.29	1.73
Categories of Hb1Ac level before index date (closest recording prior to index date)	<6.5 (Ref.)	18 (5.5)	12 (3.6)	**1.00**	----	----
	6.5 - 7.4	5 (1.5)	6 (1.8)	**0.57**	0.14	2.30
	7.5 - 8.9	6 (1.8)	3 (0.9)	**1.45**	0.30	6.91
	>=9.0	7 (2.1)	3 (0.9)	**1.63**	0.35	7.56
	Unknown	294 (89.1)	306 (92.7)	**0.61**	0.28	1.31
Categories of average level of Hb1Ac before index date	<6.5 (Ref.)	17 (5.2)	9 (2.7)	**1.00**	----	----
	6.5 - 7.4	6 (1.8)	4 (1.2)	**0.78**	0.18	3.47
	7.5 - 8.9	5 (1.5)	7 (2.1)	**0.43**	0.10	1.77
	>=9.0	8 (2.4)	4 (1.2)	**0.96**	0.22	4.23
	Unknown	294 (89.1)	306 (92.7)	**0.49**	0.21	1.16

Characteristics		Cases (n=330) n (%)	Controls (n=330) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Categories of no. of practice visits prior to the index date based on diagnoses recordings	0 - 29 (Ref.)	84 (25.5)	144 (43.6)	**1.00**	----	----
	30 - 58	102 (30.9)	98 (29.7)	**3.09**	1.88	5.08
	59 - 104	83 (25.2)	53 (16.1)	**5.96**	3.26	10.93
	105+	61 (18.5)	35 (10.6)	**8.98**	4.33	18.61
Categories of no. of practice visits prior to index date based on diagnoses and prescriptions recordings	0 - 54 (Ref.)	111 (33.6)	165 (50.0)	**1.00**	----	----
	55 - 111	115 (34.8)	86 (26.1)	**2.65**	1.70	4.12
	112 - 199	64 (19.4)	44 (13.3)	**3.60**	2.00	6.47
	200+	40 (12.1)	35 (10.6)	**3.21**	1.58	6.53
Categories of no. of practice visits based on diagnoses recordings (falling on separate dates) during 1 year prior to index date (index date visit excluded)	0 - 4 (Ref.)	46 (13.9)	176 (53.3)	**1.00**	----	----
	5 - 10	115 (34.8)	87 (26.4)	**6.61**	3.75	11.66
	11 - 18	88 (26.7)	42 (12.7)	**11.85**	6.13	22.92
	19+	81 (24.5)	25 (7.6)	**23.31**	10.84	50.13
Categories of no. of practice visits based on diagnoses and prescriptions recordings (falling on separate dates) during 1 year prior to index date (index date visit excluded)	0 - 9 (Ref.)	81 (24.5)	198 (60.0)	**1.00**	----	----
	10 - 18	115 (34.8)	63 (19.1)	**5.08**	3.15	8.17
	19 - 28	80 (24.2)	39 (11.8)	**7.99**	4.41	14.46
	29+	54 (16.4)	30 (9.1)	**8.32**	4.28	16.17
Categories of no. of drug prescriptions ever, prior to index date (index date excluded)	0 - 42 (Ref.)	127 (38.5)	171 (51.8)	**1.00**	----	----
	43 - 135	113 (34.2)	81 (24.5)	**2.08**	1.40	3.10
	136 - 323	51 (15.5)	46 (13.9)	**1.88**	1.08	3.27
	324+	39 (11.8)	32 (9.7)	**2.17**	1.15	4.11
Categories of no. of drug prescriptions during 1 year prior to index date (index date excluded)	0 - 7 (Ref.)	131 (39.7)	184 (55.8)	**1.00**	----	----
	8 - 24	110 (33.3)	77 (23.3)	**2.38**	1.56	3.62
	25 - 51	52 (15.8)	39 (11.8)	**2.33**	1.37	3.97
	52+	37 (11.2)	30 (9.1)	**2.33**	1.25	4.33

CL=Confidence Limit

4.4.2.2 Wegener's Granulomatosis

Three hundred and one incident cases of WG were identified between 1995 and 2009. The mean (SD) age was 59 (16.5) years and 142 (47%) were male. Higher frequencies of practice visits and drug prescriptions prior to index date were

statistically significantly associated with a diagnosis of WG. Further characteristics of Wegener's Granulomatosis cases and controls can be found in Table 4.4.2.1 below.

Table 4.4.2.2 Characteristics of WG cases and matched controls at / prior to index date

Characteristics		Cases (n=301) n (%)	Controls (n=301) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Age in years [mean (sd)]		58.99(16.52)	58.97(16.48)	**----**	----	----
	Min.	9	9	**----**	----	----
	Max.	92	92	**----**	----	----
Gender	Males	142 (47.2)	142 (47.2)	**----**	----	----
	Females	159 (52.8)	159 (52.8)	**----**	----	----
BMI(kg/m2)	18.5 - 24.9 (Ref.)	88 (29.2)	90 (29.9)	**1.00**	----	----
	14.0 - 18.4	5 (1.7)	1 (0.3)	**5.05**	0.58	44.19
	25.0 - 29.9	82 (27.2)	86 (28.6)	**0.96**	0.63	1.46
	30.0 - 39.9	52 (17.3)	45 (15.0)	**1.16**	0.70	1.93
	40.0 - 55.9	6 (2.0)	11 (3.7)	**0.56**	0.19	1.61
	Unknown	68 (22.6)	68 (22.6)	**1.04**	0.63	1.71
Smoking status	Non-smkrs (Ref.)	155 (51.5)	161 (53.5)	**1.00**	----	----
	Curr-smkrs	43 (14.3)	53 (17.6)	**0.79**	0.48	1.30
	Ex-smkrs	71 (23.6)	51 (16.9)	**1.49**	0.97	2.31
	Unknown	32 (10.6)	36 (12.0)	**0.79**	0.42	1.51
Categories of no. of cigarettes smoked/day	0 (Ref.)	21 (7.0)	23 (7.6)	**1.00**	----	----
	1 - 10	28 (9.3)	28 (9.3)	**1.12**	0.49	2.54
	11 - 20	23 (7.6)	24 (8.0)	**1.06**	0.45	2.46
	21+	8 (2.7)	3 (1.0)	**2.98**	0.68	12.97
	Unknown	221 (73.4)	223 (74.1)	**1.12**	0.59	2.12
Last alcohol status prior to index date	None (Ref.)	58 (19.3)	63 (20.9)	**1.00**	----	----
	Current	186 (61.8)	194 (64.5)	**1.10**	0.67	1.82
	Never	51 (16.9)	38 (12.6)	**1.59**	0.84	3.02
	Ex	6 (2.0)	6 (2.0)	**1.14**	0.30	4.35
Categories of alcohol units/week (for last recording prior to index date)	0 (Ref.)	177 (58.8)	165 (54.8)	**1.00**	----	----
	1 - 7	69 (22.9)	75 (24.9)	**0.83**	0.54	1.26
	8 - 14	25 (8.3)	33 (11.0)	**0.67**	0.37	1.21
	15 - 29	23 (7.6)	24 (8.0)	**0.86**	0.44	1.66
	30+	7 (2.3)	4 (1.3)	**1.65**	0.48	5.68
Categories of avg. alcohol units/week (for all recorded alcohol units recorded prior to index date)	0 units/wk (Ref.)	156 (51.8)	148 (49.2)	**1.00**	----	----
	0.01 - 7.99	89 (29.6)	99 (32.9)	**0.80**	0.52	1.22
	8.00 - 14.99	30 (10.0)	28 (9.3)	**0.95**	0.51	1.79
	15.00 - 29.99	20 (6.6)	24 (8.0)	**0.80**	0.41	1.57
	30+	6 (2.0)	2 (0.7)	**2.69**	0.53	13.63
Categories of Hb1Ac level before index date (closest recording prior to index date)	<6.5 (Ref.)	15 (5.0)	12 (4.0)	**1.00**	----	----
	6.5 - 7.4	2 (0.7)	6 (2.0)	**0.28**	0.05	1.62
	7.5 - 8.9	4 (1.3)	5 (1.7)	**0.63**	0.12	3.30
	>=9.0	3 (1.0)	3 (1.0)	**0.85**	0.15	4.82
	Unknown	277 (92.0)	275 (91.4)	**0.82**	0.37	1.83

Characteristics		Cases (n=301) n (%)	Controls (n=301) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Categories of average level of Hb1Ac before index date	<6.5 (Ref.)	14 (4.7)	10 (3.3)	**1.00**	----	----
	6.5 - 7.4	4 (1.3)	7 (2.3)	**0.41**	0.10	1.75
	7.5 - 8.9	4 (1.3)	5 (1.7)	**0.51**	0.10	2.50
	>=9.0	2 (0.7)	4 (1.3)	**0.36**	0.05	2.43
	Unknown	277 (92.0)	275 (91.4)	**0.73**	0.31	1.71
Categories of no. of practice visits prior to index date based on diagnoses recordings	0 - 29 (Ref.)	70 (23.3)	127 (42.2)	**1.00**	----	----
	30 - 58	81 (26.9)	72 (23.9)	**3.01**	1.75	5.18
	59 - 104	80 (26.6)	62 (20.6)	**4.29**	2.41	7.66
	105+	70 (23.3)	40 (13.3)	**8.08**	3.96	16.48
Categories of no. of practice visits prior to index date based on diagnoses and prescriptions recordings	0 - 54 (Ref.)	83 (27.6)	125 (41.5)	**1.00**	----	----
	55 - 111	84 (27.9)	78 (25.9)	**2.00**	1.24	3.21
	112 - 199	75 (24.9)	52 (17.3)	**3.14**	1.81	5.44
	200+	59 (19.6)	46 (15.3)	**3.51**	1.79	6.87
Categories of no. of practice visits based on diagnoses recordings (falling on separate dates) during 1 year prior to index date (index date visit excluded)	0 - 4 (Ref.)	32 (10.6)	146 (48.5)	**1.00**	----	----
	5 - 10	75 (24.9)	102 (33.9)	**4.04**	2.19	7.46
	11 - 18	86 (28.6)	29 (9.6)	**26.62**	11.35	62.46
	19+	108 (35.9)	24 (8.0)	**46.54**	19.04	113.7
Categories of no. of practice visits based on diagnoses and prescriptions recordings (falling on separate dates) during 1 year prior to index date (index date visit excluded)	0 - 9 (Ref.)	41 (13.6)	152 (50.5)	**1.00**	----	----
	10 - 18	86 (28.6)	83 (27.6)	**6.12**	3.18	11.79
	19 - 28	78 (25.9)	42 (14.0)	**14.89**	6.81	32.56
	29+	96 (31.9)	24 (8.0)	**48.83**	19.36	123.1
Categories of no. of drug prescriptions ever, prior to index date (index date excluded)	0 - 42 (Ref.)	83 (27.6)	122 (40.5)	**1.00**	----	----
	43 - 135	97 (32.2)	76 (25.2)	**2.38**	1.47	3.86
	136 - 323	70 (23.3)	55 (18.3)	**2.39**	1.43	4.00
	324+	51 (16.9)	48 (15.9)	**2.14**	1.14	3.99
Categories of no. of drug prescriptions during 1 year prior to index date (index date excluded)	0 - 7 (Ref.)	59 (19.6)	146 (48.5)	**1.00**	----	----
	8 - 24	103 (34.2)	70 (23.3)	**5.39**	3.09	9.40
	25 - 51	74 (24.6)	47 (15.6)	**6.55**	3.52	12.16
	52+	65 (21.6)	38 (12.6)	**7.64**	3.93	14.84

CL=Confidence Limit

4.4.3 ILD of known cause or associated with other diseases

4.4.3.1 Extrinsic Allergic Alveolitis

Four hundred and sixty-six incident cases of EAA were identified between 1995 and 2009. The mean (SD) age was 59 (14.2) years and there were equal numbers of males and females. Higher frequencies of practice visits and drug prescriptions prior to index date were statistically significantly associated with a diagnosis of EAA. Further characteristics of EAA cases and controls can be found in Table 4.4.3.1 below.

Table 4.4.3.1 Characteristics of EAA cases and matched controls at / prior to index date

Characteristics		Cases (n=466) n (%)	Controls (n=466) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Age in years [mean (sd)]		59.18(14.26)	59.16(14.25)	**----**	----	----
	Min.	13	13	**----**	----	----
	Max.	90	90	**----**	----	----
Gender	Males	233 (50.0)	233 (50.0)	**----**	----	----
	Females	233 (50.0)	233 (50.0)	**----**	----	----
BMI(kg/m2)	18.5 - 24.9 (Ref.)	136 (29.2)	115 (24.7)	**1.00**	----	----
	14.0 - 18.4	10 (2.1)	3 (0.6)	**2.92**	0.79	10.78
	25.0 - 29.9	156 (33.5)	161 (34.5)	**0.82**	0.57	1.16
	30.0 - 39.9	92 (19.7)	83 (17.8)	**0.91**	0.62	1.34
	40.0 - 55.9	1 (0.2)	7 (1.5)	**0.13**	0.02	1.10
	Unknown	71 (15.2)	97 (20.8)	**0.55**	0.36	0.86
Smoking status	Non-smkrs (Ref.)	251 (53.9)	240 (51.5)	**1.00**	----	----
	Curr-smkrs	64 (13.7)	86 (18.5)	**0.71**	0.49	1.04
	Ex-smkrs	121 (26.0)	98 (21.0)	**1.24**	0.87	1.75
	Unknown	30 (6.4)	42 (9.0)	**0.60**	0.34	1.07
Categories of no. of cigarettes smoked/day	0 (Ref.)	27 (5.8)	37 (7.9)	**1.00**	----	----
	1 - 10	26 (5.6)	45 (9.7)	**0.82**	0.41	1.65
	11 - 20	42 (9.0)	36 (7.7)	**1.61**	0.83	3.12
	21+	12 (2.6)	7 (1.5)	**2.27**	0.78	6.60
	Unknown	359 (77.0)	341 (73.2)	**1.46**	0.86	2.49
Last alcohol status prior to index date	None (Ref.)	77 (16.5)	88 (18.9)	**1.00**	----	----
	Current	313 (67.2)	305 (65.5)	**1.20**	0.82	1.75
	Never	74 (15.9)	65 (13.9)	**1.34**	0.81	2.21
	Ex	2 (0.4)	8 (1.7)	**0.31**	0.06	1.53
Categories of alcohol units/week (for last recording prior to index date)	0 (Ref.)	248 (53.2)	249 (53.4)	**1.00**	----	----
	1 - 7	139 (29.8)	115 (24.7)	**1.25**	0.90	1.75
	8 - 14	46 (9.9)	53 (11.4)	**0.85**	0.55	1.32
	15 - 29	24 (5.2)	35 (7.5)	**0.68**	0.38	1.20
	30+	9 (1.9)	14 (3.0)	**0.67**	0.29	1.56

Characteristics		Cases (n=466) n (%)	Controls (n=466) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Categories of avg. alcohol units/week (for all recorded alcohol units recorded prior to index date)	0 units/wk (Ref.)	218 (46.8)	216 (46.4)	**1.00**	----	----
	0.01 - 7.99	164 (35.2)	143 (30.7)	**1.14**	0.84	1.56
	8.00 - 14.99	47 (10.1)	58 (12.4)	**0.78**	0.50	1.22
	15.00 - 29.99	29 (6.2)	36 (7.7)	**0.77**	0.44	1.33
	30+	8 (1.7)	13 (2.8)	**0.62**	0.25	1.52
Categories of Hb1Ac level before index date (closest recording prior to index date)	<6.5 (Ref.)	20 (4.3)	17 (3.6)	**1.00**	----	----
	6.5 - 7.4	11 (2.4)	6 (1.3)	**1.67**	0.47	5.96
	7.5 - 8.9	8 (1.7)	2 (0.4)	**3.33**	0.61	18.14
	>=9.0	6 (1.3)	6 (1.3)	**0.85**	0.23	3.09
	Unknown	421 (90.3)	435 (93.3)	**0.83**	0.42	1.65
Categories of average level of Hb1Ac before index date	<6.5 (Ref.)	17 (3.6)	20 (4.3)	**1.00**	----	----
	6.5 - 7.4	12 (2.6)	4 (0.9)	**3.79**	0.99	14.46
	7.5 - 8.9	8 (1.7)	5 (1.1)	**2.13**	0.56	8.10
	>=9.0	7 (1.5)	3 (0.6)	**2.83**	0.62	13.04
	Unknown	422 (90.6)	434 (93.1)	**1.21**	0.60	2.46
Categories of no. of practice visits prior to the index date based on diagnoses recordings	0 - 29 (Ref.)	136 (29.2)	182 (39.1)	**1.00**	----	----
	30 - 58	105 (22.5)	131 (28.1)	**1.35**	0.93	1.97
	59 - 104	114 (24.5)	95 (20.4)	**2.55**	1.65	3.94
	105+	111 (23.8)	58 (12.4)	**5.58**	3.20	9.72
Categories of no. of practice visits prior to index date based on diagnoses and prescriptions recordings	0 - 54 (Ref.)	153 (32.8)	192 (41.2)	**1.00**	----	----
	55 - 111	110 (23.6)	129 (27.7)	**1.26**	0.87	1.83
	112 - 199	105 (22.5)	87 (18.7)	**2.45**	1.54	3.90
	200+	98 (21.0)	58 (12.4)	**4.32**	2.47	7.56
Categories of no. of practice visits based on diagnoses recordings (falling on separate dates) during 1 year prior to index date (index date visit excluded)	0 - 4 (Ref.)	77 (16.5)	222 (47.6)	**1.00**	----	----
	5 - 10	137 (29.4)	138 (29.6)	**5.22**	3.19	8.55
	11 - 18	131 (28.1)	71 (15.2)	**10.16**	5.86	17.62
	19+	121 (26.0)	35 (7.5)	**25.02**	12.92	48.45
Categories of no. of practice visits based on diagnoses and prescriptions recordings (falling on separate dates) during 1 year prior to index date (index date visit excluded)	0 - 9 (Ref.)	105 (22.5)	236 (50.6)	**1.00**	----	----
	10 - 18	135 (29.0)	111 (23.8)	**3.67**	2.43	5.55
	19 - 28	103 (22.1)	79 (17.0)	**4.73**	2.95	7.58
	29+	123 (26.4)	40 (8.6)	**10.52**	6.24	17.76
Categories of no. of drug prescriptions ever, prior to index date (index date excluded)	0 - 42 (Ref.)	149 (32.0)	186 (39.9)	**1.00**	----	----
	43 - 135	123 (26.4)	135 (29.0)	**1.31**	0.92	1.87
	136 - 323	94 (20.2)	82 (17.6)	**1.89**	1.21	2.95
	324+	100 (21.5)	63 (13.5)	**2.80**	1.74	4.51

Characteristics		Cases (n=466) n (%)	Controls (n=466) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Categories of no. of drug prescriptions during 1 year prior to index date (index date excluded)	0 - 7 (Ref.)	125 (26.8)	219 (47.0)	**1.00**	----	----
	8 - 24	137 (29.4)	105 (22.5)	**2.83**	1.93	4.15
	25 - 51	101 (21.7)	85 (18.2)	**2.60**	1.73	3.90
	52+	103 (22.1)	57 (12.2)	**4.45**	2.79	7.08

CL=Confidence Limit

4.4.3.2 Pneumoconioses

Two thousand four hundred and eighteen incident pneumoconiosis cases were identified between 1995 and 2009. The mean (SD) age was 68 (12.5) years and 2191 (90%) were male. The proportion of current and ex-smokers was higher among Pneumoconiosis cases compared to controls (20.9% vs. 17.9% and 40.6% vs. 31.9%, respectively), and the raised odds ratios for current (OR=1.48, 95%CI:1.3 to 1.8) and ex-smokers (OR=1.71, 95%CI:1.5 to 2.0) vs. non-smokers were significant at the 5% level. Higher frequencies of practice visits and drug prescriptions prior to index date were statistically significantly associated with a diagnosis of Pneumoconiosis. Further characteristics of Pneumoconiosis cases and their matched controls can be found in Table 4.4.3.2 below.

Table 4.4.3.2 Characteristics of Pneumoconioses cases and matched controls at / prior to index date

Characteristics		Cases (n=2418) n (%)	Controls (n=2418) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Age in years [mean (sd)]		67.90(12.54)	67.88(12.53)	**----**	----	----
	Min.	4	4	**----**	----	----
	Max.	96	94	**----**	----	----
Gender	Males	2191 (90.6)	2191 (90.6)	**----**	----	----
	Females	227 (9.4)	227 (9.4)	**----**	----	----
BMI(kg/m2)	18.5 - 24.9 (Ref.)	672 (27.8)	676 (28.0)	**1.00**	----	----
	14.0 - 18.4	40 (1.7)	33 (1.4)	**1.20**	0.75	1.91
	25.0 - 29.9	940 (38.9)	847 (35.0)	**1.12**	0.97	1.29
	30.0 - 39.9	352 (14.6)	385 (15.9)	**0.92**	0.77	1.11
	40.0 - 55.9	25 (1.0)	12 (0.5)	**2.05**	1.02	4.11
	Unknown	389 (16.1)	465 (19.2)	**0.80**	0.66	0.96

Characteristics		Cases (n=2418) n (%)	Controls (n=2418) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Smoking status	Non-smkrs (Ref.)	785 (32.5)	998 (41.3)	**1.00**	----	----
	Curr-smkrs	505 (20.9)	434 (17.9)	**1.48**	1.26	1.75
	Ex-smkrs	982 (40.6)	772 (31.9)	**1.71**	1.49	1.97
	Unknown	146 (6.0)	214 (8.9)	**0.76**	0.59	0.99
Categories of no. of cigarettes smoked/day	0 (Ref.)	274 (11.3)	224 (9.3)	**1.00**	----	----
	1 - 10	339 (14.0)	239 (9.9)	**1.18**	0.92	1.51
	11 - 20	213 (8.8)	174 (7.2)	**1.01**	0.76	1.33
	21+	56 (2.3)	54 (2.2)	**0.89**	0.58	1.37
	Unknown	1536 (63.5)	1727 (71.4)	**0.71**	0.59	0.87
Last alcohol status prior to index date	None (Ref.)	331 (13.7)	411 (17.0)	**1.00**	----	----
	Current	1733 (71.7)	1685 (69.7)	**1.37**	1.15	1.65
	Never	282 (11.7)	267 (11.0)	**1.39**	1.10	1.76
	Ex	72 (3.0)	55 (2.3)	**1.77**	1.20	2.62
Categories of alcohol units/week (for last recording prior to index date)	0 (Ref.)	1147 (47.4)	1167 (48.3)	**1.00**	----	----
	1 - 7	546 (22.6)	594 (24.6)	**0.94**	0.81	1.10
	8 - 14	334 (13.8)	283 (11.7)	**1.21**	1.01	1.46
	15 - 29	250 (10.3)	246 (10.2)	**1.04**	0.85	1.27
	30+	141 (5.8)	128 (5.3)	**1.13**	0.87	1.47
Categories of avg. alcohol units/week (for all recorded alcohol units recorded prior to index date)	0 units/wk (Ref.)	913 (37.8)	946 (39.1)	**1.00**	----	----
	0.01 - 7.99	744 (30.8)	776 (32.1)	**1.01**	0.87	1.17
	8.00 - 14.99	326 (13.5)	313 (12.9)	**1.10**	0.91	1.34
	15.00 - 29.99	298 (12.3)	266 (11.0)	**1.19**	0.97	1.45
	30+	137 (5.7)	117 (4.8)	**1.24**	0.95	1.62
Categories of Hb1Ac level before index date (closest recording prior to index date)	<6.5 (Ref.)	129 (5.3)	119 (4.9)	**1.00**	----	----
	6.5 - 7.4	84 (3.5)	98 (4.1)	**0.79**	0.54	1.16
	7.5 - 8.9	53 (2.2)	50 (2.1)	**0.99**	0.63	1.56
	>=9.0	25 (1.0)	23 (1.0)	**1.01**	0.55	1.87
	Unknown	2127 (88.0)	2128 (88.0)	**0.92**	0.71	1.20
Categories of average level of Hb1Ac before index date	<6.5 (Ref.)	112 (4.6)	111 (4.6)	**1.00**	----	----
	6.5 - 7.4	84 (3.5)	83 (3.4)	**1.00**	0.68	1.49
	7.5 - 8.9	72 (3.0)	75 (3.1)	**0.95**	0.62	1.45
	>=9.0	23 (1.0)	22 (0.9)	**1.03**	0.54	1.96
	Unknown	2127 (88.0)	2127 (88.0)	**0.99**	0.75	1.31
Categories of no. of practice visits prior to the index date based on diagnoses recordings	0 - 29 (Ref.)	552 (22.8)	801 (33.1)	**1.00**	----	----
	30 - 58	620 (25.6)	628 (26.0)	**1.82**	1.52	2.17
	59 - 104	652 (27.0)	557 (23.0)	**2.63**	2.15	3.22
	105+	594 (24.6)	432 (17.9)	**3.59**	2.86	4.52
Categories of no. of practice visits prior to index date based on diagnoses and prescriptions recordings	0 - 54 (Ref.)	564 (23.3)	752 (31.1)	**1.00**	----	----
	55 - 111	620 (25.6)	609 (25.2)	**1.52**	1.28	1.80
	112 - 199	644 (26.6)	559 (23.1)	**1.97**	1.63	2.38
	200+	590 (24.4)	498 (20.6)	**2.23**	1.80	2.76

Characteristics		Cases (n=2418) n (%)	Controls (n=2418) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Categories of no. of practice visits based on diagnoses recordings (falling on separate dates) during 1 year prior to index date (index date visit excluded)	0 - 4 (Ref.)	410 (17.0)	931 (38.5)	**1.00**	----	----
	5 - 10	719 (29.7)	722 (29.9)	**2.86**	2.39	3.43
	11 - 18	693 (28.7)	470 (19.4)	**4.65**	3.81	5.68
	19+	596 (24.6)	295 (12.2)	**7.43**	5.91	9.34
Categories of no. of practice visits based on diagnoses and prescriptions recordings (falling on separate dates) during 1 year prior to index date (index date visit excluded)	0 - 9 (Ref.)	464 (19.2)	847 (35.0)	**1.00**	----	----
	10 - 18	658 (27.2)	686 (28.4)	**2.06**	1.73	2.45
	19 - 28	650 (26.9)	501 (20.7)	**3.14**	2.60	3.80
	29+	646 (26.7)	384 (15.9)	**4.36**	3.55	5.35
Categories of no. of drug prescriptions ever, prior to index date (index date excluded)	0 - 42 (Ref.)	553 (22.9)	720 (29.8)	**1.00**	----	----
	43 - 135	624 (25.8)	611 (25.3)	**1.47**	1.24	1.74
	136 - 323	652 (27.0)	558 (23.1)	**1.81**	1.50	2.17
	324+	589 (24.4)	529 (21.9)	**1.82**	1.48	2.22
Categories of no. of drug prescriptions during 1 year prior to index date (index date excluded)	0 - 7 (Ref.)	526 (21.8)	784 (32.4)	**1.00**	----	----
	8 - 24	609 (25.2)	598 (24.7)	**1.65**	1.40	1.95
	25 - 51	636 (26.3)	535 (22.1)	**2.11**	1.76	2.52
	52+	647 (26.8)	501 (20.7)	**2.41**	2.00	2.92

CL=Confidence Limit

4.4.3.3 Drug-/radiation-induced ILD (DRAD-ILD)

One hundred and forty-five incident cases of drug/radiation-induced ILD were identified between 1995 and 2009. The mean (SD) age was 67 (12) years and 80 (55%) were female. Higher frequencies of practice visits and drug prescriptions prior to index date were statistically significantly associated with a diagnosis of drug/radiation-induced ILD. Further characteristics of cases and matched controls can be found in Table 4.4.3.3 below.

Table 4.4.3.3 Characteristics of DRAD-ILD cases and matched controls at / prior to index date

Characteristics		Cases (n=145) n (%)	Controls (n=145) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Age in years [mean (sd)]		66.86(12.01)	66.88(12.04)	**----**	----	----
	Min.	20	20	**----**	----	----
	Max.	87	87	**----**	----	----
Gender	Males	65 (44.8)	65 (44.8)	**----**	----	----
	Females	80 (55.2)	80 (55.2)	**----**	----	----
BMI(kg/m2)	18.5 - 24.9 (Ref.)	51 (35.2)	45 (31.0)	**1.00**	----	----
	14.0 - 18.4	2 (1.4)	3 (2.1)	**0.49**	0.08	3.14
	25.0 - 29.9	49 (33.8)	41 (28.3)	**1.13**	0.61	2.11
	30.0 - 39.9	24 (16.6)	23 (15.9)	**0.82**	0.39	1.73
	40.0 - 55.9	0 (0.0)	3 (2.1)	**0.00**	0.00	----
	Unknown	19 (13.1)	30 (20.7)	**0.49**	0.22	1.07
Smoking status	Non-smkrs (Ref.)	59 (40.7)	74 (51.0)	**1.00**	----	----
	Curr-smkrs	25 (17.2)	27 (18.6)	**1.18**	0.56	2.52
	Ex-smkrs	55 (37.9)	31 (21.4)	**2.19**	1.23	3.89
	Unknown	6 (4.1)	13 (9.0)	**0.38**	0.10	1.45
Categories of no. of cigarettes smoked/day	0 (Ref.)	13 (9.0)	14 (9.7)	**1.00**	----	----
	1 - 10	26 (17.9)	14 (9.7)	**2.03**	0.75	5.48
	11 - 20	16 (11.0)	9 (6.2)	**1.81**	0.61	5.43
	21+	3 (2.1)	3 (2.1)	**1.11**	0.19	6.51
	Unknown	87 (60.0)	105 (72.4)	**0.77**	0.33	1.78
Last alcohol status prior to index date	None (Ref.)	17 (11.7)	23 (15.9)	**1.00**	----	----
	Current	99 (68.3)	91 (62.8)	**1.70**	0.73	3.95
	Never	27 (18.6)	25 (17.2)	**1.57**	0.60	4.08
	Ex	2 (1.4)	6 (4.1)	**0.54**	0.09	3.32
Categories of alcohol units/week (for last recording prior to index date)	0 (Ref.)	86 (59.3)	86 (59.3)	**1.00**	----	----
	1 - 7	28 (19.3)	28 (19.3)	**0.96**	0.49	1.88
	8 - 14	20 (13.8)	18 (12.4)	**1.17**	0.55	2.47
	15 - 29	6 (4.1)	12 (8.3)	**0.46**	0.15	1.37
	30+	5 (3.4)	1 (0.7)	**5.24**	0.60	45.94
Categories of avg. alcohol units/week (for all recorded alcohol units recorded prior to index date)	0 units/wk (Ref.)	70 (48.3)	67 (46.2)	**1.00**	----	----
	0.01 - 7.99	43 (29.7)	48 (33.1)	**0.82**	0.44	1.53
	8.00 - 14.99	19 (13.1)	18 (12.4)	**0.97**	0.46	2.04
	15.00 - 29.99	8 (5.5)	10 (6.9)	**0.80**	0.29	2.22
	30+	5 (3.4)	2 (1.4)	**2.21**	0.40	12.04
Categories of Hb1Ac level before index date (closest recording prior to index date)	<6.5 (Ref.)	6 (4.1)	8 (5.5)	**1.00**	----	----
	6.5 - 7.4	5 (3.4)	5 (3.4)	**1.41**	0.29	6.85
	7.5 - 8.9	5 (3.4)	5 (3.4)	**1.29**	0.24	6.89
	>=9.0	5 (3.4)	2 (1.4)	**3.35**	0.47	23.70
	Unknown	124 (85.5)	125 (86.2)	**1.33**	0.46	3.87
Categories of average level of Hb1Ac before index date	<6.5 (Ref.)	5 (3.4)	8 (5.5)	**1.00**	----	----
	6.5 - 7.4	5 (3.4)	5 (3.4)	**1.51**	0.25	9.08
	7.5 - 8.9	8 (5.5)	4 (2.8)	**2.60**	0.58	11.66
	>=9.0	3 (2.1)	3 (2.1)	**1.40**	0.19	10.06
	Unknown	124 (85.5)	125 (86.2)	**1.40**	0.44	4.43

Characteristics		Cases (n=145) n (%)	Controls (n=145) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Categories of no. of practice visits prior to the index date based on diagnoses recordings	0 - 29 (Ref.)	18 (12.4)	43 (29.7)	**1.00**	----	----
	30 - 58	31 (21.4)	37 (25.5)	**7.99**	1.81	35.34
	59 - 104	38 (26.2)	25 (17.2)	**19.02**	4.07	88.89
	105+	58 (40.0)	40 (27.6)	**38.28**	7.26	201.9
Categories of no. of practice visits prior to index date based on diagnoses and prescriptions recordings	0 - 54 (Ref.)	21 (14.5)	45 (31.0)	**1.00**	----	----
	55 - 111	33 (22.8)	33 (22.8)	**3.44**	1.36	8.67
	112 - 199	40 (27.6)	34 (23.4)	**7.02**	2.45	20.17
	200+	51 (35.2)	33 (22.8)	**16.35**	4.73	56.54
Categories of no. of practice visits based on diagnoses recordings (falling on separate dates) during 1 year prior to index date (index date visit excluded)	0 - 4 (Ref.)	10 (6.9)	49 (33.8)	**1.00**	----	----
	5 - 10	22 (15.2)	42 (29.0)	**7.12**	1.60	31.71
	11 - 18	32 (22.1)	29 (20.0)	**19.01**	3.95	91.60
	19+	81 (55.9)	25 (17.2)	**84.37**	16.20	439.4
Categories of no. of practice visits based on diagnoses and prescriptions recordings (falling on separate dates) during 1 year prior to index date (index date visit excluded)	0 - 9 (Ref.)	11 (7.6)	54 (37.2)	**1.00**	----	----
	10 - 18	22 (15.2)	32 (22.1)	**5.38**	1.70	16.99
	19 - 28	38 (26.2)	36 (24.8)	**9.76**	3.21	29.71
	29+	74 (51.0)	23 (15.9)	**46.82**	13.18	166.3
Categories of no. of drug prescriptions ever, prior to index date (index date excluded)	0 - 42 (Ref.)	23 (15.9)	46 (31.7)	**1.00**	----	----
	43 - 135	37 (25.5)	37 (25.5)	**2.57**	1.22	5.43
	136 - 323	45 (31.0)	26 (17.9)	**5.32**	2.23	12.70
	324+	40 (27.6)	36 (24.8)	**3.91**	1.52	10.05
Categories of no. of drug prescriptions during 1 year prior to index date (index date excluded)	0 - 7 (Ref.)	13 (9.0)	52 (35.9)	**1.00**	----	----
	8 - 24	38 (26.2)	35 (24.1)	**15.60**	3.57	68.23
	25 - 51	45 (31.0)	28 (19.3)	**21.59**	4.95	94.15
	52+	49 (33.8)	30 (20.7)	**27.55**	6.11	124.1

CL=Confidence Limit

4.4.3.4 ILD associated with other diseases (ILD-ODIS)

Five hundred and sixty incident cases of ILD associated with other diseases were identified between 1995 and 2009. The mean (SD) age was 68 (12.6) years and 283 (50.5%) were female. For those cases and controls where smoking status was available, the proportion of ex-smokers among cases was higher than in the control

group (25% vs. 19%, respectively). The elevated odds ratio of ex- vs. non-smokers (OR=1.7, 95%CI:1.2 to 2.4) was significant at the 5% level. Higher frequencies of practice visits and drug prescriptions prior to index date were statistically significantly associated with a diagnosis of ILD associated with other diseases. Further characteristics of cases and controls can be found in Table 4.4.3.4 below.

Table 4.4.3.4 Characteristics of ILD-ODIS cases and matched controls at / prior to index date

Characteristics		Cases (n=560) n (%)	Controls (n=560) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Age in years [mean (sd)]		68.02(12.58)	68.02(12.56)	**----**	----	----
	Min.	12	12	**----**	----	----
	Max.	96	97	**----**	----	----
Gender	Males	277 (49.5)	277 (49.5)	**----**	----	----
	Females	283 (50.5)	283 (50.5)	**----**	----	----
BMI(kg/m2)	18.5 - 24.9 (Ref.)	198 (35.4)	186 (33.2)	**1.00**	----	----
	14.0 - 18.4	18 (3.2)	9 (1.6)	**1.87**	0.83	4.21
	25.0 - 29.9	166 (29.6)	163 (29.1)	**0.96**	0.72	1.27
	30.0 - 39.9	59 (10.5)	77 (13.8)	**0.73**	0.50	1.07
	40.0 - 55.9	4 (0.7)	7 (1.3)	**0.52**	0.13	2.12
	Unknown	115 (20.5)	118 (21.1)	**0.92**	0.64	1.30
Smoking status	Non-smkrs (Ref.)	251 (44.8)	285 (50.9)	**1.00**	----	----
	Curr-smkrs	108 (19.3)	106 (18.9)	**1.19**	0.85	1.68
	Ex-smkrs	140 (25.0)	104 (18.6)	**1.67**	1.19	2.35
	Unknown	61 (10.9)	65 (11.6)	**1.06**	0.69	1.64
Categories of no. of cigarettes smoked/day	0 (Ref.)	47 (8.4)	47 (8.4)	**1.00**	----	----
	1 - 10	63 (11.3)	49 (8.8)	**1.24**	0.71	2.18
	11 - 20	51 (9.1)	34 (6.1)	**1.43**	0.79	2.57
	21+	8 (1.4)	10 (1.8)	**0.83**	0.30	2.34
	Unknown	391 (69.8)	420 (75.0)	**0.90**	0.57	1.41
Last alcohol status prior to index date	None (Ref.)	99 (17.7)	107 (19.1)	**1.00**	----	----
	Current	334 (59.6)	340 (60.7)	**1.08**	0.77	1.52
	Never	120 (21.4)	105 (18.8)	**1.28**	0.85	1.93
	Ex	7 (1.3)	8 (1.4)	**0.95**	0.33	2.76
Categories of alcohol units/week (for last recording prior to index date)	0 (Ref.)	334 (59.6)	321 (57.3)	**1.00**	----	----
	1 - 7	126 (22.5)	142 (25.4)	**0.85**	0.64	1.13
	8 - 14	45 (8.0)	43 (7.7)	**1.00**	0.64	1.56
	15 - 29	39 (7.0)	40 (7.1)	**0.94**	0.58	1.52
	30+	16 (2.9)	14 (2.5)	**1.09**	0.53	2.27
Categories of avg. alcohol units/week (for all recorded alcohol units recorded prior to index date)	0 units/wk (Ref.)	299 (53.4)	282 (50.4)	**1.00**	----	----
	0.01 - 7.99	160 (28.6)	177 (31.6)	**0.84**	0.63	1.11
	8.00 - 14.99	48 (8.6)	48 (8.6)	**0.92**	0.59	1.45
	15.00 - 29.99	36 (6.4)	36 (6.4)	**0.92**	0.55	1.54
	30+	17 (3.0)	17 (3.0)	**0.94**	0.47	1.87

Characteristics		Cases (n=560) n (%)	Controls (n=560) n (%)	Univar. Odds Ratio	Lower 95% CL	Upper 95% CL
Categories of Hb1Ac level before index date (closest recording prior to index date)	<6.5 (Ref.)	18 (3.2)	16 (2.9)	**1.00**	----	----
	6.5 - 7.4	13 (2.3)	13 (2.3)	**0.89**	0.33	2.43
	7.5 - 8.9	8 (1.4)	14 (2.5)	**0.50**	0.17	1.53
	>=9.0	7 (1.3)	7 (1.3)	**0.85**	0.24	2.99
	Unknown	514 (91.8)	510 (91.1)	**0.88**	0.44	1.77
Categories of average level of Hb1Ac before index date	<6.5 (Ref.)	18 (3.2)	17 (3.0)	**1.00**	----	----
	6.5 - 7.4	11 (2.0)	10 (1.8)	**1.02**	0.35	2.94
	7.5 - 8.9	12 (2.1)	16 (2.9)	**0.70**	0.25	1.94
	>=9.0	5 (0.9)	7 (1.3)	**0.67**	0.18	2.56
	Unknown	514 (91.8)	510 (91.1)	**0.94**	0.47	1.86
Categories of no. of practice visits prior to the index date based on diagnoses recordings	0 - 29 (Ref.)	109 (19.5)	206 (36.8)	**1.00**	----	----
	30 - 58	147 (26.3)	170 (30.4)	**2.93**	1.93	4.46
	59 - 104	146 (26.1)	100 (17.9)	**6.35**	3.89	10.39
	105+	158 (28.2)	84 (15.0)	**12.68**	7.16	22.46
Categories of no. of practice visits prior to index date based on diagnoses and prescriptions recordings	0 - 54 (Ref.)	80 (14.3)	183 (32.7)	**1.00**	----	----
	55 - 111	162 (28.9)	166 (29.6)	**3.27**	2.16	4.95
	112 - 199	164 (29.3)	137 (24.5)	**4.81**	3.06	7.57
	200+	154 (27.5)	74 (13.2)	**12.98**	7.40	22.78
Categories of no. of practice visits based on diagnoses recordings (falling on separate dates) during 1 year prior to index date (index date visit excluded)	0 - 4 (Ref.)	84 (15.0)	223 (39.8)	**1.00**	----	----
	5 - 10	121 (21.6)	164 (29.3)	**2.68**	1.77	4.04
	11 - 18	170 (30.4)	105 (18.8)	**7.92**	4.93	12.71
	19+	185 (33.0)	68 (12.1)	**19.91**	11.34	34.94
Categories of no. of practice visits based on diagnoses and prescriptions recordings (falling on separate dates) during 1 year prior to index date (index date visit excluded)	0 - 9 (Ref.)	52 (9.3)	209 (37.3)	**1.00**	----	----
	10 - 18	122 (21.8)	170 (30.4)	**3.72**	2.32	5.96
	19 - 28	174 (31.1)	95 (17.0)	**12.13**	7.19	20.47
	29+	212 (37.9)	86 (15.4)	**18.95**	10.99	32.68
Categories of no. of drug prescriptions ever, prior to index date (index date excluded)	0 - 42 (Ref.)	70 (12.5)	170 (30.4)	**1.00**	----	----
	43 - 135	141 (25.2)	161 (28.8)	**2.84**	1.87	4.32
	136 - 323	169 (30.2)	142 (25.4)	**4.62**	2.95	7.23
	324+	180 (32.1)	87 (15.5)	**9.60**	5.82	15.84
Categories of no. of drug prescriptions during 1 year prior to index date (index date excluded)	0 - 7 (Ref.)	60 (10.7)	182 (32.5)	**1.00**	----	----
	8 - 24	108 (19.3)	156 (27.9)	**2.44**	1.60	3.74
	25 - 51	173 (30.9)	125 (22.3)	**5.69**	3.63	8.91
	52+	219 (39.1)	97 (17.3)	**10.26**	6.39	16.46

CL=Confidence Limit

4.5 All-cause mortality and comorbidity after index date

4.5.1 Idiopathic Interstitial Pneumonia (IIP)

4.5.1.1 Idiopathic Pulmonary Fibrosis (IPF)

During the follow-up period 755 (60%) IPF and 315 (25%) non-IPF subjects died. When investigating all-cause mortality as the outcome of interest, the mean (SD) survival time in the IPF cohort was 3.1 (3.0) years versus 5.3 (3.5) years in the control group. The crude rate for all-cause mortality in the IPF cohort was more than 5 times higher than the crude rate in the control group (RR 5.3 95%CI: 4.4 to 6.4). Furthermore, no decrease in this rate ratio was observed when simultaneously adjusting for smoking status, body mass index, and alcohol consumption status (RR 5.5 95%CI:4.5 to 6.8). Similar analyses for non-incident outcomes such as pneumonia and respiratory (non-pneumonia) infections yielded elevated, adjusted rate ratios for IPF vs. non-IPF subjects (RR 4.8, 95%CI:3.0 to 7.8, RR 2.3, 95%CI:1.9 to 2.7, respectively). Likewise, elevated rate ratios were observed for several incident cardiovascular outcomes such as congestive heart failure, ischemic heart disease, myocardial infarction, deep vein thrombosis and pulmonary embolism. Further details of these analyses can be found in tables 4.5.1.1a-c below.

Table 4.5.1.1a IPF: Results of proportional hazards regression analyses for mortality and selected, non-incident comorbidities after index date

IPF	IPF (n=1269)	Non-IPF (n=1269)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
All-cause mortality								
Failures [n (%)]	755 (59.5)	315 (24.8)						
Surv. time in yrs [mean (sd)]	3.1 (3.0)	5.3 (3.5)						
IPF vs. Non-IPF			**5.34**	4.40	6.47	**5.51**	4.49	6.77

IPF	IPF (n=1269)	Non-IPF (n=1269)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**1.51**	0.65	3.55	**2.20**	0.72	6.77
		25.0 - 29.9	**0.88**	0.68	1.13	**0.81**	0.57	1.15
		30.0 - 39.9	**1.30**	0.93	1.82	**1.32**	0.82	2.12
		40.0 - 55.9	**1.47**	0.35	6.24	**7.30**	1.57	34.09
		Unknown	**0.71**	0.52	0.97	**1.00**	0.61	1.63
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.41**	1.02	1.94	**1.52**	0.97	2.37
		Ex-smkrs	**1.95**	1.50	2.54	**1.57**	1.10	2.24
		Unknown	**0.69**	0.46	1.05	**0.80**	0.40	1.63
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.18**	0.86	1.61	**0.68**	0.39	1.18
		Never	**1.35**	0.92	1.97	**0.89**	0.48	1.67
		Ex	**1.11**	0.49	2.50	**0.66**	0.20	2.20
Pneumonia								
Failures [n (%)]	140 (11.0)	68 (5.4)						
Surv. time in yrs [mean (sd)]	3.0 (2.9)	5.2 (3.4)						
IPF vs. Non-IPF			**4.65**	3.05	7.11	**4.84**	3.02	7.76
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**3.90**	0.42	35.99	**2.51**	0.16	38.57
		25.0 - 29.9	**1.22**	0.68	2.19	**1.55**	0.72	3.35
		30.0 - 39.9	**0.58**	0.25	1.32	**0.94**	0.31	2.87
		40.0 - 55.9	**2.29**	0.20	26.16	**4.90**	0.26	92.48
		Unknown	**0.84**	0.40	1.76	**1.70**	0.50	5.77
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.32**	0.62	2.82	**1.09**	0.36	3.28
		Ex-smkrs	**1.44**	0.82	2.54	**1.33**	0.62	2.81
		Unknown	**0.86**	0.35	2.10	**0.80**	0.18	3.53
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.50**	0.24	1.06	**0.56**	0.16	1.88
		Never	**0.64**	0.27	1.52	**0.70**	0.19	2.63
		Ex	**1.62**	0.14	18.49	**1.39**	0.05	40.11
Respiratory (non-pneumonia) infections								
Failures [n (%)]	634 (50.0)	534 (42.1)						
Surv. time in yrs [mean (sd)]	1.3 (1.9)	3.6 (3.1)						
IPF vs. Non-IPF			**2.33**	1.98	2.75	**2.26**	1.91	2.67
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**1.62**	0.45	5.85	**1.76**	0.43	7.19
		25.0 - 29.9	**1.21**	0.93	1.57	**1.10**	0.82	1.47
		30.0 - 39.9	**1.55**	1.09	2.21	**1.44**	0.98	2.13
		40.0 - 55.9	**1.69**	0.55	5.24	**2.25**	0.65	7.80
		Unknown	**0.80**	0.58	1.12	**1.04**	0.69	1.58

IPF	IPF (n=1269)	Non-IPF (n=1269)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.97**	0.71	1.33	**0.91**	0.64	1.28
		Ex-smkrs	**1.59**	1.21	2.10	**1.34**	0.99	1.82
		Unknown	**0.61**	0.39	0.95	**0.65**	0.36	1.19
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.17**	0.84	1.64	**0.86**	0.54	1.37
		Never	**1.18**	0.79	1.75	**0.78**	0.46	1.32
		Ex	**3.21**	1.11	9.26	**1.99**	0.61	6.52
Pneumothorax								
Failures [n (%)]	10 (0.79)	5 (0.39)						
Surv. time in yrs [mean (sd)]	3.1 (3.0)	5.3 (3.5)						
IPF vs. Non-IPF			**2.3**	0.7	7.3	**2.00**	0.18	22.06
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**0.43**	0.03	6.21	**.**	.	.
		30.0 - 39.9	**1.00**	0.06	15.99	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.66**	0.03	15.05	**.**	.	.
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.50**	0.05	5.51	**.**	.	.
		Ex-smkrs	**.**	.	.	**.**	.	.
		Unknown	**.**	.	.	**.**	.	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**.**	.	.	**.**	.	.
		Never	**.**	.	.	**.**	.	.
		Ex	**.**	.	.	**.**	.	.
Bone fractures								
Failures [n (%)]	52 (4.1)	109 (8.6)						
Surv. time in yrs [mean (sd)]	3.0 (2.9)	5.0 (3.4)						
IPF vs. Non-IPF			**0.80**	0.53	1.21	**0.71**	0.44	1.15
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**1.65**	0.77	3.55	**1.43**	0.62	3.30
		30.0 - 39.9	**0.57**	0.20	1.60	**0.38**	0.12	1.25
		40.0 - 55.9	**0.75**	0.04	12.99	**0.39**	0.01	12.74
		Unknown	**0.50**	0.17	1.43	**0.24**	0.06	0.96
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.56**	0.24	1.32	**0.51**	0.20	1.30
		Ex-smkrs	**1.42**	0.58	3.46	**1.30**	0.48	3.51
		Unknown	**1.26**	0.26	6.07	**2.99**	0.23	38.24
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.02**	0.36	2.90	**0.91**	0.17	4.94

IPF	IPF (n=1269)	Non-IPF (n=1269)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
		Never	**0.82**	0.20	3.32	**0.79**	0.11	5.90
		Ex	**1.89**	0.14	26.35	**1.59**	0.08	32.81

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status; **L**=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio, **.** = Non-estimable

Table 4.5.1.1b IPF: Results of proportional hazards regression analyses for incident cardiovascular-cerebrovascular-/pulmonary-related comorbidities after index date

IPF	IPF (Cases)	Non-IPF (Controls)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Congestive Heart Failure								
No. of subjects for analysis	**948**	**948**						
Failures [n (%)]	73 (7.7)	57 (6.0)						
Surv. time in yrs [mean (sd)]	3.3 (3.0)	5.3 (3.5)						
IPF vs. Non-IPF			**2.21**	1.42	3.42	**2.59**	1.50	4.46
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**1.98**	0.18	22.12	**3.22**	0.18	56.74
		25.0 - 29.9	**0.98**	0.50	1.92	**1.27**	0.56	2.91
		30.0 - 39.9	**1.06**	0.41	2.74	**1.28**	0.40	4.05
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.69**	0.27	1.74	**0.32**	0.06	1.92
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**2.09**	0.87	5.00	**1.88**	0.62	5.75
		Ex-smkrs	**1.10**	0.49	2.45	**0.89**	0.32	2.43
		Unknown	**1.08**	0.39	3.02	**0.10**	0.01	1.25
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.52**	0.22	1.26	**0.05**	0.00	0.54
		Never	**0.45**	0.16	1.27	**0.02**	0.00	0.28
		Ex	**.**	.	.	**.**	.	.
Ischemic Heart Disease								
No. of subjects for analysis	**736**	**736**						
Failures [n (%)]	72 (9.8)	50 (6.8)						
Surv. time in yrs [mean (sd)]	3.3 (3.1)	5.3 (3.4)						
IPF vs. Non-IPF			**2.07**	1.34	3.20	**1.80**	1.06	3.06
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**3.49**	0.27	44.65	**5.84**	0.36	94.06
		25.0 - 29.9	**1.75**	0.74	4.11	**1.78**	0.64	4.95
		30.0 - 39.9	**1.82**	0.65	5.06	**1.59**	0.46	5.47
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.42**	0.15	1.15	**0.20**	0.04	1.03

IPF	IPF (Cases)	Non-IPF (Controls)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.08**	0.44	2.67	**1.17**	0.39	3.51
		Ex-smkrs	**2.38**	1.08	5.25	**1.83**	0.72	4.61
		Unknown	**1.20**	0.33	4.35	**2.62**	0.43	16.08
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.07**	0.50	2.29	**0.39**	0.09	1.62
		Never	**1.14**	0.42	3.15	**0.39**	0.08	1.88
		Ex	**.**	.	.	**.**	.	.
Myocardial Infarction								
No. of subjects for analysis	**1024**	**1024**						
Failures [n (%)]	48 (4.7)	26 (2.5)						
Surv. time in yrs [mean (sd)]	3.2 (3.0)	5.3 (3.4)						
IPF vs. Non-IPF			**2.8**	1.6	4.9	**2.58**	1.20	5.55
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**1.54**	0.49	4.88	**1.13**	0.23	5.71
		30.0 - 39.9	**1.43**	0.45	4.59	**0.93**	0.17	4.94
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.30**	0.09	1.05	**0.08**	0.01	0.99
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.22**	0.34	4.34	**1.04**	0.16	6.66
		Ex-smkrs	**3.06**	1.01	9.23	**3.61**	0.79	16.62
		Unknown	**0.79**	0.21	3.05	**7.62**	0.56	102.92
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.30**	0.49	3.48	**0.50**	0.07	3.49
		Never	**2.28**	0.63	8.29	**1.14**	0.15	8.96
		Ex	**.**	.	.	**.**	.	.
Stroke / Transient Ischemic Attack (TIA)								
No. of subjects for analysis	**1059**	**1059**						
Failures [n (%)]	47 (4.4)	74 (7.0)						
Surv. time in yrs [mean (sd)]	3.1 (3.0)	5.2 (3.4)						
IPF vs. Non-IPF			**1.21**	0.74	1.97	**1.37**	0.78	2.41
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**1.42**	0.58	3.48	**1.61**	0.61	4.24
		30.0 - 39.9	**1.47**	0.48	4.50	**2.33**	0.63	8.61
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.88**	0.29	2.66	**1.32**	0.31	5.60
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.86**	0.25	2.95	**1.10**	0.29	4.24
		Ex-smkrs	**1.44**	0.57	3.62	**1.98**	0.70	5.60
		Unknown	**0.47**	0.12	1.88	**0.50**	0.08	3.31

IPF	IPF (Cases)	Non-IPF (Controls)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.42**	0.50	4.03	**1.00**	0.18	5.47
		Never	**2.15**	0.57	8.17	**1.78**	0.27	11.77
		Ex	**.**	.	.	**.**	.	.
Deep Vein Thrombosis								
No. of subjects for analysis	**1198**	**1198**						
Failures [n (%)]	19 (1.6)	22 (1.8)						
Surv. time in yrs [mean (sd)]	3.1 (2.9)	5.3 (3.4)						
IPF vs. Non-IPF			**2.43**	1.01	5.86	**5.74**	1.33	24.82
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**1.66**	0.08	33.85	**2.29**	0.04	127.78
		25.0 - 29.9	**2.74**	0.40	18.86	**3.21**	0.24	42.40
		30.0 - 39.9	**2.21**	0.20	24.95	**3.88**	0.05	324.65
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**1.44**	0.18	11.38	**26.03**	0.05	14350.89
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.34**	0.05	2.35	**0.09**	0.01	1.80
		Ex-smkrs	**0.66**	0.16	2.75	**0.28**	0.03	2.63
		Unknown	**0.38**	0.06	2.34	**0.11**	0.00	50.04
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**2.33**	0.41	13.45	**2.26**	0.01	437.18
		Never	**1.00**	0.11	9.27	**1.39**	0.01	166.99
		Ex	**.**	.	.	**.**	.	.
Pulmonary Embolism								
No. of subjects for analysis	**1216**	**1216**						
Failures [n (%)]	30 (2.5)	16 (1.3)						
Surv. time in yrs [mean (sd)]	3.1 (2.9)	5.3 (3.4)						
IPF vs. Non-IPF			**3.57**	1.55	8.26	**11.83**	1.91	73.19
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**0.90**	0.25	3.17	**0.26**	0.02	3.17
		30.0 - 39.9	**1.36**	0.23	7.93	**2.21**	0.08	57.86
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**1.06**	0.25	4.53	**0.71**	0.01	62.84
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.81**	0.12	5.62	**0.11**	0.00	3.69
		Ex-smkrs	**1.38**	0.39	4.86	**0.54**	0.06	5.04
		Unknown	**1.60**	0.26	9.81	**1.01**	0.00	518.91
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.25**	0.34	4.66	**1.47**	0.04	51.51
		Never	**1.25**	0.16	9.92	**0.07**	0.00	26.37
		Ex	**.**	.	.	**.**	.	.

IPF	IPF (Cases)	Non-IPF (Controls)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Pulmonary Hypertension								
No. of subjects for analysis	**1266**	**1266**						
Failures [n (%)]	12 (0.9)	2 (0.2)						
Surv. time in yrs [mean (sd)]	3.1 (3.0)	5.3 (3.5)						
IPF vs. Non-IPF			**10.00**	1.28	78.11	**.**	.	.
BMI (kg/m^2)	18.5 - 24.9 (Ref.)		**1.00**	--	--	**1.00**	--	--
	14.0 - 18.4		**.**	.	.	**.**	.	.
	25.0 - 29.9		**0.33**	0.04	3.21	**.**	.	.
	30.0 - 39.9		**.**	.	.	**.**	.	.
	40.0 - 55.9		**.**	.	.	**.**	.	.
	Unknown		**.**	.	.	**.**	.	.
Smoking status	Non-smkrs (Ref.)		**1.00**	--	--	**1.00**	--	--
	Curr-smkrs		**2.44**	0.16	37.13	**.**	.	.
	Ex-smkrs		**1.34**	0.21	8.53	**.**	.	.
	Unknown		**.**	.	.	**.**	.	.
Alcohol status	None (Ref.)		**1.00**	--	--	**1.00**	--	--
	Current		**.**	.	.	**.**	.	.
	Never		**.**	.	.	**.**	.	.
	Ex		**.**	.	.	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status
L=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

Table 4.5.1.1c IPF: Results of proportional hazards regression analyses for an incident diagnosis of cancer after index date

IPF	IPF (Cases)	Non-IPF (Controls)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Cancer in Situ Metastasis								
No. of subjects for analysis	**1039**	**1039**						
Failures [n (%)]	109 (10.5)	126 (12.1)						
Surv. time in yrs [mean (sd)]	3.1 (3.0)	5.2 (3.4)						
IPF vs. Non-IPF			**1.64**	1.17	2.29	**1.38**	0.95	2.00
BMI (kg/m^2)	18.5 - 24.9 (Ref.)		**1.00**	--	--	**1.00**	--	--
	14.0 - 18.4		**0.18**	0.02	1.60	**0.12**	0.01	1.39
	25.0 - 29.9		**1.63**	0.92	2.86	**1.64**	0.89	3.02
	30.0 - 39.9		**0.43**	0.18	1.04	**0.42**	0.17	1.05
	40.0 - 55.9		**.**	.	.	**0.00**	0.00	.
	Unknown		**1.20**	0.57	2.55	**1.64**	0.65	4.11
Smoking status	Non-smkrs (Ref.)		**1.00**	--	--	**1.00**	--	--
	Curr-smkrs		**1.54**	0.78	3.07	**1.54**	0.70	3.36
	Ex-smkrs		**2.10**	1.09	4.03	**1.89**	0.92	3.88
	Unknown		**0.73**	0.26	2.06	**0.75**	0.19	3.00

IPF	IPF (Cases)	Non-IPF (Controls)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.27**	0.60	2.72	**1.34**	0.47	3.80
		Never	**1.65**	0.65	4.19	**1.79**	0.54	5.88
		Ex	**0.76**	0.06	9.57	**0.32**	0.01	11.03

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status
L=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

4.5.2 Granulomatous ILD

4.5.2.1 Sarcoidosis

During the follow-up period 33 (10%) sarcoidosis and 17 (5%) non-sarcoidosis subjects died. When investigating all-cause mortality as the outcome of interest, the mean (SD) survival time in the sarcoidosis cohort was 4.9 (3.5) years versus 4.6 (3.5) years in the control group. After adjusting for smoking status, body mass index, and alcohol consumption status, the rate of all-cause mortality in the Sarcoidosis cohort was more than 5 times higher than the rate in the control group (RR 5.2, 95%CI:1.3 to 21.4). Likewise, among the non-incident comorbidities investigated, the adjusted rate ratio for respiratory (non-pneumonia) infections was significantly elevated (RR 2.2, 95% CI:1.6 to 3.1). Adjusted rate ratios and confidence intervals for other non-incident and incident comorbidities under investigation were largely non-estimable due to sparsely populated strata. Further details of these analyses can be found in tables 4.5.2.1a-c below.

Table 4.5.2.1a Sarcoidosis: Results of proportional hazards regression analyses for all-cause mortality and selected, non-incident comorbidities after index date

Sarcoidosis	Cases (n=330)	Controls (n=330)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
All-cause mortality								
Failures [n (%)]	33 (10.0)	17 (5.2)						
Surv. time in yrs [mean (sd)]	4.9 (3.5)	4.6 (3.5)						
Sarcoidosis vs. Non-sarcoidosis			**1.86**	0.97	3.56	**5.20**	1.26	21.42
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**2.05**	0.17	25.06	**0.33**	0.02	7.17
		25.0 - 29.9	**0.89**	0.25	3.21	**1.89**	0.30	11.85
		30.0 - 39.9	**1.20**	0.32	4.48	**0.56**	0.05	6.01
		40.0 - 55.9	**0.89**	0.10	7.94	**0.23**	0.01	7.85
		Unknown	**0.85**	0.23	3.13	**1.03**	0.15	6.89

Sarcoidosis	Cases (n=330)	Controls (n=330)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**5.13**	1.03	25.49	**2.70**	0.39	19.01
		Ex-smkrs	**2.64**	0.75	9.30	**5.66**	0.80	40.10
		Unknown	**1.11**	0.17	7.36	**2.75**	0.10	77.60
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.27**	0.42	3.90	**5.45**	0.38	78.33
		Never	**0.39**	0.07	2.19	**0.41**	0.03	6.52
		Ex	**.**	.	.	**.**	.	.
Pneumonia								
Failures [n (%)]	10 (3.0)	7 (2.1)						
Surv. time in yrs [mean (sd)]	4.8 (3.5)	4.5 (3.5)						
Sarcoidosis vs. Non-sarcoidosis			**1.33**	0.46	3.84	**.**	.	.
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**0.38**	0.02	6.63	**.**	.	.
		30.0 - 39.9	**1.09**	0.05	22.00	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**1.51**	0.12	19.33	**.**	.	.
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**2.00**	0.18	22.05	**.**	.	.
		Ex-smkrs	**1.00**	0.14	7.10	**.**	.	.
		Unknown	**.**	.	.	**.**	.	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	0.25	0.03	2.24	**.**	.	.
		Never	**.**	.	.	**.**	.	.
		Ex	**.**	.	.	**.**	.	.
Respiratory (non-pneumonia) infections								
Failures [n (%)]	183 (55.5)	116 (35.2)						
Surv. time in yrs [mean (sd)]	2.5 (2.6)	3.2 (3.0)						
Sarcoidosis vs. Non-sarcoidosis			**2.09**	1.55	2.82	**2.23**	1.59	3.14
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**4.37**	0.46	41.57	**3.30**	0.32	33.83
		25.0 - 29.9	**1.12**	0.67	1.89	**1.12**	0.63	1.96
		30.0 - 39.9	**1.30**	0.71	2.38	**1.16**	0.60	2.24
		40.0 - 55.9	**1.31**	0.46	3.72	**1.49**	0.47	4.70
		Unknown	**0.66**	0.36	1.19	**1.51**	0.66	3.47
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.80**	0.45	1.41	**1.29**	0.68	2.48
		Ex-smkrs	**1.18**	0.66	2.10	**1.39**	0.73	2.65
		Unknown	**0.42**	0.21	0.86	**0.53**	0.20	1.39
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.74**	1.02	2.97	**1.32**	0.57	3.04

Sarcoidosis	Cases (n=330)	Controls (n=330)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
		Never	**1.92**	0.92	3.98	**1.71**	0.63	4.61
		Ex	**3.49**	0.30	40.75	**3.22**	0.23	45.28
Pneumothorax								
Failures [n (%)]	0 (0)	1 (0.3)						
Surv. time in yrs [mean (sd)]	4.9 (3.5)	4.6 (3.5)						
Bone fractures								
Failures [n (%)]	16 (4.8)	8 (2.4)						
Surv. time in yrs [mean (sd)]	4.7 (3.5)	4.6 (3.5)						
Sarcoidosis vs. Non-sarcoidosis			**1.3**	0.5	3.2			
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**2.62**	0.39	17.53	**.**	.	.
		30.0 - 39.9	**1.63**	0.16	17.16	**.**	.	.
		40.0 - 55.9	**0.26**	0.01	5.68	**.**	.	.
		Unknown	**0.39**	0.03	4.94	**.**	.	.
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**2.00**	0.37	10.92			
		Ex-smkrs	**2.00**	0.18	22.05	**.**	.	.
		Unknown	**0.50**	0.05	5.51	**.**	.	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.42**	0.04	4.32	**.**	.	.
		Never	**0.12**	0.01	2.45	**.**	.	.
		Ex	**.**	.	.	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status
L=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

Table 4.5.2.1b Sarcoidosis: Results of proportional hazards regression analyses for incident cardiovascular-/ cerebrovascular-/pulmonary-related comorbidities after index date

Sarcoidosis	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Congestive Heart Failure								
No. of subjects for analysis	**319**	**319**						
Failures [n (%)]	8 (2.5)	1 (0.3)						
Surv. time in yrs [mean (sd)]	4.8 (3.5)	4.7 (3.5)						
Sarcoidosis vs. Non-sarcoidosis			**7.0**	0.9	56.9	**.**	.	.
Ischemic Heart Disease								
No. of subjects for analysis	**294**	**294**						
Failures [n (%)]	7 (2.4)	4 (1.4)						
Surv. time in yrs [mean (sd)]	4.8 (3.5)	4.7 (3.6)						
Sarcoidosis vs. Non-sarcoidosis			**3.0**	0.6	14.9	**.**	.	.

Myocardial Infarction								
No. of subjects for analysis	**330**	**330**						
Failures [n (%)]	5 (1.5)	0 (0)						
Surv. time in yrs [mean (sd)]	4.8 (3.5)	4.6 (3.5)						
Sarcoidosis vs. Non-sarcoidosis			**.**	.	.	**.**	.	.
Stroke / Transient Ischemic Attack (TIA)								
No. of subjects for analysis	**313**	**313**						
Failures [n (%)]	3 (0.01)	4 (0.01)						
Surv. time in yrs [mean (sd)]	4.8 (3.5)	4.6 (3.5)						
Sarcoidosis vs. Non-sarcoidosis			**0.50**	0.09	2.73	**.**	.	.
Deep Vein Thrombosis								
No. of subjects for analysis	**317**	**317**						
Failures [n (%)]	7 (2.2)	0 (0)						
Surv. time in yrs [mean (sd)]	4.8 (3.5)	4.6 (3.5)						
Sarcoidosis vs. Non-sarcoidosis			.	.	.	**.**	.	.
Pulmonary Embolism								
No. of subjects for analysis	**320**	**320**						
Failures [n (%)]	4 (1.3)	0 (0)						
Surv. time in yrs [mean (sd)]	4.9 (3.5)	4.7 (3.5)						
Sarcoidosis vs. Non-sarcoidosis			**.**	.	.	**.**	.	.
Pulmonary Hypertension								
No. of subjects for analysis	**329**	**329**						
Failures [n (%)]	2 (0.6)	0 (0)						
Surv. time in yrs [mean (sd)]	4.9 (3.5)	4.6 (3.5)						
Sarcoidosis vs. Non-sarcoidosis			**.**	.	.	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status
L=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

Table 4.5.2.1c Sarcoidosis: Results of proportional hazards regression analyses for an incident diagnosis of cancer after index date

Sarcoidosis	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Cancer in Situ Metastasis								
No. of subjects for analysis	**295**	**295**						
Failures [n (%)]	16 (5.4)	13 (4.4)						
Surv. time in yrs [mean (sd)]	4.9 (3.5)	4.5 (3.5)						
Sarcoidosis vs. Non-sarcoidosis			**0.92**	0.41	2.08	**0.97**	0.28	3.37
BMI (kg/m^2)	18.5 - 24.9 (Ref.)		**1.00**	--	--	**1.00**	--	--
	14.0 - 18.4		**.**	.	.	**0.00**	0.00	.
	25.0 - 29.9		**1.00**	0.23	4.41	**0.90**	0.11	7.60
	30.0 - 39.9		**1.00**	0.22	4.53	**1.67**	0.25	11.14
	40.0 - 55.9		**1.00**	0.12	8.57	**2.14**	0.14	32.64
	Unknown		**1.00**	0.18	5.49	**0.37**	0.01	16.43

Smoking status	Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
	Curr-smkrs	**2.00**	0.37	10.92	**3.24**	0.38	27.98
	Ex-smkrs	**1.50**	0.25	8.98	**1.12**	0.07	18.70
	Unknown	**2.00**	0.18	22.05	**2.30**	0.08	63.87
Alcohol status	None (Ref.)	**1.00**	--	--	**1.00**	--	--
	Current	**0.74**	0.16	3.41	**0.45**	0.03	6.63
	Never	**0.80**	0.08	7.77	**0.66**	0.04	11.99
	Ex	**.**	.	.	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status
L=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

4.5.2.2 Wegener's Granulomatosis (WG)

During the follow-up period 69 (23%) WG and 24 (8%) non-WG subjects died. When investigating all-cause mortality as the outcome of interest, the mean (SD) survival time in the Sarcoidosis cohort was 4.4 (3.7) years versus 5.2 (3.7) years in the control group. After adjusting for smoking status, body mass index, and alcohol consumption status, the rate of all-cause mortality in the WG cohort was more than 7 times higher than the rate in the control group (RR 7.2, 95%CI:3.2 to 16.3). Likewise, among the non-incident comorbidities investigated, the adjusted rate ratios for respiratory (non-pneumonia) infections and bone fractures were significantly elevated (RR 2.5 95% CI:1.8 to 3.6 and RR 13.3 95% CI:1.9 to 91.8, respectively). Crude and adjusted rate ratios for other non-incident and incident comorbidities under investigation were largely non-estimable due to lack of failures and/or sparsely populated strata. Further details of these analyses can be found in tables 4.5.2.2a-c below.

Table 4.5.2.2a WG: Results of proportional hazards regression analyses for all-cause mortality and selected, non-incident comorbidities after index date

WG	Cases (n=301)	Controls (n=301)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
All-cause mortality								
Failures [n (%)]	69 (22.9)	24 (8.0)						
Surv. time in yrs [mean (sd)]	4.4 (3.7)	5.2 (3.7)						
WG (cases) vs. Non-WG (controls)			**4.13**	2.35	7.27	**7.21**	3.20	16.26
BMI (kg/m^2)	18.5 - 24.9 (Ref.)		**1.00**	--	--	**1.00**	--	--
	14.0 - 18.4		**.**	.	.	**.**	.	.
	25.0 - 29.9		**1.44**	0.60	3.47	**1.85**	0.46	7.48
	30.0 - 39.9		**1.32**	0.45	3.87	**1.31**	0.26	6.56
	40.0 - 55.9		**.**	.	.	**.**	.	.
	Unknown		**1.82**	0.72	4.60	**1.16**	0.27	5.03
Smoking status	Non-smkrs (Ref.)		**1.00**	--	--	**1.00**	--	--
	Curr-smkrs		**4.32**	1.28	14.60	**10.99**	2.10	57.68
	Ex-smkrs		**0.96**	0.41	2.26	**0.67**	0.18	2.59
	Unknown		**2.32**	0.63	8.50	**1.67**	0.12	22.88
Alcohol status	None (Ref.)		**1.00**	--	--	**1.00**	--	--
	Current		**0.73**	0.29	1.86	**0.60**	0.08	4.78
	Never		**0.70**	0.22	2.26	**0.40**	0.04	4.16
	Ex		**0.37**	0.03	4.82	**0.13**	0.00	455.24
Pneumonia								
Failures [n (%)]	21 (7.0)	6 (2.0)						
Surv. time in yrs [mean (sd)]	4.2 (3.6)	5.1 (3.7)						
WG (cases) vs. Non-WG (controls)			**3.0**	1.2	7.6			
BMI (kg/m^2)	18.5 - 24.9 (Ref.)		**1.00**	--	--	**1.00**	--	--
	14.0 - 18.4		**.**	.	.	**.**	.	.
	25.0 - 29.9		**1.47**	0.22	9.67	**.**	.	.
	30.0 - 39.9		**1.89**	0.22	16.16	**.**	.	.
	40.0 - 55.9		**.**	.	.	**.**	.	.
	Unknown		**0.15**	0.02	1.22	**.**	.	.
Smoking status	Non-smkrs (Ref.)		**1.00**	--	--	**1.00**	--	--
	Curr-smkrs		**1.21**	0.30	4.84	**.**	.	.
	Ex-smkrs		**1.37**	0.30	6.21	**.**	.	.
	Unknown		**0.72**	0.11	4.66	**.**	.	.
Alcohol status	None (Ref.)		**1.00**	--	--	**1.00**	--	--
	Current		**0.73**	0.16	3.47	**.**	.	.
	Never		**0.79**	0.13	4.87	**.**	.	.
	Ex		**0.73**	0.03	17.60	**.**	.	.
Respiratory (non-pneumonia) infections								
Failures [n (%)]	155 (51.5)	104 (34.6)						
Surv. time in yrs [mean (sd)]	2.2 (2.5)	3.8 (3.4)						
WG (cases) vs. Non-WG (controls)			**2.44**	1.77	3.37	**2.50**	1.76	3.56

WG	Cases (n=301)	Controls (n=301)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**0.54**	0.05	6.11	**0.38**	0.03	5.00
		25.0 - 29.9	**1.12**	0.66	1.92	**1.24**	0.67	2.32
		30.0 - 39.9	**1.78**	0.85	3.74	**2.19**	0.96	5.04
		40.0 - 55.9	**1.92**	0.50	7.40	**1.81**	0.40	8.20
		Unknown	**0.51**	0.26	1.02	**0.50**	0.20	1.28
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.35**	0.72	2.55	**1.69**	0.79	3.59
		Ex-smkrs	**2.41**	1.26	4.59	**1.94**	0.94	4.02
		Unknown	**0.48**	0.20	1.12	**0.54**	0.16	1.85
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.26**	0.65	2.43	**0.49**	0.17	1.41
		Never	**1.95**	0.87	4.38	**0.83**	0.26	2.67
		Ex	**1.35**	0.24	7.63	**0.34**	0.04	2.87
Pneumothorax								
Failures [n (%)]	2 (0.7)	0 (0)						
Surv. time in yrs [mean (sd)]	4.4 (3.7)	5.2 (3.7)						
WG (cases) vs. Non-WG (controls)			**.**	.	.	**.**	.	.
Bone fractures								
Failures [n (%)]	27 (9.0)	16 (5.3)						
Surv. time in yrs [mean (sd)]	4.0 (3.5)	4.9 (3.6)						
WG (cases) vs. Non-WG (controls)			**2.20**	1.04	4.65	**13.33**	1.94	91.77
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**1.04**	0.32	3.41	**3.04**	0.37	24.67
		30.0 - 39.9	**0.53**	0.09	3.37	**0.51**	0.03	9.80
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**1.34**	0.21	8.64	**1.50**	0.12	19.59
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.00**	0.15	6.89	**0.02**	0.00	1.29
		Ex-smkrs	**3.00**	0.56	15.96	**0.94**	0.10	9.21
		Unknown	**0.33**	0.02	6.53	**.**	.	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.61**	0.10	3.87	**.**	.	.
		Never	**0.77**	0.11	5.18	**.**	.	.
		Ex	**.**	.	.	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status
L=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

Table 4.5.2.2b WG: Results of proportional hazards regression analyses for incident cardiovascular-/ cerebrovascular-/pulmonary-related comorbidities after index date

WG	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Congestive Heart Failure								
No. of subjects for analysis	**289**	**289**						
Failures [n (%)]	9 (2.5)	10 (0.3)						
Surv. time in yrs [mean (sd)]	4.4 (3.6)	5.1 (3.7)						
WG (cases) vs. Non-WG (controls)			**1.40**	0.44	4.41	**.**	.	.
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**0.50**	0.05	5.51	**.**	.	.
		30.0 - 39.9	**.**	.	.	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.50**	0.05	5.51	**.**	.	.
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**.**	.	.	**.**	.	.
		Ex-smkrs	**0.50**	0.05	5.51	**.**	.	.
		Unknown	**.**	.	.	**.**	.	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.33**	0.04	3.21	**1.00**	0.06	15.99
		Never	**0.67**	0.03	18.06	**.**	.	.
		Ex	**.**	.	.	**.**	.	.
Ischemic Heart Disease								
No. of subjects for analysis	**244**	**244**						
Failures [n (%)]	12 (2.4)	10 (1.0)						
Surv. time in yrs [mean (sd)]	4.4 (3.6)	5.0 (3.7)						
WG (cases) vs. Non-WG (controls)			**1.57**	0.61	4.05	**.**	.	.
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**1.37**	0.19	9.77	**.**	.	.
		30.0 - 39.9	**3.07**	0.19	50.83	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.73**	0.10	5.23	**.**	.	.
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.53**	0.09	3.21	**.**	.	.
		Ex-smkrs	**0.33**	0.04	3.21	**.**	.	.
		Unknown	**0.45**	0.05	3.83	**.**	.	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.70**	0.15	3.22	**.**	.	.
		Never	**1.13**	0.13	9.81	**.**	.	.
		Ex	**.**	.	.	**.**	.	.

WG	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Myocardial Infarction								
No. of subjects for analysis	**301**	**301**						
Failures [n (%)]	11 (3.7)	7 (2.3)						
Surv. time in yrs [mean (sd)]	4.2 (3.6)	5.1 (3.7)						
WG (cases) vs. Non-WG (controls)			**2.50**	0.78	7.97	**.**	.	.
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**1.00**	0.14	7.10	**0.40**	0.02	7.93
		30.0 - 39.9	**.**	.	.	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**.**	.	.	**.**	.	.
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**.**	.	.	**.**	.	.
		Ex-smkrs	**1.00**	0.06	15.99	**3.56**	0.09	148.59
		Unknown	**.**	.	.	**.**	.	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.82**	0.18	3.79	**12.65**	0.09	1706.08
		Never	**1.87**	0.16	21.73	**15.08**	0.24	942.71
		Ex	**.**	.	.	**.**	.	.
Stroke / Transient Ischemic Attack (TIA)								
No. of subjects for analysis	**274**	**274**						
Failures [n (%)]	12 (1.0)	5 (1.3)						
Surv. time in yrs [mean (sd)]	4.3 (3.6)	5.2 (3.8)						
WG (cases) vs. Non-WG (controls)			**4.50**	0.97	20.83	**.**	.	.
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**2.08**	0.18	24.55	**.**	.	.
		30.0 - 39.9	**2.08**	0.05	85.13	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**1.13**	0.21	5.92	**.**	.	.
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**.**	.	.	**.**	.	.
		Ex-smkrs	**1.00**	0.04	24.55	**.**	.	.
		Unknown	**1.00**	0.04	24.55	**.**	.	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.00**	0.14	7.10	**.**	.	.
		Never	**0.33**	0.02	6.65	**.**	.	.
		Ex	**.**	.	.	**.**	.	.
Deep Vein Thrombosis								
No. of subjects for analysis	**286**	**286**						
Failures [n (%)]	9 (3.1)	2 (0.7)						
Surv. time in yrs [mean (sd)]	4.3 (3.7)	5.2 (3.7)						

WG	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
WG (cases) vs. Non-WG (controls)			**4.00**	0.85	18.84	**.**	.	.
Pulmonary Embolism								
No. of subjects for analysis	**295**	**295**						
Failures [n (%)]	2 (0.7)	0 (0)						
Surv. time in yrs [mean (sd)]	4.4 (3.7)	5.2 (3.7)						
WG (cases) vs. Non-WG (controls)			**.**	.	.	**.**	.	.
Pulmonary Hypertension								
No. of subjects for analysis	**301**	**301**						
Failures [n (%)]	0 (0)	0 (0)						
Surv. time in yrs [mean (sd)]	4.4 (3.7)	5.2 (3.7)						
WG (cases) vs. Non-WG (controls)			**.**	.	.	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status
L=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

Table 4.5.2.2c WG: Results of proportional hazards regression analyses for an incident diagnosis of cancer after index date

WG	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted RR**	L 95% CL	U 95% CL
Cancer in Situ Metastasis								
No. of subjects for analysis	**253**	**253**						
Failures [n (%)]	19 (7.5)	15 (5.9)						
Surv. time in yrs [mean (sd)]	4.2 (3.6)	5.0 (3.7)						
WG (cases) vs. Non-WG (controls)			**1.89**	0.84	4.24	**12.14**	0.45	325.98
BMI (kg/m^2)	18.5 - 24.9 (Ref.)		**1.00**	--	--	**1.00**	--	--
	14.0 - 18.4		**.**	.	.	**.**	.	.
	25.0 - 29.9		**1.58**	0.41	6.07	**23.12**	0.20	2710.93
	30.0 - 39.9		**.**	.	.	**.**	.	.
	40.0 - 55.9		**.**	.	.	**.**	.	.
	Unknown		**0.75**	0.16	3.61	**3.08**	0.04	217.14
Smoking status	Non-smkrs (Ref.)		**1.00**	--	--	**1.00**	--	--
	Curr-smkrs		**.**	.	.	**.**	.	.
	Ex-smkrs		**0.33**	0.04	3.21	**0.25**	0.01	5.78
	Unknown		**2.00**	0.18	22.06	**.**	.	.
Alcohol status	None (Ref.)		**1.00**	--	--	**1.00**	--	--
	Current		**3.00**	0.61	14.86	**.**	.	.
	Never		**1.50**	0.25	8.98	**.**	.	.
	Ex		**.**	.	.	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status
L=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

4.5.3 ILD of known cause or associated with other diseases

4.5.3.1 Extrinsic Allergic Alveolitis (EAA)

During the follow-up period 89 (19%) EAA and 49 (11%) non-EAA subjects died. When investigating all-cause mortality as the outcome of interest, the mean (SD) survival time in the EAA cohort was 5.1 (3.8) years versus 5.4 (3.8) years in the control group. After adjusting for smoking status, body mass index, and alcohol consumption status, the rate of all-cause mortality in the EAA cohort was around 3 times higher than the rate in the control group (RR 2.9, 95%CI: 1.8 to 4.8). Likewise, among the non-incident comorbidities investigated, the adjusted rate ratio for respiratory (non-pneumonia) infections was significantly elevated (RR 1.9 95% CI: 1.5 to 2.4). Crude and adjusted rate ratios for other non-incident and incident comorbidities under investigation were largely non-estimable due to lack of failures and/or sparsely populated strata. Further details of these analyses can be found in tables 4.5.3.1a-c below.

Table 4.5.3.1a EAA: Results of proportional hazards regression analyses for all-cause mortality and selected, non-incident comorbidities after index date

EAA	Cases (n=466)	Controls (n=466)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
All-cause mortality								
Failures [n (%)]	89 (19.1)	49 (10.5)						
Surv. time in yrs [mean (sd)]	5.1 (3.8)	5.4 (3.8)						
EAA (cases) vs. Non-EAA (controls)			**2.40**	1.57	3.67	**2.91**	1.76	4.81
BMI (kg/m^2) 18.5 - 24.9 (Ref.)			**1.00**	--	--	**1.00**	--	--
14.0 - 18.4			**1.00**	0.06	15.99	**0.22**	0.01	4.27
25.0 - 29.9			**0.80**	0.38	1.68	**0.93**	0.37	2.32
30.0 - 39.9			**1.05**	0.45	2.42	**1.46**	0.53	4.01
40.0 - 55.9			**.**	.	.	**.**	.	.
Unknown			**1.54**	0.62	3.85	**2.17**	0.57	8.21

EAA	Cases (n=466)	Controls (n=466)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.32**	0.57	3.07	1.28	0.45	3.66
		Ex-smkrs	**0.83**	0.40	1.72	0.88	0.37	2.10
		Unknown	**1.36**	0.46	4.08	0.53	0.10	2.81
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.51**	0.23	1.15	**0.43**	0.14	1.31
		Never	**0.38**	0.14	1.04	**0.21**	0.05	0.88
		Ex	**.**	.	.	**.**	.	.
Pneumonia								
Failures [n (%)]	28 (6.0)	9 (1.9)						
Surv. time in yrs [mean (sd)]	4.9 (3.8)	5.4 (3.8)						
EAA (cases) vs. Non-EAA (controls)			**5.20**	2.00	13.54	**.**	.	.
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**1.21**	0.27	5.36	**.**	.	.
		30.0 - 39.9	**0.53**	0.05	6.16	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**1.12**	0.24	5.18	**.**	.	.
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.79**	0.21	3.04	**.**	.	.
		Ex-smkrs	**0.95**	0.27	3.40	**.**	.	.
		Unknown	**.**	.	.	**.**	.	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.47**	0.11	1.89	**.**	.	.
		Never	**0.86**	0.13	5.65	**.**	.	.
		Ex	**.**	.	.	**.**	.	.
Respiratory (non-pneumonia) infections								
Failures [n (%)]	275 (59.0)	198 (42.5)						
Surv. time in yrs [mean (sd)]	2.7 (2.9)	3.4 (3.0)						
EAA (cases) vs. Non-EAA (controls)			**1.86**	1.47	2.35	**1.87**	1.46	2.41
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**0.74**	0.19	2.85	**0.55**	0.13	2.25
		25.0 - 29.9	**0.97**	0.63	1.50	**1.06**	0.66	1.70
		30.0 - 39.9	**0.93**	0.56	1.54	**0.96**	0.56	1.63
		40.0 - 55.9	**4.88**	0.57	42.05	**7.72**	0.85	70.21
		Unknown	**0.62**	0.36	1.07	**0.69**	0.34	1.40
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.78**	0.49	1.25	**0.80**	0.48	1.32
		Ex-smkrs	**1.32**	0.84	2.06	**1.14**	0.70	1.86
		Unknown	**1.03**	0.54	1.96	**1.23**	0.53	2.90
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.93**	0.59	1.46	**0.81**	0.44	1.46

EAA	Cases (n=466)	Controls (n=466)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
		Never	**1.35**	0.73	2.49	**1.13**	0.54	2.39
		Ex	**0.43**	0.08	2.40	**0.64**	0.10	4.08
Pneumothorax								
Failures [n (%)]	6 (1.9)	0 (0)						
Surv. time in yrs [mean (sd)]	5.1 (3.8)	5.4 (3.8)						
EAA (cases) vs. Non-EAA (controls)			**.**	.	.	**.**	.	.
Bone fractures								
Failures [n (%)]	33 (7.1)	32 (6.9)						
Surv. time in yrs [mean (sd)]	4.8 (3.7)	5.1 (3.8)						
EAA (cases) vs. Non-EAA (controls)			**1.12**	0.65	1.92	**1.04**	0.55	1.97
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**0.52**	0.17	1.64	**0.40**	0.11	1.44
		30.0 - 39.9	**0.35**	0.11	1.14	**0.29**	0.08	1.08
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.34**	0.10	1.24	**0.52**	0.12	2.25
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.58**	0.14	2.38	**0.79**	0.16	3.86
		Ex-smkrs	**0.99**	0.36	2.73	**1.13**	0.33	3.86
		Unknown	**0.53**	0.08	3.57	**1.23**	0.12	12.62
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**3.23**	0.84	12.46	**4.04**	0.73	22.50
		Never	**2.44**	0.51	11.75	**2.58**	0.40	16.58
		Ex	**.**	.	.	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status; **L**=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

Table 4.5.3.1b EAA: Results of proportional hazards regression analyses for incident cardiovascular-/cerebrovascular-/pulmonary-related comorbidities after index date

EAA	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Congestive Heart Failure								
No. of subjects for analysis	**421**	**421**						
Failures [n (%)]	18 (4.3)	7 (1.7)						
Surv. time in yrs [mean (sd)]	5.1 (3.8)	5.4 (3.9)						
EAA (cases) vs. Non-EAA (controls)			**4.50**	1.52	13.30	**.**	.	.
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**1.00**	0.06	15.99	**.**	.	.
		25.0 - 29.9	**0.63**	0.07	5.53	**.**	.	.
		30.0 - 39.9	**1.46**	0.18	11.85	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.57**	0.11	2.95	**.**	.	.

EAA	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.50**	0.09	2.73	**.**	.	.
		Ex-smkrs	**1.00**	0.06	15.99	**.**	.	.
		Unknown	**.**	.	.	**.**	.	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.25**	0.26	5.96	**.**	.	.
		Never	**1.57**	0.24	10.21	**.**	.	.
		Ex	**.**	.	.	**.**	.	.
Ischemic Heart Disease								
No. of subjects for analysis	**366**	**366**						
Failures [n (%)]	20 (5.5)	15 (4.1)						
Surv. time in yrs [mean (sd)]	5.2 (3.8)	5.2 (3.9)						
EAA (cases) vs. Non-EAA (controls)			**1.23**	0.59	2.56	**0.19**	0.01	2.49
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**.**	.	.	**.**	.	.
		30.0 - 39.9	**.**	.	.	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**.**	.	.	**.**	.	.
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.29**	0.24	6.78	**0.88**	0.00	.
		Ex-smkrs	**1.29**	0.17	9.95	**2.72**	0.02	331.79
		Unknown	**0.19**	0.02	1.66	**0.04**	0.00	11.70
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**10.35**	1.21	88.60	**67.68**	0.62	7410.15
		Never	**6.82**	0.70	66.76	**8.99**	0.23	355.73
		Ex	**.**	.	.	**.**	.	.
Myocardial Infarction								
No. of subjects for analysis	**466**	**466**						
Failures [n (%)]	8 (1.7)	11 (2.4)						
Surv. time in yrs [mean (sd)]	5.1 (3.8)	5.3 (3.8)						
EAA (cases) vs. Non-EAA (controls)			**0.75**	0.26	2.16	**.**	.	.
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**0.23**	0.02	2.67	**.**	.	.
		30.0 - 39.9	**0.61**	0.04	8.62	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.14**	0.01	2.55	**.**	.	.
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**2.74**	0.27	28.14	**.**	.	.
		Ex-smkrs	**4.08**	0.20	83.13	**.**	.	.
		Unknown	**.**	.	.	**.**	.	.

EAA	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**3.52**	0.36	34.68	**.**	.	.
		Never	**4.95**	0.41	59.93	**.**	.	.
		Ex	**.**	.	.	**.**	.	.
Stroke / Transient Ischemic Attack (TIA)								
No. of subjects for analysis	**431**	**431**						
Failures [n (%)]	18 (4.2)	19 (4.4)						
Surv. time in yrs [mean (sd)]	5.2 (3.8)	5.3 (3.9)						
EAA (cases) vs. Non-EAA (controls)			**1.00**	0.49	2.05	1.47	0.55	3.97
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**2.31**	0.51	10.54	**2.81**	0.48	16.35
		30.0 - 39.9	**2.09**	0.43	10.19	**3.50**	0.40	31.00
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**1.20**	0.28	5.13	**1.03**	0.11	9.42
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**2.38**	0.56	10.10	**4.64**	0.71	30.40
		Ex-smkrs	**1.39**	0.38	5.11	**1.83**	0.34	9.87
		Unknown	**0.31**	0.03	2.87	**0.60**	0.03	10.99
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.84**	0.53	6.40	**0.76**	0.10	5.96
		Never	**1.08**	0.14	8.43	**0.91**	0.05	17.31
		Ex	**.**	.	.	**.**	.	.
Deep Vein Thrombosis								
No. of subjects for analysis	**447**	**447**						
Failures [n (%)]	5 (1.1)	5 (1.1)						
Surv. time in yrs [mean (sd)]	5.1 (3.8)	5.4 (3.9)						
EAA (cases) vs. Non-EAA (controls)			**1.00**	0.25	4.00			
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**0.26**	0.02	4.48	**.**	.	.
		30.0 - 39.9	**1.46**	0.07	30.97	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.61**	0.01	33.61	**.**	.	.
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**4.54**	0.29	69.98	**.**	.	.
		Ex-smkrs	**2.13**	0.17	26.15	**.**	.	.
		Unknown	**.**	.	.	**.**	.	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.00**	0.05	19.36	**.**	.	.
		Never	**1.00**	0.05	19.36	**.**	.	.
		Ex	**.**	.	.	**.**	.	.

EAA		Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Pulmonary Embolism									
No. of subjects for analysis		**451**	**451**						
Failures [n (%)]		7 (1.6)	5 (1.1)						
Surv. time in yrs [mean (sd)]		5.1 (3.8)	5.4 (3.9)						
EAA (cases) vs. Non-EAA (controls)				**1.75**	0.51	5.98	**.**	.	.
BMI (kg/m^2)	18.5 - 24.9 (Ref.)			**1.00**	--	--	**1.00**	--	--
	14.0 - 18.4			**.**	.	.	**.**	.	.
	25.0 - 29.9			**3.00**	0.31	28.84	**.**	.	.
	30.0 - 39.9			**.**	.	.	**.**	.	.
	40.0 - 55.9			**.**	.	.	**.**	.	.
	Unknown			**.**	.	.	**.**	.	.
Smoking status	Non-smkrs (Ref.)			**1.00**	--	--	**1.00**	--	--
	Curr-smkrs			**1.00**	0.06	15.99	**.**	.	.
	Ex-smkrs			**1.00**	0.06	15.99	**.**	.	.
	Unknown			**.**	.	.	**.**	.	.
Alcohol status	None (Ref.)			**1.00**	--	--	**1.00**	--	--
	Current			**.**	.	.	**.**	.	.
	Never			**.**	.	.	**.**	.	.
	Ex			**.**	.	.	**.**	.	.
Pulmonary Hypertension									
No. of subjects for analysis		**465**	**465**						
Failures [n (%)]		4 (0.9)	0 (0)						
Surv. time in yrs [mean (sd)]		4.1 (3.8)	5.4 (3.9)						
EAA (cases) vs. Non-EAA (controls)				**.**	.	.	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status
L=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

Table 4.5.3.1c EAA: Results of proportional hazards regression analyses for an incident diagnosis of cancer after index date

EAA		Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Cancer in Situ Metastasis									
No. of subjects for analysis		**403**	**403**						
Failures [n (%)]		27 (6.7)	26 (6.5)						
Surv. time in yrs [mean (sd)]		5.1 (3.8)	5.4 (3.9)						
EAA (cases) vs. Non-EAA (controls)				**1.05**	0.58	1.88	**1.24**	0.58	2.66
BMI (kg/m^2)	18.5 - 24.9 (Ref.)			**1.00**	--	--	**1.00**	--	--
	14.0 - 18.4			**0.79**	0.05	13.97	**0.56**	0.03	12.90
	25.0 - 29.9			**0.63**	0.16	2.43	**1.03**	0.16	6.82
	30.0 - 39.9			**1.29**	0.39	4.26	**2.07**	0.43	10.02
	40.0 - 55.9			**.**	.	.	**.**	.	.
	Unknown			**1.60**	0.39	6.64	**1.83**	0.23	14.40

EAA	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.38**	0.41	4.69	**1.24**	0.58	2.66
		Ex-smkrs	**1.68**	0.57	4.93	**1.41**	0.34	5.94
		Unknown	**1.62**	0.34	7.71	**1.53**	0.41	5.68
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.24**	0.34	4.51	**1.49**	0.25	8.96
		Never	**0.23**	0.04	1.39	**0.28**	0.03	2.57
		Ex	**.**	.	.	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status
L=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

4.5.3.2 Pneumoconioses

During the follow-up period 545 (23%) subjects with pneumoconioses and 363 (15%) non-pneumoconioses subjects died. When investigating all-cause mortality as the outcome of interest, the mean (SD) survival time in the pneumoconioses cohort was 4.0 (3.2) years versus 4.4 (3.3) years in the control group. After adjusting for smoking status, body mass index, and alcohol consumption status, the rate of all-cause mortality in the pneumoconioses cohort remained twice as high as the rate in the control group (RR 2.0, 95%CI:1.7 to 2.4). Likewise, among the non-incident comorbidities investigated, rate ratios for pneumonia, respiratory (non-pneumonia) infections, and haemoptysis remained elevated after adjustment for smoking status, body mass index, and alcohol consumption status (see RRs and 95% CIs below). Among the incident cardiovascular outcomes investigated, adjusted rate ratios for myocardial infarction, ischemic heart disease, and congestive heart failure were all significantly elevated. Among these incident outcomes of interest, the highest adjusted rate ratio was observed for congestive heart failure (RR 2.9, 95%CI:1.9 to 4.4). Among the other incident comorbidities under investigation, the rate ratio for

cancer remained elevated after adjustment (RR 1.6, 95%CI:1.3 to 2.0). Crude and adjusted rate ratios for certain incident comorbidities under investigation were non-estimable due to lack of failures and/or sparsely populated strata. Further details of these analyses can be found in tables 4.5.3.2a-c below.

Table 4.5.3.2a Pneumoconioses: Results of proportional hazards regression analyses for all-cause mortality and selected, non-incident comorbidities after index date

Pneumoconioses	Cases (n=2418)	Controls (n=2418)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
All-cause mortality								
Failures [n (%)]	545 (22.5)	363 (15.0)						
Surv. time in yrs [mean (sd)]	4.0 (3.2)	4.4 (3.3)						
Pneumocon. (cases) vs. Non-Pneumocon. (controls)			**2.01**	1.71	2.36	**2.01**	1.70	2.37
BMI (kg/m^2) 18.5 - 24.9 (Ref.)			**1.00**	--	--	**1.00**	--	--
14.0 - 18.4			**3.14**	1.34	7.35	**2.46**	0.99	6.08
25.0 - 29.9			**0.85**	0.65	1.11	**0.87**	0.65	1.16
30.0 - 39.9			**0.68**	0.47	0.98	**0.74**	0.49	1.10
40.0 - 55.9			**.**	.	.	**.**	.	.
Unknown			**0.87**	0.62	1.22	**0.94**	0.62	1.42
Smoking status Non-smkrs (Ref.)			**1.00**	--	--	**1.00**	--	--
Curr-smkrs			**2.04**	1.50	2.79	**1.72**	1.23	2.42
Ex-smkrs			**1.28**	0.97	1.69	**1.12**	0.82	1.52
Unknown			**1.11**	0.72	1.71	**1.21**	0.69	2.11
Alcohol status None (Ref.)			**1.00**	--	--	**1.00**	--	--
Current			**0.96**	0.70	1.34	**0.92**	0.60	1.41
Never			**1.13**	0.76	1.70	**1.08**	0.66	1.76
Ex			**1.06**	0.49	2.28	**1.04**	0.46	2.36
Pneumonia								
Failures [n (%)]	162 (6.7)	73 (3.0)						
Surv. time in yrs [mean (sd)]	3.9 (3.2)	4.4 (3.3)						
Pneumocon. (cases) vs. Non-Pneumocon. (controls)			**2.98**	2.12	4.17	**3.17**	2.18	4.63
BMI (kg/m^2) 18.5 - 24.9 (Ref.)			**1.00**	--	--	**1.00**	--	--
14.0 - 18.4			**3.06**	0.59	15.90	**5.03**	0.76	33.26
25.0 - 29.9			**1.07**	0.66	1.71	**1.16**	0.65	2.04
30.0 - 39.9			**1.16**	0.61	2.22	**1.20**	0.54	2.67
40.0 - 55.9			**.**	.	.	**.**	.	.
Unknown			**0.70**	0.36	1.39	**0.68**	0.27	1.71
Smoking status Non-smkrs (Ref.)			**1.00**	--	--	**1.00**	--	--
Curr-smkrs			**1.94**	1.04	3.61	**0.88**	0.41	1.89

Pneumoconioses	Cases (n=2418)	Controls (n=2418)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
		Ex-smkrs	**1.44**	0.85	2.43	**1.01**	0.54	1.88
		Unknown	**0.84**	0.33	2.13	**0.43**	0.11	1.70
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.89**	0.46	1.74	**0.33**	0.11	0.98
		Never	**0.63**	0.29	1.36	**0.30**	0.10	0.94
		Ex	**0.87**	0.22	3.45	**0.59**	0.11	3.30
Respiratory (non-pneumonia) infections								
Failures [n (%)]	1233 (51.0)	862 (35.6)						
Surv. time in yrs [mean (sd)]	2.3 (2.4)	3.1 (2.8)						
Pneumocon. (cases) vs. Non-Pneumocon. (controls)			**2.00**	1.79	2.24	**1.93**	1.72	2.16
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**0.75**	0.40	1.39	**0.78**	0.40	1.52
		25.0 - 29.9	**0.98**	0.82	1.19	**0.95**	0.78	1.17
		30.0 - 39.9	**0.91**	0.71	1.16	**0.95**	0.73	1.23
		40.0 - 55.9	**1.77**	0.74	4.21	**1.72**	0.69	4.29
		Unknown	**0.65**	0.51	0.84	**0.75**	0.55	1.02
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.48**	1.20	1.83	**1.39**	1.11	1.74
		Ex-smkrs	**1.68**	1.40	2.03	**1.50**	1.23	1.83
		Unknown	**0.84**	0.61	1.17	**1.08**	0.71	1.62
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.44**	1.13	1.82	**1.06**	0.76	1.47
		Never	**1.44**	1.06	1.96	**1.11**	0.76	1.63
		Ex	**1.45**	0.85	2.47	**0.95**	0.52	1.73
Pneumothorax								
Failures [n (%)]	10 (0.4)	2 (0.08)						
Surv. time in yrs [mean (sd)]	4.0 (3.2)	4.4 (3.3)						
Pneumocon. (cases) vs. Non-Pneumocon. (controls)			**10.00**	1.28	78.11			
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**0.47**	0.08	2.79	**.**	.	.
		30.0 - 39.9	**0.68**	0.04	13.20	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.00**	0.00	.	**.**	.	.
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**.**	.	.	**.**	.	.
		Ex-smkrs	**1.00**	0.14	7.10	**.**	.	.
		Unknown	**.**	.	.	**.**	.	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.00**	0.06	15.99	**.**	.	.
		Never	**1.00**	0.02	50.40	**.**	.	.
		Ex	**.**	.	.	**.**	.	.

Pneumoconioses	Cases (n=2418)	Controls (n=2418)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Bone fractures								
Failures [n (%)]	144 (6.0)	133 (5.5)						
Surv. time in yrs [mean (sd)]	3.8 (3.2)	4.3 (3.2)						
Pneumocon. (cases) vs. Non-Pneumocon. (controls)			**1.14**	0.87	1.50	**1.11**	0.83	1.49
BMI (kg/m^2)	18.5 - 24.9 (Ref.)		**1.00**	--	--	**1.00**	--	--
	14.0 - 18.4		**.**	.	.	**.**	.	.
	25.0 - 29.9		**0.56**	0.35	0.90	**0.58**	0.35	0.95
	30.0 - 39.9		**0.38**	0.20	0.73	**0.37**	0.18	0.73
	40.0 - 55.9		**.**	.	.	**.**	.	.
	Unknown		**0.73**	0.39	1.39	**0.66**	0.30	1.45
Smoking status	Non-smkrs (Ref.)		**1.00**	--	--	**1.00**	--	--
	Curr-smkrs		**1.23**	0.75	2.03	**1.05**	0.61	1.81
	Ex-smkrs		**0.98**	0.60	1.57	**0.91**	0.54	1.53
	Unknown		**1.55**	0.69	3.47	**2.07**	0.74	5.83
Alcohol status	None (Ref.)		**1.00**	--	--	**1.00**	--	--
	Current		**0.98**	0.55	1.75	**1.31**	0.59	2.93
	Never		**0.90**	0.37	2.18	**1.07**	0.37	3.07
	Ex		**3.35**	0.63	17.68	**3.97**	0.65	24.08

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status
L=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

Table 4.5.3.2b Pneumoconioses: Results of proportional hazards regression analyses for incident cardiovascular- / cerebrovascular- / pulmonary-related comorbidities after index date

Pneumoconioses	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Congestive Heart Failure								
No. of subjects for analysis	**2084**	**2084**						
Failures [n (%)]	121 (5.8)	66 (3.2)						
Surv. time in yrs [mean (sd)]	4.0 (3.3)	4.4 (3.3)						
Pneumocon. (cases) vs. Non-Pneumocon. (controls)			**2.53**	1.75	3.64	**2.90**	1.91	4.42
BMI (kg/m^2)	18.5 - 24.9 (Ref.)		**1.00**	--	--	**1.00**	--	--
	14.0 - 18.4		**1.15**	0.07	18.78	**1.52**	0.04	54.14
	25.0 - 29.9		**1.32**	0.71	2.43	**1.44**	0.69	3.01
	30.0 - 39.9		**2.62**	1.10	6.23	**4.52**	1.64	12.43
	40.0 - 55.9		**.**	.	.	**.**	.	.
	Unknown		**1.11**	0.51	2.41	**2.08**	0.77	5.59
Smoking status	Non-smkrs (Ref.)		**1.00**	--	--	**1.00**	--	--
	Curr-smkrs		**0.81**	0.41	1.58	**0.63**	0.28	1.40
	Ex-smkrs		**1.32**	0.74	2.36	**0.97**	0.47	1.98
	Unknown		**0.42**	0.15	1.14	**0.32**	0.08	1.33

Pneumoconioses	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.36**	0.67	2.77	**0.97**	0.31	3.05
		Never	**0.95**	0.38	2.37	**0.54**	0.14	2.05
		Ex	**1.05**	0.24	4.65	**0.66**	0.09	4.81
Ischemic Heart Disease								
No. of subjects for analysis	**1518**	**1518**						
Failures [n (%)]	112 (7.4)	74 (4.9)						
Surv. time in yrs [mean (sd)]	4.0 (3.3)	4.4 (3.4)						
Pneumocon. (cases) vs. Non-Pneumocon. (controls)			**1.71**	1.23	2.38	**1.81**	1.26	2.59
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**1.02**	0.61	1.71	**1.04**	0.59	1.83
		30.0 - 39.9	**0.88**	0.42	1.85	**1.06**	0.48	2.34
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.72**	0.33	1.56	**0.46**	0.18	1.17
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.03**	0.59	1.80	**1.33**	0.71	2.50
		Ex-smkrs	**0.84**	0.47	1.48	**0.78**	0.41	1.49
		Unknown	**0.81**	0.27	2.48	**0.52**	0.14	1.92
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.67**	0.31	1.44	**0.46**	0.17	1.24
		Never	**1.00**	0.39	2.54	**0.80**	0.27	2.43
		Ex	**1.47**	0.31	6.85	**1.31**	0.24	7.22
Myocardial Infarction								
No. of subjects for analysis	**2418**	**2418**						
Failures [n (%)]	85 (3.5)	70 (2.9)						
Surv. time in yrs [mean (sd)]	3.9 (3.2)	4.3 (3.3)						
Pneumocon. (cases) vs. Non-Pneumocon. (controls)			**1.58**	1.10	2.27	**1.70**	1.14	2.52
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**0.63**	0.06	7.26	**0.34**	0.02	5.51
		25.0 - 29.9	**1.43**	0.78	2.64	**1.68**	0.85	3.30
		30.0 - 39.9	**1.03**	0.42	2.52	**1.30**	0.51	3.32
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**1.62**	0.69	3.81	**1.99**	0.62	6.34
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.72**	0.84	3.54	**1.77**	0.81	3.90
		Ex-smkrs	**1.01**	0.54	1.88	**0.86**	0.44	1.66
		Unknown	**0.53**	0.13	2.25	**0.33**	0.04	2.58
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.02**	0.43	2.42	**0.79**	0.21	2.98
		Never	**1.52**	0.50	4.60	**1.23**	0.29	5.33
		Ex	**1.69**	0.33	8.54	**1.34**	0.19	9.30

Pneumoconioses	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Stroke / Transient Ischemic Attack (TIA)								
No. of subjects for analysis	**2041**	**2041**						
Failures [n (%)]	105 (5.1)	82 (4.0)						
Surv. time in yrs [mean (sd)]	4.0 (3.2)	4.4 (3.3)						
Pneumocon. (cases) vs. Non-Pneumocon. (controls)			**1.77**	1.24	2.52	**1.96**	1.27	3.03
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**0.98**	0.06	15.94	**0.89**	0.03	27.50
		25.0 - 29.9	**0.96**	0.54	1.73	**0.80**	0.40	1.59
		30.0 - 39.9	**0.58**	0.25	1.35	**0.68**	0.26	1.81
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.70**	0.31	1.57	**0.47**	0.16	1.37
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**2.05**	1.01	4.18	**2.16**	0.94	4.96
		Ex-smkrs	**2.22**	1.18	4.17	**2.17**	1.06	4.45
		Unknown	**4.73**	1.38	16.20	**13.57**	2.66	69.27
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.98**	0.44	2.19	**1.13**	0.35	3.72
		Never	**1.67**	0.57	4.88	**3.42**	0.84	13.93
		Ex	**0.72**	0.16	3.21	**1.54**	0.25	9.42
Deep Vein Thrombosis								
No. of subjects for analysis	**2305**	**2305**						
Failures [n (%)]	27 (1.2)	22 (1.0)						
Surv. time in yrs [mean (sd)]	4.0 (3.2)	4.5 (3.3)						
Pneumocon. (cases) vs. Non-Pneumocon. (controls)			**1.50**	0.80	2.82	**1.66**	0.73	3.80
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**2.33**	0.52	10.41	**4.67**	0.57	38.47
		30.0 - 39.9	**2.50**	0.51	12.41	**3.06**	0.41	22.66
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**2.04**	0.38	10.97	**6.85**	0.41	114.70
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.50**	0.09	2.82	**0.40**	0.03	5.38
		Ex-smkrs	**2.00**	0.65	6.17	**1.42**	0.33	6.18
		Unknown	**0.50**	0.05	5.51	**3.51**	0.11	112.95
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.28**	0.21	7.98	**16.78**	0.28	992.51
		Never	**3.09**	0.31	30.45	**60.09**	0.43	8495.36
		Ex	**.**	.	.	**.**	.	.
Pulmonary Embolism								
No. of subjects for analysis	**2334**	**2334**						
Failures [n (%)]	21 (0.9)	9 (0.4)						
Surv. time in yrs [mean (sd)]	4.0 (3.2)	4.4 (3.3)						

Pneumoconioses	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Pneumocon. (cases) vs. Non-Pneumocon. (controls)			**2.00**	0.86	4.67	**1.45**	0.27	7.73
BMI (kg/m^2)	18.5 - 24.9 (Ref.)		**1.00**	--	--	**1.00**	--	--
	14.0 - 18.4		**.**	.	.	**.**	.	.
	25.0 - 29.9		**.**	.	.	**.**	.	.
	30.0 - 39.9		**2.00**	0.18	22.06	**.**	.	.
	40.0 - 55.9		**.**	.	.	**.**	.	.
	Unknown		**.**	.	.	**.**	.	.
Smoking status	Non-smkrs (Ref.)		**1.00**	--	--	**1.00**	--	--
	Curr-smkrs		**0.32**	0.03	2.99	**.**	.	.
	Ex-smkrs		**1.94**	0.48	7.86	**0.26**	0.02	3.61
	Unknown		**.**	.	.	**.**	.	.
Alcohol status	None (Ref.)		**1.00**	--	--	**1.00**	--	--
	Current		**2.00**	0.18	22.06	**.**	.	.
	Never		**.**	.	.	**.**	.	.
	Ex		**.**	.	.	**.**	.	.
Pulmonary Hypertension								
No. of subjects for analysis	**2409**	**2409**						
Failures [n (%)]	5 (0.2)	2 (0.08)						
Surv. time in yrs [mean (sd)]	4.0 (3.2)	4.4 (3.3)						
Pneumocon. (cases) vs. Non-Pneumocon. (controls)			**4.00**	0.45	35.79	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status; **L**=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

Table 4.5.3.2c Pneumoconioses: Results of proportional hazards regression analyses for an incident diagnosis of cancer after index date

Pneumoconioses	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Cancer in Situ Metastasis								
No. of subjects for analysis	**1955**	**1955**						
Failures [n (%)]	255 (13.0)	184 (9.4)						
Surv. time in yrs [mean (sd)]	4.0 (3.2)	4.5 (3.3)						
Pneumocon. (cases) vs. Non-Pneumocon. (controls)			**1.61**	1.30	1.99	**1.61**	1.28	2.03
BMI (kg/m^2)	18.5 - 24.9 (Ref.)		**1.00**	--	--	**1.00**	--	--
	14.0 - 18.4		**2.30**	0.59	8.90	**1.39**	0.34	5.68
	25.0 - 29.9		**0.93**	0.65	1.32	**0.95**	0.65	1.39
	30.0 - 39.9		**0.68**	0.41	1.12	**0.79**	0.46	1.34
	40.0 - 55.9		**0.82**	0.05	13.48	**0.32**	0.02	5.71
	Unknown		**0.46**	0.28	0.76	**0.44**	0.24	0.82
Smoking status	Non-smkrs (Ref.)		**1.00**	--	--	**1.00**	--	--
	Curr-smkrs		**2.04**	1.34	3.11	**1.80**	1.14	2.85
	Ex-smkrs		**1.01**	0.70	1.46	**0.84**	0.57	1.25
	Unknown		**0.58**	0.29	1.17	**0.71**	0.30	1.72

Pneumoconioses	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.42**	0.87	2.34	**0.75**	0.37	1.52
		Never	**1.56**	0.83	2.92	**0.93**	0.42	2.07
		Ex	**1.70**	0.51	5.61	**0.99**	0.25	3.94

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status
L=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

4.5.3.3 Drug-/radiation-induced ILD (DRAD)

During the follow-up period 68 (47%) subjects with DRAD-ILD and 16 (11%) non-DRAD-ILD subjects died. When investigating all-cause mortality as the outcome of interest, the mean (SD) survival time in the DRAD-ILD cohort was 2.8 (3.0) years versus 4.5 (3.3) years in the non-DRAD-ILD group. After adjusting for smoking status, body mass index, and alcohol consumption status, the rate of all-cause mortality in the DRAD-ILD cohort remained significantly elevated compared with the rate in the control group (RR 23.0, 95%CI: 3.8 to 139.4). Likewise, among the non-incident comorbidities investigated, the rate ratio for respiratory (non-pneumonia) infections remained elevated after adjustment for smoking status, body mass index, and alcohol consumption status (RR 3.3, 95%CI: 1.7 to 6.4). Crude and adjusted rate ratios for incident comorbidities under investigation were largely non-estimable due to lack of failures and/or sparsely populated strata. Further details of these analyses can be found in tables 4.5.3.2a-c below.

Table 4.5.3.3a Drug-/radiation-induced ILD: Results of proportional hazards regression analyses for all-cause mortality and selected non-incident comorbidities after index date

DRAD-ILD	Cases (n=145)	Controls (n=145)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
All-cause mortality								
Failures [n (%)]	68 (46.9)	16 (11.0)						
Surv. time in yrs [mean (sd)]	2.8 (3.0)	4.5 (3.3)						
DRAD-ILD (cases) vs. Non-DRAD-ILD (controls)			**7.63**	3.65	15.93	**23.01**	3.80	139.35
BMI (kg/m^2) 18.5 - 24.9 (Ref.)			**1.00**	--	--	**1.00**	--	--
14.0 - 18.4			**.**	.	.	**.**	.	.
25.0 - 29.9			**0.78**	0.33	1.86	**0.09**	0.01	0.86
30.0 - 39.9			**0.69**	0.23	2.12	**0.33**	0.02	4.69
40.0 - 55.9			**.**	.	.	**.**	.	.
Unknown			**0.33**	0.10	1.01	**0.34**	0.03	4.48
Smoking status Non-smkrs (Ref.)			**1.00**	--	--	**1.00**	--	--
Curr-smkrs			**2.28**	0.77	6.74	**2.30**	0.22	24.59
Ex-smkrs			**3.48**	1.32	9.17	**11.47**	0.94	140.26
Unknown			**1.02**	0.16	6.43	**5.95**	0.08	465.13
Alcohol status None (Ref.)			**1.00**	--	--	**1.00**	--	--
Current			**2.52**	0.59	10.72	**0.85**	0.03	29.36
Never			**0.98**	0.18	5.28	**0.05**	0.00	4.57
Ex			**0.65**	0.04	11.64	**0.45**	0.00	68.88
Pneumonia								
Failures [n (%)]	9 (6.2)	5 (3.4)						
Surv. time in yrs [mean (sd)]	2.8 (3.0)	4.5 (3.3)						
DRAD-ILD (cases) vs. Non-DRAD-ILD (controls)			**2.67**	0.71	10.05	**1.00**	0.06	15.99
BMI (kg/m^2) 18.5 - 24.9 (Ref.)			**1.00**	--	--	**1.00**	--	--
14.0 - 18.4			**.**	.	.	**.**	.	.
25.0 - 29.9			**.**	.	.	**.**	.	.
30.0 - 39.9			**.**	.	.	**.**	.	.
40.0 - 55.9			**.**	.	.	**.**	.	.
Unknown			**.**	.	.	**.**	.	.
Smoking status Non-smkrs (Ref.)			**1.00**	--	--	**1.00**	--	--
Curr-smkrs			**3.23**	0.31	33.47	**.**	.	.
Ex-smkrs			**2.44**	0.16	37.14	**.**	.	.
Unknown			**.**	.	.	**.**	.	.
Alcohol status None (Ref.)			**1.00**	--	--	**1.00**	--	--
Current			**.**	.	.	**.**	.	.
Never			**.**	.	.	**.**	.	.
Ex			**.**	.	.	**.**	.	.

DRAD-ILD	Cases (n=145)	Controls (n=145)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Respiratory (non-pneumonia) infections								
Failures [n (%)]	74 (51.0)	61 (42.1)						
Surv. time in yrs [mean (sd)]	1.4 (2.1)	2.8 (2.6)						
DRAD-ILD (cases) vs. Non-DRAD-ILD (controls)			**3.71**	2.17	6.33	**3.31**	1.72	6.38
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**0.71**	0.09	5.60	**3.30**	0.15	74.79
		25.0 - 29.9	**1.05**	0.41	2.69	**1.02**	0.31	3.33
		30.0 - 39.9	**0.36**	0.12	1.11	**0.43**	0.11	1.74
		40.0 - 55.9	**.**	.	.	**0.00**	0.00	.
		Unknown	**0.23**	0.07	0.79	**0.23**	0.03	1.65
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.37**	0.46	4.07	**1.48**	0.38	5.77
		Ex-smkrs	**3.85**	1.57	9.46	**3.69**	1.10	12.35
		Unknown	**0.33**	0.04	3.00	**2.75**	0.08	100.02
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**5.82**	1.22	27.81	**3.03**	0.37	24.85
		Never	**3.83**	0.76	19.30	**4.77**	0.46	50.00
		Ex	**3.27**	0.31	34.52	**3.78**	0.13	107.80
Pneumothorax								
Failures [n (%)]	2 (1.4)	0 (0)						
Surv. time in yrs [mean (sd)]	2.8 (3.0)	4.5 (3.3)						
DRAD-ILD (cases) vs. Non-DRAD-ILD (controls)			**.**	.	.	**.**	.	.
Bone fractures								
Failures [n (%)]	8 (5.5)	8 (5.5)						
Surv. time in yrs [mean (sd)]	2.7 (3.0)	4.3 (3.3)						
DRAD-ILD (cases) vs. Non-DRAD-ILD (controls)			**1.40**	0.44	4.41	**.**	.	.
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**0.37**	0.04	3.89	**.**	.	.
		30.0 - 39.9	**1.65**	0.10	28.06	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**1.28**	0.06	29.44	**.**	.	.
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**.**	.	.	**.**	.	.
		Ex-smkrs	**0.50**	0.05	5.51	**.**	.	.
		Unknown	**.**	.	.	**.**	.	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.00**	0.12	8.13	**.**	.	.
		Never	**1.00**	0.05	19.36	**.**	.	.
		Ex	**.**	.	.	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status; **L**=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

Table 4.5.3.3b DRAD-ILD: Results of proportional hazards regression analyses for incident cardiovascular-/cerebrovascular-/pulmonary-related comorbidities after index date

DRAD-ILD	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Congestive Heart Failure								
No. of subjects for analysis	**121**	**121**						
Failures [n (%)]	5 (4.1)	1 (0.8)						
Surv. time in yrs [mean (sd)]	2.8 (3.1)	4.7 (3.5)						
DRAD-ILD (cases) vs. Non-DRAD-ILD (controls)			**5.00**	0.58	42.79	**.**	.	.
Ischemic Heart Disease								
No. of subjects for analysis	**101**	**101**						
Failures [n (%)]	1 (1.0)	3 (3.0)						
Surv. time in yrs [mean (sd)]	2.9 (3.1)	4.5 (3.4)						
DRAD-ILD (cases) vs. Non-DRAD-ILD (controls)			**0.50**	0.05	5.51	**.**	.	.
Myocardial Infarction								
No. of subjects for analysis	**145**	**145**						
Failures [n (%)]	3 (2.1)	1 (0.7)						
Surv. time in yrs [mean (sd)]	2.8 (3.0)	4.5 (3.3)						
DRAD-ILD (cases) vs. Non-DRAD-ILD (controls)			**.**	.	.	**.**	.	.
Stroke / Transient Ischemic Attack (TIA)								
No. of subjects for analysis	**122**	**122**						
Failures [n (%)]	2 (1.6)	3 (2.5)						
Surv. time in yrs [mean (sd)]	2.9 (3.0)	4.8 (3.4)						
DRAD-ILD (cases) vs. Non-DRAD-ILD (controls)			**1.00**	0.14	7.10	**.**	.	.
Deep Vein Thrombosis								
No. of subjects for analysis	**135**	**135**						
Failures [n (%)]	3 (2.2)	1 (0.7)						
Surv. time in yrs [mean (sd)]	2.8 (2.9)	4.4 (3.3)						
DRAD-ILD (cases) vs. Non-DRAD-ILD (controls)			.	.	**.**	.	.	.
Pulmonary Embolism								
No. of subjects for analysis	**139**	**139**						
Failures [n (%)]	6 (4.3)	0 (0)						
Surv. time in yrs [mean (sd)]	2.8 (3.1)	4.5 (3.3)						
DRAD-ILD (cases) vs. Non-DRAD-ILD (controls)			**.**	.	.	**.**	.	.
Pulmonary Hypertension								
No. of subjects for analysis	**139**	**139**						
Failures [n (%)]	3 (2.2)	0 (0)						
Surv. time in yrs [mean (sd)]	2.8 (3.0)	4.5 (3.3)						
DRAD-ILD (cases) vs. Non-DRAD-ILD (controls)			**.**	.	.	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status; **L**=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

Table 4.5.3.3c DRAD-ILD: Results of proportional hazards regression analyses for an incident diagnosis of cancer after index date

DRAD-ILD	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Cancer in Situ Metastasis								
No. of subjects for analysis	**32**	**32**						
Failures [n (%)]	5 (15.6)	3 (9.4)						
Surv. time in yrs [mean (sd)]	3.2 (2.8)	4.6 (3.6)						
DRAD-ILD (cases) vs. Non-DRAD-ILD (controls)			**1.33**	0.30	5.96	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status; **L**=Lower, **U**=Upper, **CL**=Confidence Limit, **RR**=Rate ratio
. = Non-estimable

4.5.3.4 ILD associated with other diseases (ILD-ODIS)

During the follow-up period 271 (48%) subjects with ILD-ODIS and 128 (29%) non-ILD-ODIS subjects died. When investigating all-cause mortality as the outcome of interest, the mean (SD) survival time in the ILD-ODIS cohort was 4.5 (3.8) years versus 6.6 (4.2) years in the control group. After adjusting for smoking status, body mass index, and alcohol consumption status, the rate of all-cause mortality in the ILD-ODIS cohort remained approximately 5 times higher than the rate in the non-ILD-ODIS control group (RR 5.1, 95%CI: 3.6 to 7.2). Likewise, among the non-incident comorbidities investigated, rate ratios for pneumonia and respiratory (non-pneumonia) infections remained elevated after adjustment for smoking status, body mass index, and alcohol consumption status (see RRs and 95% CIs below). Among the incident cardiovascular outcomes investigated, the adjusted rate ratio for congestive heart failure was elevated (RR 3.4, 95%CI: 1.5 to 7.7). Among the other incident outcomes under investigation, the adjusted rate ratio for rheumatoid arthritis significantly elevated (RR 15.9, 95%CI: 3.2 to 79.6). Crude and adjusted rate ratios for certain incident comorbidities under investigation were non-estimable due to lack

of failures and/or sparsely populated strata. Further details of these analyses can be found in tables 4.5.3.4a-c below.

Table 4.5.3.4a ILD-ODIS: Results of proportional hazards regression analyses for all-cause mortality and selected non-incident comorbidities after index date

ILD-ODIS	Cases (n=560)	Controls (n=560)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
All-cause mortality								
Failures [n (%)]	271 (48.4)	128 (28.9)						
Surv. time in yrs [mean (sd)]	4.5 (3.8)	6.6 (4.2)						
ILD-ODIS (cases) vs. Non-ILD-ODIS (controls)			**4.60**	3.37	6.29	**5.11**	3.62	7.21
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**1.91**	0.48	7.56	**0.96**	0.17	5.47
		25.0 - 29.9	**0.74**	0.47	1.16	**0.72**	0.39	1.34
		30.0 - 39.9	**0.38**	0.20	0.71	**0.42**	0.18	0.98
		40.0 - 55.9	**2.80**	0.29	27.02	**15.92**	1.52	166.68
		Unknown	**0.83**	0.51	1.37	**0.74**	0.32	1.73
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.66**	1.00	2.73	**1.24**	0.61	2.52
		Ex-smkrs	**1.46**	0.86	2.46	**1.16**	0.58	2.34
		Unknown	**0.99**	0.56	1.74	**0.50**	0.18	1.41
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.98**	0.61	1.56	**0.49**	0.19	1.30
		Never	**0.96**	0.55	1.67	**0.37**	0.13	1.06
		Ex	**0.98**	0.19	5.15	**0.46**	0.05	4.02
Pneumonia								
Failures [n (%)]	78 (13.9)	31 (5.5)						
Surv. time in yrs [mean (sd)]	4.3 (3.7)	6.5 (4.2)						
ILD-ODIS (cases) vs. Non-ILD-ODIS (controls)			**7.22**	3.60	14.50	**16.72**	4.71	59.43
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**1.21**	0.57	2.58	**1.12**	0.27	4.66
		30.0 - 39.9	**0.93**	0.29	2.95	**2.49**	0.29	21.28
		40.0 - 55.9	**1.10**	0.07	18.10	**30.70**	0.92	1029.05
		Unknown	**1.10**	0.43	2.79	**3.65**	0.61	21.74
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.85**	0.36	2.01	**0.48**	0.09	2.53
		Ex-smkrs	**2.91**	0.97	8.74	**4.43**	0.44	44.48
		Unknown	**0.85**	0.31	2.33	**2.39**	0.15	37.02

ILD-ODIS	Cases (n=560)	Controls (n=560)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.39**	0.61	3.18	**4.20**	0.50	35.05
		Never	**1.45**	0.46	4.57	**1.39**	0.12	16.54
		Ex	**.**	.	.	**0.00**	0.00	.
Respiratory (non-pneumonia) infections								
Failures [n (%)]	369 (65.9)	270 (48.2)						
Surv. time in yrs [mean (sd)]	1.9 (2.3)	4.0 (3.5)						
ILD-ODIS (cases) vs. Non-ILD-ODIS (controls)			**3.03**	2.40	3.83	**3.25**	2.52	4.19
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**2.56**	0.90	7.31	**2.60**	0.80	8.49
		25.0 - 29.9	**0.76**	0.53	1.09	**0.74**	0.49	1.13
		30.0 - 39.9	**0.87**	0.54	1.41	**1.28**	0.72	2.27
		40.0 - 55.9	**2.18**	0.38	12.55	**5.32**	0.73	38.61
		Unknown	**0.86**	0.57	1.31	**1.21**	0.66	2.20
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.25**	0.83	1.88	**1.23**	0.76	2.00
		Ex-smkrs	**1.59**	1.05	2.40	**1.16**	0.71	1.89
		Unknown	**0.93**	0.55	1.57	**0.73**	0.33	1.63
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.17**	0.79	1.75	**1.25**	0.64	2.45
		Never	**0.98**	0.60	1.60	**0.79**	0.38	1.65
		Ex	**1.16**	0.32	4.20	**1.02**	0.20	5.31
Pneumothorax								
Failures [n (%)]	6 (1.1)	1 (0.18)						
Surv. time in yrs [mean (sd)]	4.5 (3.8)	6.6 (4.2)						
ILD-ODIS (cases) vs. Non-ILD-ODIS (controls)			**5.00**	0.58	42.79	**.**	.	.
Bone fractures								
Failures [n (%)]	46 (8.2)	56 (10.0)						
Surv. time in yrs [mean (sd)]	4.3 (3.7)	6.2 (4.1)						
ILD-ODIS (cases) vs. Non-ILD-ODIS (controls)			**1.46**	0.91	2.37	**1.64**	0.91	2.94
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**2.46**	0.21	28.92	**2.54**	0.14	45.74
		25.0 - 29.9	**0.80**	0.35	1.80	**0.61**	0.24	1.56
		30.0 - 39.9	**1.80**	0.53	6.06	**2.07**	0.55	7.75
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**1.12**	0.40	3.13	**0.89**	0.26	3.05
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**0.87**	0.34	2.19	**0.62**	0.21	1.84
		Ex-smkrs	**1.60**	0.64	4.02	**1.41**	0.47	4.22
		Unknown	**1.20**	0.38	3.79	**0.63**	0.12	3.41
					--			

ILD-ODIS	Cases (n=560)	Controls (n=560)	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Alcohol status		None (Ref.)	**1.00**	--		**1.00**	--	--
		Current	**0.60**	0.21	1.71	**0.55**	0.11	2.83
		Never	**0.57**	0.14	2.38	**0.46**	0.07	3.23
		Ex	**0.77**	0.05	13.26	**1.12**	0.03	40.88

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status; **CL**=Confidence Limit, **L**=Lower, **U**=Upper, **RR**=Rate ratio
. = Non-estimable

Table 4.5.3.4b ILD-ODIS: Results of proportional hazards regression analyses for incident cardiovascular- / cerebrovascular- / pulmonary-related comorbidities after index date

ILD-ODIS	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Congestive Heart Failure								
No. of subjects for analysis	**429**	**429**						
Failures [n (%)]	40 (9.3)	19 (4.4)						
Surv. time in yrs [mean (sd)]	4.8 (3.8)	6.8 (4.2)						
ILD-ODIS (cases) vs. Non-ILD-ODIS (controls)			**3.60**	1.79	7.25	**3.40**	1.50	7.70
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**2.03**	0.18	23.00	**1.28**	0.05	35.36
		25.0 - 29.9	**1.12**	0.37	3.44	**1.73**	0.33	9.00
		30.0 - 39.9	**0.87**	0.23	3.28	**1.48**	0.27	8.08
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**1.04**	0.34	3.18	**1.62**	0.14	18.71
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**4.58**	0.90	23.35	**4.26**	0.49	36.79
		Ex-smkrs	**3.18**	0.81	12.49	**3.78**	0.59	24.05
		Unknown	**2.65**	0.61	11.57	**0.86**	0.05	13.74
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.60**	0.16	2.28	**0.64**	0.01	28.90
		Never	**0.83**	0.18	3.86	**0.32**	0.01	15.40
		Ex	**.**	.	.	**.**	.	.
Ischemic Heart Disease								
No. of subjects for analysis	**366**	**366**						
Failures [n (%)]	28 (7.7)	29 (7.9)						
Surv. time in yrs [mean (sd)]	4.7 (3.9)	6.5 (4.2)						
ILD-ODIS (cases) vs. Non-ILD-ODIS (controls)			**1.75**	0.86	3.56	**4.21**	0.52	34.18
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**1.02**	0.06	18.41	**0.76**	0.02	33.42
		25.0 - 29.9	**4.55**	0.92	22.53	**43.57**	0.84	2262.43
		30.0 - 39.9	**4.06**	0.41	40.22	**21.21**	0.33	1359.81
		40.0 - 55.9	**.**	.	.	**.**	.	.

ILD-ODIS	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
		Unknown	**1.04**	0.20	5.46	**0.90**	0.03	31.66
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**8.83**	1.24	63.05	**241.62**	0.33	177061.40
		Ex-smkrs	**2.92**	0.74	11.49	**7.19**	0.53	98.26
		Unknown	**2.37**	0.25	23.04	**52.41**	0.04	71792.94
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.41**	0.44	4.47	**0.14**	0.01	2.60
		Never	**1.33**	0.20	8.64	**0.04**	0.00	3.68
		Ex	**.**	.	.	**.**	.	.
Myocardial Infarction								
No. of subjects for analysis	**560**	**560**						
Failures [n (%)]	20 (3.6)	25 (4.5)						
Surv. time in yrs [mean (sd)]	4.5 (3.8)	6.4 (4.2)						
ILD-ODIS (cases) vs. Non-ILD-ODIS (controls)			**1.00**	0.45	2.23	**0.62**	0.11	3.49
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**1.77**	0.42	7.54	**6.12**	0.22	169.36
		30.0 - 39.9	**0.58**	0.10	3.37	**0.03**	0.00	1.76
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**1.58**	0.35	7.18	**0.37**	0.00	33.83
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**6.03**	0.59	62.04	**607.01**	1.23	300739.80
		Ex-smkrs	**2.31**	0.41	12.92	**16.73**	0.41	676.46
		Unknown	**3.10**	0.34	28.49	**0.00**	0.00	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.51**	0.09	2.89	**.**	.	.
		Never	**0.48**	0.08	3.09	**.**	.	.
		Ex	**.**	.	.	**.**	.	.
Stroke / Transient Ischemic Attack (TIA)								
No. of subjects for analysis	**467**	**467**						
Failures [n (%)]	26 (5.6)	37 (7.9)						
Surv. time in yrs [mean (sd)]	4.6 (3.9)	6.5 (4.2)						
ILD-ODIS (cases) vs. Non-ILD-ODIS (controls)			**1.75**	0.86	3.56	**3.00**	0.86	10.49
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**1.00**	0.06	15.99	**0.59**	0.02	15.75
		25.0 - 29.9	**1.14**	0.31	4.22	**1.11**	0.23	5.41
		30.0 - 39.9	**.**	.	.	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**0.46**	0.10	2.20	**0.43**	0.04	4.16
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--

ILD-ODIS	Cases	Controls	Crude RR	L 95% CL	U 95% CL	Adjusted* RR	L 95% CL	U 95% CL
		Curr-smkrs	**2.05**	0.51	8.30	**1.00**	0.12	8.78
		Ex-smkrs	**3.05**	0.85	11.01	**2.84**	0.43	18.60
		Unknown	**1.47**	0.27	8.14	**0.00**	0.00	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**1.13**	0.22	5.88	**.**	.	.
		Never	**0.79**	0.13	4.72	**.**	.	.
		Ex	**.**	.	.	**.**	.	.
Deep Vein Thrombosis								
No. of subjects for analysis	**530**	**530**						
Failures [n (%)]	15 (2.8)	11 (2.1)						
Surv. time in yrs [mean (sd)]	4.5 (3.8)	6.6 (4.2)						
ILD-ODIS (cases) vs. Non-ILD-ODIS (controls)			**2.00**	0.81	4.96	**.**	.	.
BMI (kg/m^2)		18.5 - 24.9 (Ref.)	**1.00**	--	--	**1.00**	--	--
		14.0 - 18.4	**.**	.	.	**.**	.	.
		25.0 - 29.9	**12.35**	0.70	218.26	**.**	.	.
		30.0 - 39.9	**.**	.	.	**.**	.	.
		40.0 - 55.9	**.**	.	.	**.**	.	.
		Unknown	**2.53**	0.25	25.27	**.**	.	.
Smoking status		Non-smkrs (Ref.)	**1.00**	--	--	**1.00**	--	--
		Curr-smkrs	**1.72**	0.28	10.59	**.**	.	.
		Ex-smkrs	**0.96**	0.14	6.80	**.**	.	.
		Unknown	**4.54**	0.28	73.93	**.**	.	.
Alcohol status		None (Ref.)	**1.00**	--	--	**1.00**	--	--
		Current	**0.75**	0.17	3.35	**.**	.	.
		Never	**.**	.	.	**.**	.	.
		Ex	**.**	.	.	**.**	.	.
Pulmonary Embolism								
No. of subjects for analysis	**532**	**532**						
Failures [n (%)]	14 (2.6)	1 (0.2)						
Surv. time in yrs [mean (sd)]	4.4 (3.8)	6.7 (4.2)						
ILD-ODIS (cases) vs. Non-ILD-ODIS (controls)			**13.00**	1.70	99.35	**.**	.	.
Pulmonary Hypertension								
No. of subjects for analysis	**559**	**559**						
Failures [n (%)]	7 (1.3)	1 (0.2)						
Surv. time in yrs [mean (sd)]	4.5 (3.8)	6.6 (4.2)						
ILD assoc. w/other dis. vs. Non-ILD assoc. w/other dis.			**.**	.	.	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status
CL=Confidence Limit, **L**=Lower, **U**=Upper, **RR**=Rate ratio
. = Non-estimable

Table 4.5.3.4c ILD-ODIS: Results of proportional hazards regression analyses for an incident diagnosis of cancer after index date

ILD-ODIS	Cases	Controls	**Crude RR**	L 95% CL	U 95% CL	**Adjusted* RR**	L 95% CL	U 95% CL
Cancer in Situ Metastasis								
No. of subjects for analysis	**454**	**454**						
Failures [n (%)]	53 (11.7)	51 (11.2)						
Surv. time in yrs [mean (sd)]	4.5 (3.8)	6.6 (4.2)						
ILD-ODIS (cases) vs. Non-ILD-ODIS (controls)			**1.33**	0.83	2.14	**1.20**	0.71	2.02
BMI (kg/m^2)	18.5 - 24.9 (Ref.)		**1.00**	--	--	**1.00**	--	--
	14.0 - 18.4		**.**	.	.	**.**	.	.
	25.0 - 29.9		**0.80**	0.37	1.77	**0.88**	0.37	2.09
	30.0 - 39.9		**0.77**	0.23	2.59	**1.01**	0.27	3.85
	40.0 - 55.9		**.**	.	.	**.**	.	.
	Unknown		**0.42**	0.14	1.30	**0.45**	0.11	1.75
Smoking status	Non-smkrs (Ref.)		**1.00**	--	--	**1.00**	--	--
	Curr-smkrs		**1.60**	0.67	3.84	**2.02**	0.75	5.49
	Ex-smkrs		**1.55**	0.54	4.39	**1.32**	0.41	4.21
	Unknown		**0.74**	0.22	2.49	**1.04**	0.23	4.77
Alcohol status	None (Ref.)		**1.00**	--	--	**1.00**	--	--
	Current		**1.88**	0.67	5.30	**0.96**	0.22	4.31
	Never		**1.76**	0.57	5.42	**0.79**	0.17	3.75
	Ex		**.**	.	.	**.**	.	.

***** = Simultaneous adjustment of case-control status, smoking status, BMI, and alcohol consumption status
CL=Confidence Limit, **L**=Lower, **U**=Upper, **RR**=Rate ratio
. = Non-estimable

5 Discussion

Cases with incident ILD diagnoses were identified from the BCDSP-GPRD subset. Patients with less than 3 years of ILD-free history in the database prior to a first-time recording of an ILD diagnosis were excluded in order to increase the likelihood of capturing incident rather than prevalent cases. For this reason and in light of the fact that we did not capture existing ILD patients (i.e. those diagnosed prior to 1995 and still alive during our study window), the prevalence figures presented here (especially for the earlier years under investigation) are likely to be underestimated.

Despite implementation of the exclusion criterion mentioned above, we cannot guarantee that all prevalent cases were actually excluded from our cohort. Although it is unlikely to have played a major role in the present study, having included any prevalent cases may have resulted in an overestimation of survival time in our models, since prevalent cases are by nature 'survivors' and will have contributed greater lengths of survival time (as opposed to incident cases). Therefore, the extent to which such misclassification is present in our study population may have led to some underestimation of incidence and mortality rates.

A potential weakness in this study could be the validity of ILD diagnoses, as we have not validated it directly. However, the validity of a number diagnoses, including death, has been tested in the UK GPRD and consistently found to be high [Jick H et al. 1991, Jick H et al. 1992, Jick SS et al. 2003]. Furthermore, the validity of one type of ILD, Cryptogenic Fibrosing Alveolitis, has been assessed and was also found to be high [Hubbard R et al. 2003]. Furthermore, it is rather unlikely that GPs would record differential ILD diagnoses in their records unless they have been verified by hospital and/or specialist referrals [Gribbin J et al. 2006]. Nevertheless, the accuracy of diagnoses made by healthcare providers who do not have significant expertise in the field of ILD remains a cause of concern. While the clinico-radio-pathologic (CRP) consensus approach to ILD diagnosis functions well in the hands of "recognized, senior experts" it has been found to work less reliably outside academic specialty centers [Flaherty KR et al. 2004]. Therefore, the difficulties encountered by non-ILD specialists when applying the ATS/ERS ILD-disease classification guidelines will have limited the accuracy of the ILD diagnoses in the database. These factors are

unavoidable limitations to the present study, and for that matter, to any retrospective epidemiological investigation of ILD.

Application of the ATS/ERS diagnosis classification in the present study may have been problematic. Firstly, it is likely that some UK pulmonologists and ILD specialists were late adopters of the ATS/ERS ILD-disease classification guidelines. Secondly, it is likely that some patients under study did not undergo a full diagnostic work-up or whose ILD diagnoses were not achieved by the CRP consensus approach. Thirdly, diagnosis terminology may not be completely in line with diagnosis terminology used in the guidelines. For example, the diagnoses of Cryptogenic Fibrosing Alveolitis (CFA) and Idiopathic Fibrosing Alveolitis (IFA) have traditionally been used in the UK for the past 20-30 years, and although the ATS/ERS consensus statement explicitly states that CFA and IPF are synonymous terms, CFA was actually used as an umbrella term for a clinical presentation seen commonly in IPF, including some of the newly termed IIPs and some cases of EAA. Furthermore, no READ codes are to be found for some of the rarer IIPs such as LIP and LAM. For this reason, and due to the fact that the number of patients found with similar diagnosis was quite small, no analyses were undertaken for such disease entities.

For many ILD subgroups an increase in incidence density and prevalence over time was observed. We cannot tell whether this finding reflects a real increase, or whether such findings are, at least to a certain extent, attributable to secular trends. Firstly, during the study window of the present epidemiologic investigation, major political changes in the NHS occurred, including more than a doubling in funding. Secondly, a certain proportion of incident cases in this time period may have been due to

increased recognition of ILD via the increased use of high resolution computer tomography (HRCT). Thirdly, following release of the ATS/ERS consensus statements around 2001-2002, a greater appreciation of the value of precise diagnosis according to such criteria will likely have occurred, not to mention increased patient expectations. For the above reasons, an increase in case ascertainment may have played a role in the observed increase in incidence rates for some ILD subgroups. Furthermore, with an increase in case ascertainment comes the increased likelihood of having captured some patients with earlier-staged (and/or milder forms of) disease. The degree to which this bias is present in our investigation could have contributed to both an increase in incidence density and survival time.

Despite the potential limitations mentioned above, this study made use of data from the general population of a large, defined geographic region. Therefore, the potential for underestimation of prevalence and incidence is greatly reduced. Furthermore, the UK NHS provides universal health coverage for all UK residents, and as such, no segment of the population (e.g. elderly, based on socioeconomic status or type of health insurance plan, etc.) is excluded from the GPRD.

5.1 Epidemiology

5.1.1 Etiology

Epidemiologic data on ILD in the general population are limited. It is estimated that approximately two-thirds of ILD cases have no reported aetiology (i.e. the IIPs), while the remaining one-third results from a variety of exposures including infections, drugs, radiation, connective tissue disease and environmental/occupational

exposures [Raghu G et al. 2004]. Recently, population-based data in the UK have been used to identify potential risk factors for IPF, one of the most common IIPs. In a case-control study using general practice medical records, researchers observed that IPF patients more frequently had a history of gastro-oesophageal reflux disease (GERD) and use of ulcer drugs [Gribbin J et al. 2009]. The same researchers also found associations between both having had a diagnosis of diabetes mellitus (DM) and using insulin with an increased likelihood of developing IPF. The authors speculate that having a chronic disease such as DM or GERD could possibly be associated with greater likelihood of ascertaining a diagnosis of IPF. An argument against this theory, however, is found in their observation that IPF was not associated with having other chronic diseases such as gout or hyperlipidaemia, and therefore a conclusion was drawn that ascertainment bias is not a likely explanation of the observed associations. Nevertheless, it cannot be ignored that both DM and GERD are associated with other respiratory/pulmonary complications, and it is possible that such patients might be more frequently referred to pulmonary specialist centers.

5.1.2 Disease frequency

Historically, it has been difficult to arrive at precise estimates of incidence and prevalence of ILD in the general population. Most published studies have relied on data from disease registries and hospital clinics, where case ascertainment and selection biases have most likely led to an underestimation of the true prevalence and incidence of ILD in the general population. Nevertheless, in 1994, Coultas et al. published a landmark epidemiologic study on ILD using data from a dedicated,

population-based ILD registry in the defined region of Bernalillo County, New Mexico, USA, where multiple methods of case ascertainment and systematic medical chart-review were used.6 In that study, the overall prevalence and incidence of non-differential ILD were estimated to be 74.1 cases per 100'000 and 28.8 cases/10^5/year, respectively, with approximately one-third of the incident cases classified as IPF [Coultas DB et al. 1994]. Both incidence and prevalence were higher in men than women.

Published population-based data on the incidence and prevalence of ILD from other countries are scant. Where available, most reports are specific to IPF rather than to ILD as a whole. Nevertheless, these published reports suggest national differences in the prevalence of IPF and may also be indicative of the comparative prevalence estimates of other ILDs. In the Japanese Hokkaido registry, prevalence of IPF was estimated at approximately 4 cases / 10^5 [Munakata M et al. 1994], while in a national Finnish registry, estimates ranged from 16-18 cases / 10^5 [Hodgson U et al. 2002]. In two regions of the Czech Republic, prevalence estimates of IPF rose from 7 to 12 cases /10^5 from 1981 to 1990 [Kolek V 2009]. With respect to the incidence rates of ILD, publications on population-based data range from approximately 4-5/10^5/year in Southern Spain [Lopez-Campos JL et al. 2004] and in Greece [Karakatsani A et al. 2009] to approximately 33/10^5/year in Denmark [Kornum JB et al. 2008]. Some of this 7-8-fold difference may be explained by different case ascertainment methodologies. In a publication from 2001, a Working Group of the ERS concluded that there is little good epidemiological data on ILD, with many questions remaining unanswered [Demedts M et al. 2001] More recent reports continue to express this sentiment and

cite the need for more epidemiologic research in the full spectrum of ILD (not only in IPF) using population-based data where selection and case ascertainment biases are greatly reduced [Olson AL et al. 2008, Wells AU 2008].

Existing published data from registries and surveys suggest Sarcoidosis and IPF as the most common ILDs, followed by CTD-associated ILD (CTD-ILD) and HP. Among the seven subcategories of IIP however, IPF is the most common followed by NSIP.

5.1.3 Natural history

Most ILDs are insidious in onset, with dyspnea and non-productive cough being the predominant symptoms. Very little published data are available describing the natural histories (e.g. incident co-morbidity and complications post ILD diagnosis) of non-IPF ILDs. The clinical course of non-IPF ILDs ranges from complete remission for COP and RBILD to the rapidly progressive fatal course commonly seen in AIP [Katzenstein AL & Meyers JL 1998, Noth I & Martinez FJ 2007].

A diagnosis of IPF, the most frequent of the IIPs, is associated with a prognosis worse than most ILDs [ATS/ERS 2002, Katzenstein AL & Meyers JL 1998, Noth I & Martinez FJ 2007]. In many studies conducted after development of the ATS/ERS guidelines, median survival of IPF patients ranged from 2 to 4 years after diagnosis with only 20 to 40% of patients reaching 5-year survival [Kim DS et al 2006]. Historically, the natural history of IPF has been described as one of relentless decline in respiratory function. However, observations made during recent clinical studies indicate that rather small decreases in the diffusing capacity for carbon monoxide (DLCO) and forced vital capacity (FVC) may occur over long periods of time, as well

as variability in clinical course [Kim DS et al 2006]. Some patients exhibit slow progression over longer periods of time while others experience periods of relative stability punctuated by episodes of acute deterioration. Such acute episodes are described as abrupt, unexpected deteriorations in the underlying lung disease not attributable to (but perhaps secondary to undiagnosed) infections, pulmonary embolism, or heart failure; they are recognized as common, highly morbid clinical events (now termed Acute Exacerbations of IPF) and as such have received increasing attention during recent years [Behr J & Thannickal VL 2009, Karakatsani A et al. 2009, Kim DS et al 2006]. Acute exacerbations have also been reported in HP and may be a feature common to other fibrosing ILDs [Behr J & Thannickal VL 2009, Olson AL et al. 2008]. Several hypotheses on the etiology of acute exacerbations of IPF have been put forth such as occult viral infections (e.g. herpes virus), lung injury as a result of drug toxicity, and adverse effects from pharmacologic agents commonly used in the treatment of the underlying ILD [Collard HR et al 2007, Olson AL et al. 2008]. More research is necessary in order to characterize incident co-morbidity and clinical complications in the full spectrum of ILD.

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7 Manuscripts

7.1 Incidence of the pneumoconioses in the United Kingdom general population between 1997 and 2008

Authors:

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7.1.1 Abstract

Background

Incidence of the pneumoconioses in the UK is primarily estimated using occupational-based registries and disability pension schemes. These sources indicate a downward trend in incidence of the pneumoconioses from 1995 onwards. There are no previously published general population-based observational studies quantifying the incidence of the pneumococinoses in the UK.

Objectives

The aim of this study was to investigate the incidence of the pneumoconioses in the UK general population between 1997-2008 using data from the GPRD.

Methods

Data from the UK-based General Practice Research Database was used to estimate the incidence of pneumoconioses over a 12-year period (1997-2008). Crude incidence rates for asbestosis and non-asbestos-related pneumoconioses were stratified by gender, age group, and calendar period, and rate ratios were adjusted using Poisson regression.

Results

The majority of cases was diagnosed with asbestosis, and the overall, crude incidence density for this pneumoconiosis during the 12-year study period was 2.7 (95% CI: 2.5 to 2.9) per 100,000 person-years. Incidence increased progressively during the period 1997-2005 and then decreased slightly during the period 2006-2008, even after controlling for the strong effect of an ageing UK population. The

non-asbestos pneumoconioses, in contrast to asbestosis, showed a progressive reduction in incidence from 2003 onwards.

Conclusions

This study demonstrates that the pneumoconioses remain an important public health issue and furthermore, documents an overall increase in asbestosis incidence in the UK between 1997 and 2008.

7.1.2 Introduction

The pneumoconioses are a group of interstitial lung diseases caused by inhalation and retention of inorganic dusts. These diseases typically evolve over decades of occupational exposure to mineral dusts and are characterized by the formation of nodular, fibrotic changes to the lung parenchyma [1]. The relatively long time lag between occupational exposure and disease onset is reflected in the fact that the majority of incident cases is detected in retired workers [2].

The primary data sources used to investigate incidence and prevalence of the pneumoconioses in the United Kingdom (UK) are the Department for Work and Pensions (DWP) Industrial Injuries and Disablement Benefit (IIDB) scheme and The Health and Occupation Reporting (THOR) network. During the period 1998-2008 the number of new cases of pneumoconiosis reported by chest and occupational physicians within the THOR network fluctuated between 108 and 321 cases per year [3]. Trends in incidence of the pneumoconioses from both sources are difficult to interpret due to varying definitions of disease states and changing eligibility criteria for compensation benefits over time. Additionally, it is known that case numbers have

been affected by fluctuations in the numbers and reporting habits of participating health care practitioners over time [3]. Data from THOR and the IIDB scheme suggest a downward trend in the annual number of new pneumoconiosis cases from 2005 onward [3,4]. However, as is the case when using data from disease registries, measures of disease frequency from both of these sources may be underestimated due to case ascertainment and selection biases.

The UK General Practice Research Database (GPRD) contains anonymised electronic patient records collected from routine general practice. The geographic, age, and gender distributions of the GPRD population have been shown to be representative of the U.K. general population [5]. The aim of this study was to investigate the incidence of the pneumoconioses in the UK general population between 1997-2008 using data from the GPRD.

7.1.3 Materials and methods

Data source

The GPRD has been described elsewhere in detail [5], but briefly, it is a large and well-validated U.K.-based database that was established in June 1987. The GPRD encompasses nearly five million patients who are or were enrolled with selected general practitioners (GPs) throughout the U.K., covering approximately 50 million patient-years of follow-up. The participating GPs have been trained to record medical information in a standard manner and to provide anonymized records to the GPRD Group within the Medicines and Healthcare products Regulatory Agency (MHRA), the UK's medicines and devices regulator. The recorded data include demographic

information, medical diagnoses, and drug prescriptions. The Boston Collaborative Drug Surveillance Program (BCDSP) and its associated researchers at the Basel Pharmacoepidemiology Unit (University of Basel) use a large subset of data from the GPRD; data from general practices that have failed to report consistent numbers of drug prescriptions and diagnostic codes over time have been removed from the BCDSP GPRD [6]. Data from the GPRD have been used in previous studies involving interstitial lung disease and use of the data for respiratory epidemiology has been validated [7,8]. The GPRD is managed by the Medicines and Healthcare products Regulatory Agency (MHRA), and the present study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA database research.

Study population

We identified in the GPRD all patients with a first-time diagnosis of a pneumoconiosis between January 1, 1997 and December 31, 2008. Diagnoses in the GPRD are coded using the Read coding system, and our list of pneumoconiosis diagnoses included any Read code explicitly mentioning pneumoconiosis, silicosis, silica/silicate pneumoconiosis, silicotic fibrosis, talc pneumoconiosis, siderosis, berylliosis, stannosis, asbestosis, , and coal workers pneumoconiosis. Read codes without explicit mention of a pneumoconiosis such as “Pneumopathy due to inhalation of other dust NOS” were not used. In order to increase the likelihood of capturing incident rather than prevalent cases, we excluded patients with less than 3 years of active recording history prior to the date of the first pneumoconiosis diagnosis.

Data analysis

Person-time denominators for the calculations of incidence density were derived from the GPRD. For each calendar period, only those patients in the GPRD who were alive, actively registered, and had at least 3 years of recorded history contributed person-time to the denominators. Incident cases were grouped into four age groups (<60, 60-69, 70-79, and ≥80 years) and calendar time was divided into four 3-year periods (1997-1999, 2000-2002, 2003-2005, and 2006-2008). Crude incidence rates were calculated for the asbestos-related pneumoconiosis (i.e. asbestosis), and for non-asbestos-related pneumoconioses separately. The crude rates were stratified by gender, age group, and calendar period, with exact 95% confidence intervals being calculated from the Poisson distribution. In order to model disease incidence and estimate incidence rate ratios, fixed-effects Poisson multivariate regression was used. We accounted for overdispersion in all regression models using the quasi-likelihood approach, that is, by fixing the scaled deviance at unity and introducing a dispersion parameter into the model which adjusted the standard errors of the parameter estimates. All analyses were performed with the statistical software SAS (release 9.2, SAS Institute, Inc., Cary, NC, USA).

7.1.4 Results

A total of 1070 patients with an incident diagnosis of any type of pneumoconiosis were identified during the period 1997-2008, which included 840 (87.5%) cases of asbestosis and 230 cases of non-asbestos-related pneumoconioses. The frequency distribution of incident diagnoses is shown in Table 1.

Results: non-asbestos-related pneumoconiosis

The mean age (SD) at diagnosis was 70 (13.9) years and 217 (94%) cases were male. Females were younger than males at the time of first diagnosis (57.8 years (SD 21.8) vs. 71.1 years (SD 13.0), respectively), and the majority of diagnosed cases was 70 years of age and over.

Between 1997 and 2008 the overall incidence density rate of the non-asbestos-related pneumonconioses was 0.74 (95% CI: 0.65 to 0.84) per 100,000 person-years, and the rate in males was approximately 16-fold that of the rate in females. The incidence density increased during the period 1997-2002 (from 0.82 [95% CI: 0.62 to 1.07] during 1997-1999 to 1.09 [95% CI: 0.87 to 1.35] during 2000-2002 per 100,000 person-years), and decreased progressively thereafter from 2003-2008. Crude incidence rates by calendar period for the non-asbestos-related pneumoconioses are shown in Table 2. Poisson regression modelling of incidence rates for the non-asbestos-related pneumoconioses yielded no statistically significant heterogeneity of rates over time (p for trend = 0.1017) (see results in Table 2)

Results: asbestosis

The mean age (SD) at diagnosis was 69 (11.4) years and 784 (93%) cases were male. Females were younger than males at the time of first diagnosis (61.8 years (SD 22.1) vs. 70.0 years (SD 10.0), respectively), and the majority of cases was diagnosed in the age group 60-79 years. The age distribution of cases is shown in Figure 1.

Between 1997 and 2008 the overall incidence density rate of asbestosis was 2.7 (95% CI: 2.5 to 2.9) per 100,000 person-years, and the rate in males was approximately 18-fold that of the rate in females. The analysis of crude incidence density for asbestosis yielded progressively increasing rates during the period 1997-2005 (from 1.6 [95% CI: 1.4 to 2.0] during the period 1997-1999 to 3.2 [95% CI: 2.9 to 3.6] per 100'000 person-years), with a slight downward blip during the period 2006-2008. Crude incidence rates by calendar period for asbestosis are shown in Table 3.

In the asbestosis cohort there was evidence of statistically significant heterogeneity of incidence rate ratios over time (p=0.024), after adjusting for the effects of age and gender. The incidence density increased from the period 1997-1999 to 2000-2002 by a factor of 1.5. Using the same baseline period, the incidence nearly doubled during the period 2003-2005 (IRR=1.9). Incidence rate ratios for asbestosis are shown in Table 4.

To provide an additional estimate of the average annual increase in the incidence of asbestosis we repeated our analyses fitting year as a continuous variable. After controlling for the effects of age and gender, we estimated the average annual increase in the incidence of abestosis to be 6% during the 12-year study period (IRR 1.064, 95% CI: 1.04 to 1.09, p<0.0001).

7.1.5 Discussion

In this large, general-population-based cohort of pneumoconiosis patients, the overall incidence rates for asbestos- and non-asbestos-related pneumoconioses were

approximately 3 and 1 per 100'000 UK population per year, respectively, suggesting that each year during the period 1997-2008 there were ~ 1'800 new cases of asbestosis and 600 new cases of non-asbestos-related pneumoconiosis in the UK. The incidence of asbestosis increased progressively during the period 1997-2005 and then decreased slightly during the period 2006-2008, while the incidence of non-asbestos-related pneumoconiosis showed progressive decline from 2003 to 2008. Incidence rates were substantially higher in men than in women, likely reflecting the industrial-occupational nature of the disease etiology.

The majority of cases in our cohort (~80%) was diagnosed with asbestosis, and the observed increase in incidence during the study period would seem to be in line with the estimation that peak global incidence of asbestos-related disease is expected to occur 30 to 40 years after the period of peak asbestos usage (i.e., the 1960s and 1970s) [9]. This is further reflected in a report by the U.K. Health and Safety Executive (HSE) which predicts increasing rates of mesothelioma-related mortality until around 2015, after which rates are expected to decline [10,11]. Therefore, the projected, overall annual estimate of ~ 1'800 new cases of asbestosis will probably not continue far into the future. From the analysis of non-asbestos related pneumoconiosis, it can be seen that incidence of pneumoconiosis due to causes other than asbestos has declined over time, except for a relative rise in incidence noted during the period 2000-2002.

A potential weakness of the present study could be the validity of pneumoconiosis diagnoses, as we have not tested these directly. However, the validity of many disease diagnoses has been assessed in the UK GPRD and consistently found to be

high [6,12,13]. Furthermore, other researchers have reported a high validity of the diagnosis of idiopathic pulmonary fibrosis, another interstitial lung disease, in the GPRD [14]. Moreover, it is unlikely that general practitioners would record a pneumoconiosis diagnosis without confirmation by specialist referral. Therefore, we expect the diagnoses used for the present study to have high specificity.

On the other hand, the authors are aware that the sensitivity of the diagnoses used may not be as high as the specificity. Two main reasons for this are the potential for misclassification of true pneumoconiosis cases into less specific disease diagnosis categories and the possibility of having missed less severe cases. For instance, we did not use less specific respiratory-related diagnosis codes such as “lung disease due to other external agents NOS” or “other external agent causing respiratory condition” in our case selection algorithm. Overall there were 649 cases with such an unspecific diagnosis which we subsequently reviewed in more detail. Only 10 of them (1.5%) had some evidence of a pneumoconiosis diagnosis at a later point in time in their patient record, which makes substantial misclassification unlikely. It is also possible that less severe cases have escaped detection by general practitioners and specialists. Thus it is possible that we did not have available for analysis all true pneumoconiosis cases from the given sampling frame, which means that we may have underestimated the true incidence density of the pneumoconioses in the UK. Furthermore, we cannot be certain that all newly identified cases were indeed incident cases. However, we excluded cases with less than 3 years of recorded medical history in order to minimize the possibility of including prevalent cases in our incidence numerators, so we expect the occurrence of such error to be minimal. To

the extent that this error occurred it will have resulted in a small overestimation of the incidence density rates. Moreover, the percentage of cases disregarded due to the above exclusion criterion was 11% of the total number of cases identified during the defined study window (2'071 vs. 1'843), and the percentages of cases excluded across the study time periods remained relatively stable at 10-12%. This would support the conclusion that the results presented here are not influenced by fluctuations in the frequency of recorded diagnoses of pneumoconiosis.

Despite the potential limitations mentioned above, this study determined the best current estimates of incidence density for inorganic dust pneumoconioses in the UK general population. We have been unable to find any other general population-based cohort analyses in the U.K. with which to compare our results. Also, comparison of our incidence estimates to those published from the Surveillance of work-related and Occupational Respiratory Disease (SWORD) -- as part of the THOR network -- is difficult. Recent analyses of SWORD data yielded an average annual decline in pneumoconiosis incidence of -0.8% (95% CI: -4.8% to +3.3%) over the period 1999-2006 [15]. However, with respect to age and gender demography, some similarities can be noted; nearly all cases were males (>97%) with a mean age between 66 and 70 years, and approximately 55% of all cases were observed in the 60-75 year age range. Finally, it is acknowledged by the Health Safety Executive (HSE) – the national independent watchdog for work-related health, safety, and illness in Great Britain – that incidence figures may be substantially underestimated by THOR "since the scheme will only include those cases that are serious enough to be seen by a

chest consultant, or that occur in individuals with access to occupational physicians" [3].

The observed upward trend in asbestosis incidence in the present study should be interpreted with caution. We cannot tell whether this finding reflects a real increase, or whether it is, at least to a certain extent, attributable to secular trends. Firstly, during the study window major political changes in the NHS occurred, including more than a doubling in funding under the auspices of the New Deal [16]. This investment in national health care was in part used to boost capacity of NHS services and to modernize facilities, thus potentially increasing the likelihood of detecting new cases of pneumoconioses. Secondly, a certain proportion of incident cases in this time period may have been due to increased recognition of interstitial lung diseases in general via the increased use of high resolution computed tomography (HRCT). Thirdly, following publication of both the British Thoracic Society's guideline on diagnosis and care of diffuse parenchymal lung disease in 1999 [17] and the ATS/ERS consensus statements on idiopathic interstitial pneumonia in 2002 [18], a greater appreciation of the value of precise diagnosis according to defined criteria will likely have occurred, not to mention increased patient expectations. Finally, the observed increase in non-asbestos related pneumoconiosis from 1997-1999 to 2000-2002 could be partly attributable to a publicity campaign by the DWP around 2002 inviting people whose claims had been wrongly disallowed between 1994 and 1999 to re-claim [3]. For the above reasons, an increase in case ascertainment may have played a role in the observed increase in incidence density of asbestosis. However, the observed numeric decline in incidence of the non-asbestos pneumoconioses from

2003 onwards would argue against increased case ascertainment being responsible for the progressive upward trend in incidence of asbestosis until the end of 2005.

Conclusions

This study makes use of data from a well-validated database which has consistently been found to be representative of the UK general population. To our knowledge this is the first general population-based observational study quantifying incidence rates of pneumoconioses in the UK. Further research using data sources such as the UK GPRD is needed to assess future trends in pneumoconiosis incidence and to confirm the assumption that asbestos-related diseases are truly beginning to decline in incidence as a consequence of health and safety measures enacted at the end of the last century.

7.1.6 Tables and figures

Table 1. Frequency of incident pneumoconiosis diagnoses (N=1070).

Diagnosis codes	Frequency	Percent
Asbestos-related (Total)	**840**	100.00%
Asbestosis	826	98.33%
Asbestosis NOS	14	1.67%
Non-Asbestos-related (Total)	**230**	100.00%
Pneumoconioses NOS	173	75.22%
Coal workers pneumoconiosis	17	7.39%
Silica and silicate pneumoconiosis	7	3.04%
Talc pneumoconiosis	1	0.43%
Simple silicosis	5	2.17%
Massive silicotic fibrosis	1	0.43%
Silica pneumoconiosis NOS	6	2.61%
Pneumoconiosis due to other inorganic dust	1	0.43%
Chronic beryllium disease	1	0.43%
Siderosis	8	3.48%
Stannosis	1	0.43%
Pneumoconiosis due to inorganic dust NOS	9	3.91%

Table 2. Crude incidence rates for non-asbestos-related pneumoconiosis diagnoses (N=230)

		No. of cases	Total person-years	IR*	95% CI (exact Poisson)
OVERALL		230	31,165,672.41	0.74	0.65 to 0.84
Gender					
	Female	13	16,421,082	0.08	0.42 to 1.35
	Male	217	14,744,590	1.47	1.28 to 1.68
Age Groups					
	<60	39	23,309,579.76	0.17	0.12 to 0.23
	60 - 69	50	3,474,347.44	1.44	1.07 to 1.90
	70 - 79	78	2,689,162.52	2.90	2.29 to 3.62
	80+	63	1,692,582.69	3.72	2.86 to 4.76
Calendar period					
	1997 - 1999	55	6,696,773.29	0.82	0.62 to 1.07
	2000 - 2002	83	7,646,978.15	1.09	0.87 to 1.35
	2003 - 2005	57	8,232,635.23	0.69	0.52 to 0.90
	2006 - 2008	35	8,589,285.74	0.41	0.28 to 0.57

*IR = Incidence rate (density) per 100'000 person-years, CI = Confidence interval

Table 3. Poisson regression modelling of incidence for the non-asbestos-related pneumoconioses (N=230)

		No. of cases	Total person-years	IR*	95% CI (exact Poisson)
OVERALL		840	31,165,672.41	2.70	2.52 to 2.88
Gender					
	Female	56	16,421,082	0.34	0.26 to 0.44
	Male	784	14,744,590	5.32	4.95 to 5.70
Age Groups					
	<60	108	23,309,579.76	0.46	0.38 to 0.56
	60 - 69	280	3,474,347.44	8.06	7.14 to 9.06
	70 - 79	321	2,689,162.52	11.94	10.67 to 13.32
	80+	131	1,692,582.69	7.74	6.47 to 9.18
Calendar period					
	1997 - 1999	110	6,696,773.29	1.64	1.35 to 1.98
	2000 - 2002	195	7,646,978.15	2.55	2.20 to 2.93
	2003 - 2005	266	8,232,635.23	3.23	2.85 to 3.64
	2006 - 2008	269	8,589,285.74	3.13	2.77 to 3.53

*IR = Incidence rate (density) per 100'000 person-years, CI = Confidence interval

Table 4. Poisson regression modelling of incidence for asbestosis (N=840)

	IRR	95% CI	LRT p-value
Gender			
Female (Ref.)		-------	
Male	17.87	11.36 to 28.09	< 0.0001
Age Groups			
<60 (Ref.)	1.00	-------	
60 - 69	17.56	12.13 to 25.42	
70 - 79	28.14	19.57 to 40.48	
80+	22.58	14.77 to 34.55	< 0.0001*
Calendar period			
1997 – 1999 (Ref.)	1.00	-------	
2000 - 2002	1.54	1.04 to 2.27	
2003 - 2005	1.91	1.32 to 2.76	
2006 - 2008	1.76	1.22 to2.55	0.0238*

*IR = Incidence rate (density) per 100'000 person-years, CI = Confidence interval

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7.2 Drug-/radiation-induced interstitial lung disease in the United Kingdom general population: Incidence, all-cause mortality, and characteristics at diagnosis

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7.2.1 Abstract

Background

Radiotherapy and an increasing number of substances are implicated in the pathogenesis of interstitial lung disease (ILD). Whilst the frequency of published data on more common ILD entities such as the idiopathic interstitial pneumonias (IIPs) has increased in recent years, less attention has been given to relatively rarely occurring forms such as drug-/radiation-induced ILD.

Methods

Data from the UK-based GPRD was used to estimate the incidence of drug-/radiation-induced ILD over a 12-year period (1997-2008). Crude incidence rates were stratified by gender, age group, and calendar period, and rate ratios were adjusted using Poisson regression. All-cause mortality was modelled using Cox regression, and characteristics at diagnosis were compared to a random sample of matched, non-ILD controls using conditional logistic regression.

Results

A total of 128 patients with an incident diagnosis of drug-/radiation-induced ILD were identified, and the overall incidence density during the study period was 4.1 (95% CI: 3.4 to 4.9) per million person-years. Incidence rates increased during the time period 1997-2005 and decreased thereafter. The adjusted all-cause mortality was > 4 times higher in cases compared to controls.

Conclusions

This UK population-based study characterizes patients diagnosed with drug-/radiation-induced ILD, and quantifies incidence and all-cause mortality during 1997-2008. No statistically significant time-trend in incidence was found, despite having observed numeric increases in incidence rates during the study window. Future research using the GPRD and other data sources is required to better understand the disposition of patients diagnosed with drug-/radiation-induced ILD, and to investigate potential trends incidence and mortality over time.

7.2.2 Introduction

An increasing number of prescription drugs and novel biologics such as monoclonal antibodies, anti-Tumor Necrosis Factor (TNFα), interferons, and immunoglobulins are implicated in the pathogenesis of infiltrative and/or parenchymal lung disease [1-3]. Additionally, certain herbal remedies, dietary supplements, chemotherapeutics, and irradiation are also known to induce interstitial lung disease (ILD) [4-7]. During the 1990's, data from European ILD registries indicated that drug-induced ILD cases represented between 1.9-3.3% of all ILD cases reported [8]. Whilst the amount of published epidemiologic data on more commonly-occurring types of ILD (e.g. the idiopathic interstitial pneumonias and sarcoidosis) has increased in the recent past, less attention is devoted to the epidemiology of less frequently occurring subgroups such as drug- and radiation-induced ILD. Moreover, published data on the frequency and on mortality of patients with drug- and radiation-induced ILD cases in the UK general population are -- to the best of our knowledge -- non-existent. To better understand the epidemiology of this ILD subgroup and to predict demand on health

care resources, there is a need to describe and quantify drug- and radiation-induced ILD in the UK general population. We used the UK General Practice Research Database (GPRD) to characterize patients diagnosed with ILD induced by drugs or radiation, and to examine the incidence and all-cause mortality of these ILD subgroups in the UK general population.

7.2.3 Methods

Data source

The GPRD has been described elsewhere in detail [9]. In summary, it is a large and well-validated UK-based database that was established in June 1987. It contains anonymized electronic patient records collected from routine general practice, and the geographic, age, and gender distributions of the GPRD population have been shown to be representative of the U.K. general population [9]. The GPRD encompasses some 9 million patients who are or were enrolled with selected general practitioners (GPs) throughout the U.K., covering approximately 50 million patient-years of follow-up. The participating GPs have been trained to record medical information in a standard manner and to provide anonymized records to the GPRD Group within the Medicines and Healthcare products Regulatory Agency (MHRA), the UK's medicines and devices regulator. The recorded data include demographic information, medical diagnoses, and drug prescriptions. Data from the GPRD have been used in previous studies involving interstitial lung disease and use of the data for respiratory epidemiology has been validated [10, 11]. The GPRD is managed by the Medicines and Healthcare products Regulatory Agency (MHRA), and the present

study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA database research.

Cohort study population

We identified in the GPRD all patients with a first-time diagnosis of drug- or radiation-induced ILD between January 1, 1997 and December 31, 2008. Diagnoses in the GPRD are coded using the Read coding system, and our list of diagnoses included any Read code explicitly mentioning drug- or radiation-related lung disease: acute pulmonary radiation disease, acute radiation pneumonitis, chronic pulmonary radiation disease, chronic pulmonary fibrosis following radiation, drug-induced interstitial lung disorders, acute drug-induced interstitial lung disorders, or chronic drug-induced interstitial lung disorders. Read codes without explicit mention of a drug- or radiation-related lung disease such as “Lung disease due to external agents NOS” were not used. In order to increase the likelihood of capturing incident rather than prevalent cases, we excluded patients with less than 3 years of active recording history prior to the date of the first drug-/radiation-ILD diagnosis. In addition, we identified at random from the GPRD control subjects without diagnosis of drug-/radiation-ILD , matched 1:1 on age (same year of birth), sex, general practice, and calendar time (i.e. by using the date of the first ILD diagnosis of the case). We applied the same exclusion criteria to the control group as to the case patients. Within this study population we assessed and compared demography, prescription drug use, comorbidities, and other characteristics of cases and controls at or prior to the date of incident diagnosis.

Data analysis

An initial descriptive analysis was conducted to summarize demographics and other baseline characteristics of cases and their matched controls. Comparisons between cases and controls were then analyzed using conditional logistic regression. With respect to differences in comorbidities and prescription drug use at or prior to incident diagnosis, an a priori decision was taken to present and further adjust those ORs that reached a conventional level of statistical significance (i.e., $p \leq 0.05$).

Person-time denominators for the calculations of incidence density were derived from the GPRD. For each calendar period, only those patients in the GPRD who were alive, actively registered, and had at least 3 years of recorded history contributed person-time to the denominators. Incident cases were grouped into 10-year age bands, and calendar time was divided into four 3-year periods (1997-1999, 2000-2002, 2003-2005, 2006-2008). Crude incidence rates were calculated for the group of drug-/radiation-ILD as a whole and stratified by gender, age group, and calendar period, with exact 95% confidence intervals calculated from the Poisson distribution. In order to model disease incidence and estimate incidence rate ratios, fixed-effects Poisson multivariate regression was used. The above methods were repeated for cases diagnosed with drug-induced and radiation-induced ILD separately.

Initially, the comparison of survival between patients with drug-/radiation-induced ILD and matched non-ILD controls was summarized using Kaplan-Meier plots. Survival of cases and controls was then modelled using stratified Cox proportional hazards regression. Covariates included smoking history, body mass index (BMI), and cancer as comorbidity. All statistical analyses were performed with the statistical software

SAS (release 9.2, SAS Institute, Inc., Cary, NC, USA). The proportional hazards assumption was assessed using the RESAMPLE option within the SAS procedure PHREG.

7.2.4 Results

A total of 128 patients with an incident diagnosis of drug-/radiation-induced ILD were identified during the period 1997-2008, of which 106 (83 %) cases were diagnosed with radiation-induced lung disease. The frequency distribution of incident diagnoses is shown in Table 1. The mean age (SD) at diagnosis was 67 (11.9) years, and 73 (57%) cases were female. Males and females were of similar mean age at the time of first diagnosis (67 years [±SD 12.1] vs. 66 years [±SD 11.8], respectively), and the majority of cases was diagnosed in the age group 60-79 years. The age distribution of cases is shown in Figure 1. Compared to their matched general-population controls, cases were more likely to be ex- or current smokers than non-smokers, more likely to have a BMI ≥ 25 than < 25 kg/m2, and less likely to consume alcohol, however, none of these characteristics reached statistical significance. With respect to healthcare resource utilization, cases (as opposed to their matched controls) were almost 8 times more likely to have had ≥ 20 vs. < 20 practice visits and were greater than 3 time more likely to have had ≥ 25 vs. < 25 drug prescriptions during 1 year prior to incident diagnosis (Table 2). Likewise, cases were ≥ 1.8 times more likely than their matched general-population controls to have a range of both comorbid diagnoses and prescription drug use at or prior to diagnosis; the highest odds ratios (ORs) were observed for having a diagnosis of cancer (in situ metastasis) (OR=43.5,

95% CI 10.7 – 177.0) and use of immunosuppressives (OR=11.0, 95% CI 1.42 – 85.20), respectively. After adjusting for cancer diagnosis, elevated ORs achieving statistical significance were noted for diagnoses of RA, constipation, IHD, and CHF as well as for prescription drug use of immunosuppressives, corticosteroids, antiarrhythmics, NSAIDs, and diuretics. Results of comorbidities and prescription drug use can be found in Table 3, in which the data for each category is sorted in descending order according to the magnitude of the crude ORs.

Between 1997 and 2008 the overall incidence density of drug-/radiation-induced ILD was 4.1 (95% CI 3.4 to 4.9) per 1,000,000 (10^6) person-years, and the rate in females was approximately 20% higher than in males. Across age groups, the lowest incidence density was observed for those below the age of 60 years (1.2 [95% CI 0.8 to 1.7] / 10^6 person-years); the rates in older age groups were approximately 8-12-fold higher. Crude incidence rates increased progressively during the first three periods and then decreased from the period 2003-2005 to 2006-2008 (5.1 [95% CI 3.7 to 6.9] vs. 4.4 [95% CI 3.1 to 6.1] / 10^6 person-years, respectively). Crude incidence rates for the aggregate group of drug-/radiation-induced ILD are shown in Table 4. With respect to each diagnosis category separately (i.e. drug- vs. radiation-induced ILD), incidence density increased progressively from 1997 to 2005 for drug-induced ILD, and then dropped by more than 50% between the period 2003-2005 to 2006-2008. In the radiation-induced ILD category, incidence density remained somewhat stable during the first two 3-year periods (1997-2002, range 2.9 to 3.0/106 /year), and then increased during the following two 3-year periods (2003-2008,

approx. 3.8/10^6/year). Category-specific incidence density by calendar period can be found in Table 5.

After adjusting for the effects of age and gender in the aggregate category of drug-/radiation-induced ILD, although having observed numeric increases in incidence from 1997-2005 and a subsequent decrease from the period 2003-2005 to 2006-2008, there was no evidence of statistically significant heterogeneity of rate ratios over time (p=0.74). In contrast, after adjusting for gender and calendar period, there was evidence of statistically significant heterogeneity of rate ratios across age groups. Incidence density rates in the age groups 60-69 and 70-79 were more than 10 times higher than in those under 60 years of age. Incidence rate ratios for the aggregate category of drug-/radiation-induced are shown in Table 6.

A total of 64 cases died during follow-up, vs. 16 controls. The mean (±sd) survival time for cases was 3.1 (±3.1) vs. 4.8 (±3.1) years for general-population controls. Over the 12-year follow-up period cases were 7 times more likely to die compared to their matched general-population controls (Figure 2) (HR=7.13, 95% CI 3.40 to 14.93). After allowing for the confounding effect of baseline cancer diagnosis, the difference in 12-year survival decreased, yet remained elevated (HR=4.04, 95%CI 1.56 – 10.56 (Table 7). No evidence was found to suggest a departure from the proportional hazards assumption in the final model.

7.2.5 Discussion

In this general-population-based UK cohort of drug- and radiation-induced ILD patients, the overall incidence rate was approximately 4 per million population per

year, suggesting that each year in the UK there will be ~ 250 new cases of drug- and radiation ILD. Overall, numeric increases were observed in incidence density rates during the first 9 years of the study period, followed by a decline during the final 3 years. This drop in incidence in the aggregate category of drug- and radiation-induced ILD was clearly attributable to the >50% decrease in incidence observed in the subgroup of drug-induced ILD during the same period. Incidence density of radiation-induced ILD remained relatively stable during the first 6 years (range: 2.9 to $3.0/10^6$ person-years) and then increased to nearly $3.8/10^6$ person-years.

All-cause mortality adjusted by matching on age, gender, geography (via general practice as a proxy), and number of years of recorded medical history was 7 times higher in cases compared to general-population controls. After further adjustment by both baseline smoking status and cancer diagnosis (i.e. ~ 75% of cases had a diagnosis of cancer at/prior to incident drug-/radiation-induced ILD diagnosis), the all-cause mortality rate for cases remained elevated at > 4.5 times that of general-population based controls. The majority of cases (~54%) in our cohort was diagnosed with acute radiation pneumonitis (as opposed to 'classic' or 'sporadic' radiation pneumonitis), a condition that is associated with significant symptoms, and in some cases, develops into respiratory failure or Acute Respiratory Distress Syndrome (ARDS) [12-13]. However, the adjusted all-cause mortality rate would suggest that many of these patients suffer progressive disease resulting in premature death. Whether or not the cause of death was attributable to radiation-induced ILD, non-remissive cancer, or other comorbidities could not be examined since precise information on cause of death is not readily available in the GPRD.

A potential weakness of the present study could be the validity of the ILD diagnoses. However, the validity of many disease diagnoses has been assessed in the GPRD and has consistently found to be high [14-16]. Furthermore, other researchers have reported a high validity of the diagnosis of idiopathic pulmonary fibrosis, another interstitial lung disease, in the GPRD [17]. Moreover, it is highly unlikely that general practitioners would record a diagnosis of drug- or radiation-induced ILD without confirmation by specialist referral. In order to explore the specificity of the ILD diagnoses in our cohort, we examined the medical history in more detail and found the following: (1) Of the 106 cases with a diagnosis of radiation-induced ILD, 79 had a diagnosis of thoracic-related cancer while the remaining 27 had a diagnosis of cancer that was not otherwise specified. (2) Of the 22 cases with a diagnosis of drug-induced ILD, the last immunosuppressive prescribed for 9 of these cases was either leflunomide (n=1) or methotrexate (n=8), while 8 patients, who did not have any history immunosuppressive drug prescription (i.e. mutually exclusive of the 9 patients previously described), were prescribed amiodarone immediately prior to their ILD diagnosis. All aforementioned prescription drugs are known potential inducers of ILD. In light of the above reasons and findings, we expect the diagnoses used for the present study to have a high specificity.

On the other hand, we are aware that the sensitivity of the diagnoses used may not be as high as the specificity. Two main reasons for this are the potential for misclassification of true ILD cases into less specific disease diagnosis categories and the possibility of having missed less severe cases. For instance, we did not use less specific respiratory-related diagnosis codes such as “lung disease due to other

external agents NOS" or "other external agent causing respiratory condition" in our case selection algorithm. Overall there were 649 cases with such an unspecific diagnosis which we subsequently reviewed in more detail. None of these had evidence of a drug- or radiation-induced ILD diagnosis at a later point in time in their medical record, which indicates that misclassification is unlikely. It is also possible that less severe cases have escaped detection by general practitioners and specialists. Thus it is possible that we did not have available for analysis all true cases of drug- and radiation-induced ILD from the given sampling frame, which means that we may have underestimated the true incidence density of this ILD subgroup in the UK. Furthermore, we cannot be certain that all newly identified cases were indeed incident cases. However, we excluded cases with less than 3 years of recorded medical history in order to minimize the possibility of including prevalent cases in our incidence numerators, so we expect the occurrence of such error to be minimal. To the extent that this error occurred it will have resulted in a small overestimation of the incidence density rates. Despite the potential limitations mentioned above, this study determined current estimates of incidence density for the aggregate category of drug- and radiation-induced ILD as well as category-specific rates for drug-induced and radiation-induced ILD separately in the UK general population.

We have been unable to find any other population-based cohort analyses in the U.K. with which to compare our incidence or mortality data. However, data from various European and U.S. studies show some similarities and differences. One of the first ever population-based epidemiological studies of ILD in the late 1980s (in Bernalillo

County, New Mexico) reported an incidence of 1.45/10^5 person-years for drug and radiation ILD, which is approximately 3.5 times higher than the rate observed in our cohort [18]. One explanation might be the use of a more comprehensive case ascertainment which included ILD cases not only diagnosed by pulmonologists and general practitioners, but also those cases discovered in hospital discharge reports, death certificates, and autopsy reports. From a more recent survey of ILD-special interest Pulmonology centers in Greece, Karakatsani et al. reported an incidence rate of 0.07/10^5 person-years for drug-induced ILD, which is nearly identical to our UK category-specific incidence rate for drug-induced ILD [19]. Similarly, López-Campos et al. reported an incidence of 0.08/105 person-years for drug-induced ILD from an ILD registry encompassing nine provinces in Southern Spain; data from the same registry reported an incidence rate of 0.00/105 person-years (only 2 cases of the total 744 ILD cases reported) for radiation-related ILD, which is strikingly different to the rate observed in our study [20]. Factors influencing this difference could be the use of a different coding system (ICD codes vs. Read codes), misclassification of ILD diagnosis, differences in prevalence of thoracic cancers (for which radiotherapy would be indicated), and differences in age- and gender distribution.

In any case, it is acknowledged in the literature that the frequency of drug-induced lung disease reported from any data source is likely to underestimate true disease frequency [13,21-22]. Many drugs implicated in ILD are primarily prescribed by non-respiratory physicians, and under-diagnosis is likely. Moreover, subclinical forms of drug-induced ILD are likely to escape detection by plain chest radiography as opposed to the use of high resolution computed tomography (HRCT), which would

take place in close collaboration with a respiratory specialist. In the oncology setting, where drug-induced ILD is likely to be common, a diagnosis of drug-induced ILD will often remain inconclusive because the patient's condition precludes further (invasive) diagnostic assessment.

In this study of the aggregate category of drug-/radiation-induced ILD, no clear trend in incidence can be seen. This is evident from the lack of heterogeneity found in the numerically increasing incidence rates during 1997-2005, followed by a decrease during the final calendar period (2006-2008). However, due to the relatively small sample size of cases, the study did not have sufficient statistical power to detect a trend in incidence, had such a trend truly existed during the study window. Furthermore, we cannot tell whether the overall numeric increase reflects a real increase, or whether it is, at least to a certain extent, attributable to secular trends. Firstly, during the study window major political changes in the NHS occurred, including more than a doubling in funding under the auspices of the New Deal. [23] This investment in national health care was in part used to boost capacity of NHS services and to modernize facilities, thus potentially increasing the likelihood of detecting new cases of drug-/radiation-induced ILD. Secondly, a certain proportion of incident cases in this time period may have been due to increased recognition of interstitial lung diseases in general via the increased use of HRCT. Thirdly, following publication of both the British Thoracic Society's guideline on diagnosis and care of diffuse parenchymal lung disease in 1999 [24] and the ATS/ERS consensus statements on idiopathic interstitial pneumonia in 2002 [25], a greater appreciation of the value of precise diagnosis according to defined criteria will likely have occurred,

not to mention increased patient expectations. For the above reasons, an increase in case ascertainment may have played a role in the observed increase in incidence density rates. Furthermore, the incidence pattern seen in the drug-induced ILD subgroup might also be explained, not solely in terms of better diagnosis, but also by earlier diagnosis, which resulted in a transient increase in incidence density, followed by a corresponding decline in subsequent years.

This study makes use of data from a well-validated database which has consistently been found to be representative of the UK general population. To our knowledge, this is the first general-population-based observational study quantifying incidence and mortality rates of diagnosed drug-/radiation-induced ILD in the UK.

7.2.6 Tables and figures

Table 1. Frequency of incident diagnoses of drug-/radiation-induced ILD (N=128).

Diagnosis codes	Frequency	Percent
Acute pulmonary radiation disease	1	0.78
Acute radiation pneumonitis	69	53.91
Chronic pulmonary radiation disease	1	0.78
Chronic pulmonary fibrosis following radiation	35	27.34
Drug-induced interstitial lung disorders	18	14.06
Acute drug-induced interstitial lung disorders	3	2.34
Chronic drug-induced interstitial lung disorders	1	0.78

Table 2. Characteristics of drug-/radiation-induced ILD cases and their matched controls at incident diagnosis

Characteristics	Cases (%) [n=128]	Controls (%) [n=128]	OR (95% CI)
Mean age (years) ± sd	66.6 ±11.9	66.7±11.9	**----**
Females	73 (57.0)	73 (57.0)	**----**
BMI (kg/m^2)			
< 25	44 (34.4)	45 (35.2)	**1.00** (ref.)
≥ 25	67 (52.3)	56 (43.8)	**1.29** (0.70 – 2.37)
Unknown	17 (13.3)	27 (21.1)	**0.60** (0.27 – 1.35)
Smoking status			
Non-smokers	52 (40.6)	62 (48.4)	**1.00** (ref.)
Current/Ex-smokers	70 (54.7)	53 (41.4)	**1.68** (0.96 - 2.93)
Unknown	6 (4.7)	13 (10.2)	**0.39** (0.10 - 1.46)
No. of cigarettes per day			
0	10 (7.8)	13 (10.2)	**1.00** (ref.)
1 - 10	22 (17.2)	14 (10.9)	**2.14** (0.75 - 6.15)
11 +	16 (12.5)	10 (7.8)	**2.07** (0.66 – 6.50)
Unknown	80 (62.5)	91 (71.1)	**1.02** (0.41 - 2.54)
Alcohol consumption (no. of units/week)[1]			
0	74 (57.8)	72 (56.3)	**1.00** (ref.)
1 - 7	26 (20.3)	27 (21.1)	**0.92** (0.46 – 1.84)
8 +	28 (21.9)	29 (22.7)	**0.92** (0.48 – 1.79)
No. of practice visits[2]			
0 - 19	33 (25.8)	87 (68.0)	**1.00** (ref.)
20 +	95 (74.2)	41 (32.0)	**7.75** (3.71 – 16.18)
No. of drug prescriptions[3]			
0 - 24	46 (35.9)	83 (64.8)	**1.00** (ref.)
25 +	82 (64.1)	45 (35.2)	**3.47** (1.95 – 6.16)

CI=Confidence Interval; sd=standard deviation
1 = last recording prior to index date, 2 = based on recordings of diagnoses and prescriptions (falling on separate dates) during 1 year prior to incident diagnosis, 3 = during 1 year prior to incident diagnosis

Table 3. Odds of comorbidities and prescription drug use for drug-/radiation-induced ILD cases and their matched controls at/prior to incident diagnosis

	Cases (%) [n=128]	Controls (%) [n=128]	OR (95% CI)	
			Crude[a]	Adjusted[b]
Comorbid diagnoses				
Cancer (i.s. metastasis)	97 (75.8)	12 (9.4)	**43.5** (10.7 – 177.0)	--
RA	13 (10.2)	2 (1.6)	**6.50** (1.47 – 28.9)	21.32 (2.46 – 184.82)
Constipation	33 (25.8)	10 (12.8)	**5.60** (2.16 – 14.5)	6.09 (1.32 – 28.13)
Hypothyroidism	18 (14.1)	5 (3.9)	**4.25** (1.43 - 12.6)	0.14 (0.01 – 2.96)
Arrhythmia	25 (18.5)	7 (5.5)	**4.00** (1.64 – 9.79)	Non-estimable*
COPD	17 (13.3)	5 (3.9)	**3.40** (1.25 – 9.22)	2.04 (0.54 – 7.62)
IHD	30 (23.4)	15 (11.7)	**2.50** (1.20 – 5.21)	22.18 (2.66 – 184.98)
CHF	15 (11.7)	6 (4.7)	**2.50** (0.97 – 6.44)	6.27 (1.38 – 28.43)
GERD/Esophag./Dyspep./Gastr.	40 (31.3)	28 (21.9)	**2.00** (1.05 – 3.80)	0.87 (0.34 – 2.19)
Asthma	26 (20.3)	16 (12.5)	**1.83** (0.91 – 3.70)	1.41 (0.49 – 4.10
Rx drug use at/prior to Dx				
Immunosuppressives	11 (8.6)	1 (0.08)	**11.0** (1.42 – 85.2)	**27.72** (1.91 – 402.86)
Corticosteroids (systemic)	67 (52.3)	31 (24.2)	**4.00** (2.12 – 7.53)	**4.70** (1.70 – 12.98)
Anticholinergics	24 (18.8)	6 (4.7)	**4.00** (1.64 – 9.79)	**3.18** (0.96 – 10.58)
β – Agonists and comb.	62 (48.4)	28 (21.9)	**3.62** (1.96 – 6.68)	**2.50** (0.99 – 6.33)
Antiarrhythmics	17 (13.3)	7 (5.5)	**2.67** (1.04 – 6.81)	**27.93** (2.88 – 271.26)
Thyroid Gland Therapy	20 (15.6)	9 (7.0)	**2.57** (1.07 – 6.16)	**3.02** (0.77 – 11.95)
PPIs	54 (42.2)	33 (25.8)	**2.31** (1.29 – 4.16)	**2.86** (0.88 – 9.32)
NSAIDs	98 (76.6)	79 (61.7)	**2.12** (1.19 – 3.77)	**3.09** (1.08 – 8.80)
H2-Receptor Antagonists	47 (36.7)	31 (24.2)	**2.00** (1.10 – 3.64)	**2.04** (0.79 – 5.32)
Corticosteroids (inhaled)	51 (40.0)	34 (26.6)	**1.94** (1.10 – 3.43)	**1.27** (0.55 – 2.90)
Diuretics	59 (46.1)	41 (32.0)	**1.86** (1.09 – 3.16)	**3.00** (1.25 – 7.20)

a = adjusted by matching for age, gender, geographic location, and no. of year s of recorded history in database
b = further adjusted by cancer status at/prior to index date; Rx = prescription; Dx = diagnosis; CI = Confidence Interval; i.s. = in situ; RA = Rheumatoid Arthritis; COPD = Chronic Obstructive Pulmonary Disease; IHD = Ischaemic Heart Disease CHF = Congestive Heart Failure; GERD = Gastro-Esophageal Reflux Disorder; PPI = Proton-pump Inhibitors; NSAID=Non-steroidal Anti-inflammatory Drugs; H2 = Histamine-2; *Non-estimable due to 1 or more strata with null counts

Table 4. Crude incidence rates for drug-/radiation-induced ILD

	No. of cases	Total person-years	IR*	95% CI (exact Poisson)
OVERALL	128	31,165,672.41	4.11	3.43 to 4.88
Gender				
Female	73	16,421,082.12	4.45	3.48 to 5.59
Male	55	14,744,590.29	3.73	2.81 to 4.86
Age Groups				
<60	28	23,309,579.77	1.20	0.80 to 1.74
60 - 69	45	3,474,347.44	12.95	9.45 to 17.30
70 - 79	38	2,689,162.52	14.13	10.0 to 19.40
80+	17	1,692,582.70	10.04	5.85 to 16.10
Calendar period				
1997 - 1999	22	6,696,773.29	3.29	2.06 to 4.97
2000 - 2002	26	7,646,978.15	3.40	2.22 to 4.98
2003 - 2005	42	8,232,635.23	5.10	3.68 to 6.90
2006 - 2008	38	8,589,285.74	4.42	3.13 to 6.07

IR = Incidence rate (density) per 1,000,000 person-years; CI = Confidence interval

Table 5. Crude incidence rates for drug- and radiation-induced ILD separately

	No. of cases	Total person-years	IR	95% CI (exact Poisson)
Drug-induced ILD (N=22)				
Calendar period				
1997 - 1999	2	6,696,773.29	0.30	0.04 to 1.08
2000 - 2002	4	7,646,978.15	0.52	0.14 to 1.34
2003 - 2005	11	8,232,635.23	1.34	0.67 to 2.39
2006 - 2008	5	8,589,285.74	0.58	0.19 to 1.36
Radiation-induced ILD (106)				
Calendar period				
1997 - 1999	20	6,696,773.29	2.99	1.82 to 4.61
2000 - 2002	22	7,646,978.15	2.88	1.80 to 4.36
2003 - 2005	31	8,232,635.23	3.77	2.56 to 5.34
2006 - 2008	33	8,589,285.74	3.84	2.64 to 5.40

IR = Incidence rate (density) per million person-years; CI = Confidence interval

Table 6. Poisson regression modelling of drug-/radiation-induced incidence (aggregate group)

		IRR	95% CI	LRT p-value
Gender				
	Female (Ref.)	1.00	-------	
	Male	0.91	0.64 to 1.30	0.6254
Age Groups				
	<60 (Ref.)	1.00	-------	
	60 - 69	10.73	6.69 to 17.20	
	70 - 79	11.76	7.22 to 19.17	
	80+	8.22	4.49 to 15.04	< 0.001*
Calendar period				
	1997 – 1999 (Ref.)	1.00	-------	
	2000 - 2002	1.04	0.59 to 1.84	
	2003 - 2005	1.56	0.93 to 2.61	
	2006 - 2008	1.31	0.77 to 2.21	0.7387*

IRR = Incidence rate ratio; CI = Confidence interval; LRT = Likelihood ratio test, *p for trend

Table 7. Survival analyses for all-cause mortality (stratified Cox proportional hazards regression)

	No. of deaths	HR	95% CI	p-value (LRT)
Crude (adjusted by matching for age, gender, location, no. of years of recorded medical history)				
General-population controls	16	1.00		
Drug-/radiation-induced ILD cases	64	7.13	3.40 to 14.93	< 0.0001
Further adjusted for baseline smoking status				
General-population controls	16	1.00		
Drug-/radiation-induced ILD cases	64	8.92	3.71 to 21.45	< 0.0001
Further adjusted for baseline smoking status and baseline cancer diagnosis				
General-population controls	16	1.00		
Drug-/radiation-induced ILD cases	64	4.64	1.60 to 13.44	< 0.0001

HR = Hazard Ratio; CI=Confidence Interval

Figure 1. Age at diagnosis of drug-/radiation-induced ILD (N=128)

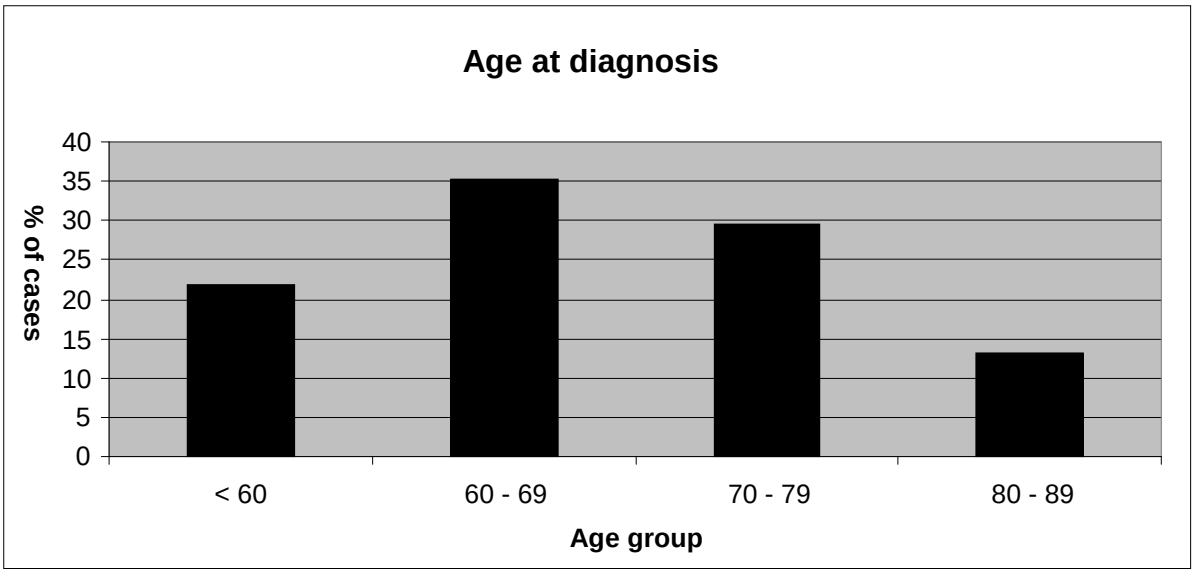
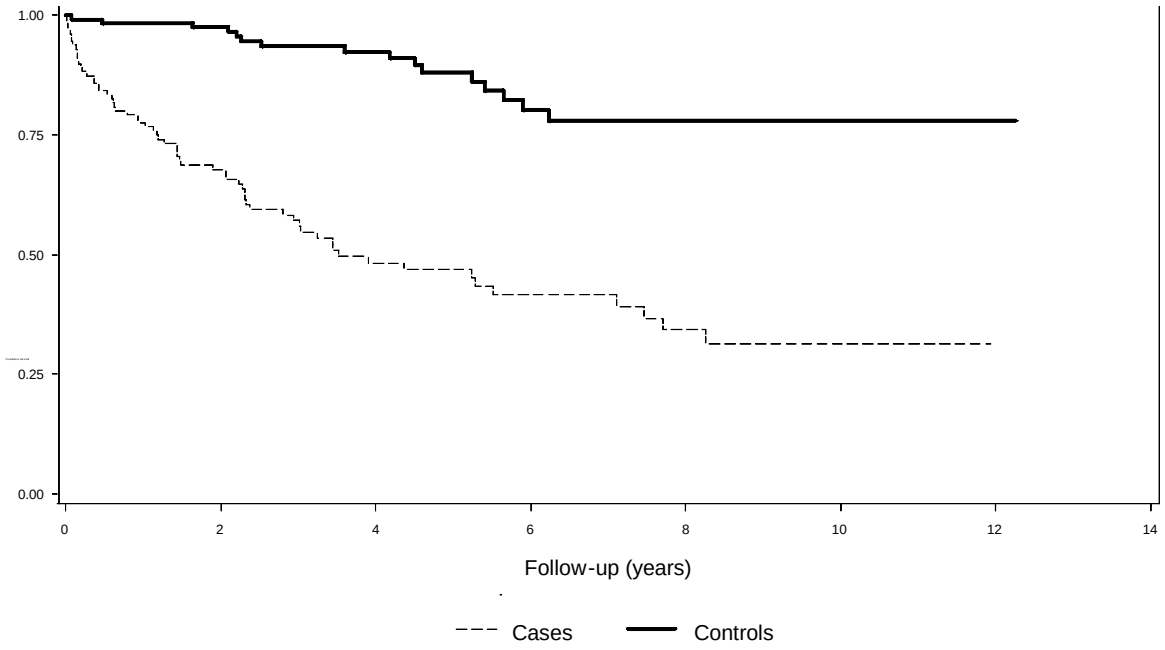


Figure 2. Kaplan-Meier plot comparing survival in cases diagnosed with drug-/radiation-induced ILD and matched general-population controls



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7.3 Interstitial lung disease in patients with connective tissue disease: A retrospective cohort study of incident cardiovascular comorbidity and all-cause mortality using the U.K. General Practice Research Database

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Under review by

Rheumatology

7.3.1 Abstract

Objectives

To investigate survivorship and incident cardiovascular outcomes in patients with connective tissue diseases, after a diagnosis of interstitial lung disease.

Methods

Data from the UK-based GPRD were used to estimate all-cause mortality rates over the 12-year study period (1997-2008). All-cause mortality and incident cardiovascular outcomes were modelled using Cox proportional hazards regression.

Results

A total of 583 CTD-patients with a first-time diagnosis of ILD were identified during the study period. The age- and gender-adjusted 12-year mortality rate was 40% lower in non-RA CTD-ILD vs. RA-ILD patients, and the risk of incident pulmonary hypertension was >8 times higher in non-RA CTD-ILD vs. RA-ILD patients ($p < 0.001$). No statistically significant risk differences for incident arrhythmia or ischemic heart disease (IHD) were observed between RA-ILD and Other CTD-ILD patients. However, adjusting for age and gender, borderline statistical significance was observed for the >50% reduced risk of incident congestive heart failure (CHF) in the Other CTD-ILD group vs. RA-ILD ($p=0.056$).

Conclusions

This study underscores the poor prognosis for CTD-ILD patients. Among CTD diagnostic subtypes, RA-ILD patients have a significantly higher risk of mortality within 12 years after their ILD diagnosis as compared to other CTD-ILD patients.

7.3.2 Introduction

Interstitial lung disease (ILD) comprises a diverse group of disorders affecting the lung parenchyma, many of which are characterized by varying degrees of inflammation and fibrosis. The fibrotic forms of ILD are rarely curable and often lead to significant morbidity and mortality [1-3]. ILD may be broadly subdivided into idiopathic interstitial pneumonia (IIP) and those secondary to external exposures or associated with a systemic connective tissue disease (CTD). CTD represents a heterogeneous group of systemic autoimmune disorders affecting a variety of tissues and organs, including the lung. Similar to ILD, many CTDs are associated with significant comorbidity, including cardiovascular disease, and elevated mortality rates [4-7].

Several studies have investigated the epidemiology of CTD-ILD; however, few have used large-scale, population-based cohorts to investigate incident cardiovascular comorbidity and survivorship in these patients. To advance the understanding of the epidemiology of CTD-ILD and to provide additional informative data on the prognosis for this disease group, we used data from the UK General Practice Research Database (GPRD) to examine all-cause mortality and incident cardiovascular comorbidity in patients diagnosed with ILD and coexistent CTD.

7.3.3 Methods

Data source

The GPRD has been described elsewhere in detail [9]. In summary, it is a large and well-validated UK-based database that was established in June 1987. It contains anonymized electronic patient records collected from routine general practice, and the geographic, age, and gender distributions of the GPRD population have been shown to be representative of the U.K. general population [9]. The GPRD encompasses approximately 7 million patients who are or were enrolled with selected general practitioners (GPs) throughout the U.K., covering approximately 50 million patient-years of follow-up. The participating GPs have been trained to record medical information in a standard manner and to provide anonymized records to the GPRD Group within the Medicines and Healthcare products Regulatory Agency (MHRA), the UK's medicines and devices regulator. The recorded data include demographic information, medical diagnoses, and drug prescriptions. Data from the GPRD have been used in previous studies involving ILD and CTD, and the use of the data for respiratory epidemiology has been validated [10-12]. The GPRD is managed by the Medicines and Healthcare products Regulatory Agency (MHRA), and the present study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA database research.

Cohort study population

We identified in the GPRD all patients having been diagnosed with a CTD (i.e. rheumatoid arthritis (RA), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), Sjögren Syndrome (SS), dermatomyositis/polymyositis (DM/PM), mixed or

undifferentiated connective tissue disease (MCTD/UCTD)) prior to (or at the same time of) a first-time diagnosis of ILD (hereinafter referred to as 'index date') between January 1, 1997 and December 31, 2008. Patients with more than one diagnosis of a CTD in their medical history were grouped into a category referred to as '> 1 CTD Dx'. Diagnoses in the GPRD are coded using the Read coding system, and our list of ILD diagnoses included any Read code explicitly mentioning an ILD or lung disease with a CTD: diffuse pulmonary fibrosis, fibrosing alveolitis, fibrosis of lung present, rheumatoid lung, lung disease with CTD. Read codes with explicit mention of sarcoidosis, allergic alveolitis, hypersensitivity pneumonitis (including fibrosis following radiotherapy), occupational lung disease (e.g. pneumoconioses), or "lung disease due to external agents NOS" were not used. With respect to our RA CTD-subgroup, patients with a Read diagnosis of "seronegative RA" were excluded from the cohort. All patients with less than three years of active history in the database prior to the index date were excluded.

Data analysis

Initially, a descriptive analysis was performed to summarize demographics and other baseline characteristics, by CTD-subgroup. Survival curves were examined using Kaplan-Meier estimates, and heterogeneity of the CTD subgroups was assessed using log-rank tests. A data-driven decision was taken to collapse the SSc, SLE, SS, DM/PM, and >1 CTD Dx populations into one group, hereinafter termed 'Other CTD.' All-cause mortality was then modelled using Cox proportional hazards regression. Similarly, Cox modelling was used for the analysis of incident cardiovascular morbidity, however, cases having such diagnoses (i.e. Arrhythmia, CHF, IHD, and

PH) at any time in their medical history prior to the index date were excluded from the respective analysis population. All statistical analyses were performed with the statistical software SAS (release 9.2, SAS Institute, Inc., Cary, NC, USA). The proportional hazards assumption was tested for the final models using the RESAMPLE option within the SAS procedure PHREG.

7.3.4 Results

Cohort characteristics

A total of 583 CTD patients with an incident diagnosis of ILD were identified during the period 1997-2008, of which 58 (10 %) cases were diagnosed with more than one type of CTD. The frequency distribution of the CTD subgroups is shown in Table 1. The mean age at ILD diagnosis was highest for RA (67 [±SD 11.9] years), and lowest in SLE patients (52 [± SD 13.5] years). The female-to-male ratio was highest among SS (21:1) and lowest in RA patients (213:172). The highest proportions of ex- or current smokers and elevated BMI (≥25 kg/m2) among the various CTD subgroups were found for RA (51%) and DM/PM (62%), respectively. Further characteristics for the individual CTD subgroups can be found in Table 2.

All-cause mortality

Of the 583 patients in the cohort, a total of 229 (39%) died during the 12-year follow-up period. Among the RA-ILD group 179 (46%) of the 385 patients died, whereas in the Other CTD-ILD group 50 (25%) of the 198 patients died. Median survival time (from ILD diagnosis until death) for in the RA-ILD group compared to the Other CTD-ILD group was similar (1.9 vs. 2.1 yrs., respectively). The Other CTD-ILD group had

significantly better survival rates than the RA-ILD group (see Figure 2; log-rank test p<0.0001). The 5- and 10-year survival estimates for the RA-ILD group were 51% and 24%, respectively, versus 73% and 51% for the Other CTD-ILD group. Kaplan–Meier plots of survival probability for individual CTD-ILD groups and for the collapsed Other CTD-ILD versus RA-ILD group can be found in Figures 1 and 2, respectively.

Multivariate Cox regression modelling was performed to evaluate the effect of baseline characteristics on all-cause mortality, and to adjust for potential confounders. Only age at index date was found to contribute significantly to goodness of model fit, however, gender was forced into the final model based on an a priori decision to include variables having an effect with $p \leq 0.1$. Therefore, the final model yielded a 40% decreased risk of all-cause mortality among the Other CTD-ILD group vs. the RA-ILD group (HR=0.60 [95% CI: 0.43 to 0.83]), adjusted for age and gender at index date (see Table 3). No evidence was found to suggest a departure from the proportional hazards assumption in the final model.

Incident cardiovascular comorbidity during follow-up

After excluding from the respective analysis populations those patients having had diagnoses of the cardiovascular outcomes of interest prior to index date, the crude risk of incident CHF after index date was significantly decreased for Other CTD-ILD vs. RA-ILD (HR=0.38 [95% CI: 0.18 to 0.79]), with a borderline statistically significant reduction in CHF risk of approximately 50% remaining even after controlling for age and gender (HR=0.48 [95% CI: 0.22 to 1.02]). An incident diagnosis of PH after index date was observed in 8.2% of the Other CTD-ILD group vs. only 1% of the RA-ILD group. After controlling for age and gender, a greater than 8-fold elevated risk of

incident PH was observed for patients in the Other CTD-ILD group versus the RA-ILD group (HR=8.32 [95% CI: 2.54 to 27.12]). No statistically significant differences (at the 5% level, after controlling for age and gender) were observed for post-index date incident arrhythmia or IHD, across CTD groups. No evidence of departure from the proportional hazards assumption was detected in the final model. Further details for all incident cardiovascular outcomes of interest can be found in Table 4.

7.3.5 Discussion

This population-based, retrospective cohort study reinforces the poor prognosis associated with ILD diagnosed in patients with CTD. Of the 229 (~40%) patients who died during the 12-year study period, the median survival time from incident ILD diagnosis to death was ~ 2 years. This estimate is similar to (yet somewhat lower than) those found in methodologically-similar, population-based studies examining mortality in CTD-ILD patients [13,14]. Using a retrospective database design with RA patients only, recent analyses presented by Bongartz et al. estimated median survival from incident ILD diagnosis to death to be 2.6 years [14], while a GPRD-cohort of patients with several types of CTDs during the period 1989-1997 presented by Hubbard and Venn reported a median survival time from incident ILD of 2.4 years [13]. The former study used data from a limited geographical region in the USA (Rochester, MN) and contained a small sample size of RA-ILD patients, while the latter only included ILD patients coded with either “idiopathic” or “cryptogenic” fibrosing alveolitis (and hence the smaller sample size compared to the present GPRD study). While our study also employed use of these codes for identification of

incident ILD patients, we further included in our selection algorithm Read codes mentioning “diffuse pulmonary fibrosis,” “fibrosis present,” and “lung disease with a CTD” (e.g. “lung disease with SLE,” etc.).

While much of the CTD-ILD outcome research found in the literature draws comparisons between CTD-ILD and idiopathic ILD or between CTD-ILD vs. CTD alone, our study compares all-cause mortality and cardiovascular outcomes between CTD diagnostic subgroups. In terms of overall patient numbers, the predominant CTD in this study was RA (66%), followed by SSc (11%) and SLE (6%). The decision to group SSc, SLE, SS, DM/PM, and the >1 Dx populations into one category was primarily based on the graphical similarity and log-rank testing (vs. RA-ILD) of the individual Kaplan-Meier estimates for these populations. Over the 12-year study period, we found a statistically significantly increased risk of all-cause mortality for RA-ILD vs. the aggregate category of other CTD-ILD. While we are unable to contextualize this risk estimate due to a lack of published data comparing risk of all-cause mortality between individual CTDs associated with ILD, our 5-, and 10-year all-cause mortality estimates for RA-ILD (51% and 24%, respectively) are similar to those reported by other researchers. In the Early Rheumatoid Arthritis Study (ERAS), which included 52 RA-ILD patients from nine centres in England between 1986 and 1998, Koduri et al. report 5- and 10-year survival probabilities of ~40% (95% CI ~23% to ~54%) and ~25% (95% CI: ~12% to ~39%), respectively [15]. A Kaplan-Meier plot from the Bongartz et al. publication shows similar 5- and 10-year survival estimates of ~40% and ~20% for their RA-ILD cohort, respectively [14].

Among the incident cardiovascular comorbidities investigated in this study, only the risk of PH in the aggregate Other CTD-ILD category was significantly elevated vs. RA-ILD. This >8-fold increased risk was clearly driven by the SSc-ILD group to which 13 of the total 16 incident PH cases were attributed. After adjusting for age and gender, a borderline statistically significant reduced risk of CHF remained for the aggregate Other CTD-ILD group vs. RA-ILD, and no statistically significant differences in risk at the 5%- lever were observed for incident diagnoses of arrhythmia or IHD. Irrespective of the potential impact of ILD in RA, risk of cardiovascular comorbidity in RA patients has been studied extensively, especially in relation to its contribution to premature mortality. In a study by Nicola et al. CHF, as opposed to IHD, was identified as an important contributor to excess mortality in a cohort of RA patients [16]. A further detrimental impact of ILD on cardiovascular comorbidity in RA and other CTD patients is however conceivable due to the restrictive lung function characteristic of ILD and its potential consequences on pulmonary circulation, e.g. pulmonary arterial hypertension and cor pulmonale.

Our study has a few potential limitations. We did not directly test the validity of mortality or diagnosis data. However, previous research has confirmed the completeness of death recording and the high validity of many disease diagnoses in the GPRD, including cardiovascular and respiratory disease [17-20]. Likewise, validity of RA diagnoses in the GPRD appears to be high, based on two previous studies [21,22]. Furthermore, Hubbard et al have reported a high validity of idiopathic ILD in the GPRD [23]. Moreover, it is highly unlikely that general practitioners would record diagnoses of ILD, CTD or cardiovascular disease without confirmation by

specialist referral. Therefore, we expect the diagnoses used in the present study to have a high specificity. On the other hand, we acknowledge that the sensitivity of the diagnoses used may not be as high as the specificity. It is possible that misclassification of CTD or ILD diagnoses play a role here, however, the extent to which this occurred is expected to be minimal in light of results from the aforementioned validation studies. A further reason contributing to potentially reduced sensitivity could be that less severe cases escaped detection by general practitioners and specialists. Thus, it is possible that we did not have available for analysis all true cases of CTD, ILD, and CV disease. However, the extent to which this occurred will likely be true for all chronic disease diagnoses in the GPRD such as CTD, CVD, and ILD, and therefore this will not have introduced any substantial bias on our risk estimates. Also, we cannot be certain that all newly identified ILD cases were indeed incident cases. However, we excluded cases with less than 3 years of recorded medical history in order to minimize the possibility of including prevalent cases, so we expect the occurrence of such error to be minimal. Likewise, for our analysis of incident CVD after ILD diagnosis, we excluded from the CVD analysis populations patients with any mention of the respective CVD under investigation prior to the index date.

With respect to our survival estimates, it is not clear to what extent lead-time bias and drug treatment affected our results. For instance, the extent to which ILD screening in CTD patients differs according to CTD subtype will have biased our estimation of survival time. We acknowledge the recommendation by published guidelines that SSc patients undergo baseline and annual screening for ILD, as this may have

contributed to earlier detection of ILD (and hence longer survival time) among our SSc-ILD subgroup [24]. Furthermore, questions relating to survival differences based on treatment modalities for different CTDs and ILDs were not explored in this study, and so we are unable to comment on potential confounding by such factors.

In summary, this study shows that CTD patients with a subsequent diagnosis of ILD have a median survival of ~ 2 years from the time of ILD diagnosis. The mortality rate in non-RA CTD-ILD patients is 40% lower than in those with RA-ILD, after adjusting for age and gender. This study not only makes use of data from a well-validated database which has consistently been found to be representative of the UK general population, but also addresses important questions relating to the natural history and prognosis of ILD occurring in patients with CTD [25].

7.3.6 Tables and figures

Table 1. Frequency of incident CTD-ILD cases by type of CTD (N=583).

Type of CTD diagnosis	Frequency	Percent
RA	385	66.05
SSc	62	10.63
SLE	35	6.00
SS	22	3.77
DM/PM	21	3.60
MCTD/UCTD	0	0.00
>1 CTD Dx	58	9.95

RA=Rheumatoid Arthritis, SSc = Systemic Sclerosis, SLE = Systemic Lupus Erythematosus, SS = Sjögren Syndrome, DM/PM=Dermatomyositis/Polymyositis, MCTD/UCTD=Mixed/Undifferentiated Connective Tissue Disease, Dx=Diagnosis

Table 2. Baseline (i.e. at index date) characteristics of CTD-ILD patients, by CTD subtype

Characteristics		RA [n=385] n (%)	SSc [n=62] n (%)	SLE [n=35] n (%)	SS [n=22] n (%)	DM-PM [n=21] n (%)	>1 CTD Dx [n=58] n (%)
Age in years [mean (sd)]		69.7(10.1)	57.5(12.7)	52.0(13.5)	69.4(12.9)	63.3(12.3)	63.0(12.2)
	Min.	39	30	23	40	39	11
	Max.	93	87	79	88	89	79
Gender	Males	172 (44.7)	11 (17.7)	7 (20.0)	1 (4.5)	5 (23.8)	10 (17.2)
	Females	213 (55.3)	51 (82.3)	28 (80.0)	21 (95.5)	16 (76.2)	48 (82.8)
BMI [kg/m2]	< 25	132 (34.3)	28 (45.2)	14 (40.0)	12 (54.5)	7 (33.3)	23 (39.7)
	>= 25	171 (44.4)	23 (37.1)	11 (31.4)	8 (36.4)	13 (61.9)	31 (53.4)
	Unknown	82 (21.3)	11 (17.7)	10 (28.6)	2 (9.1)	1 (4.8)	4 (6.9)
Smoking status	Non-smokers	155 (40.3)	34 (54.8)	20 (57.1)	13 (59.1)	12 (57.1)	32 (55.2)
	Current/Ex	198 (51.4)	24 (38.7)	12 (34.3)	8 (36.4)	8 (38.1)	25 (43.1)
	Unknown	32 (8.3)	4 (6.5)	3 (8.6)	1 (4.5)	1 (4.8)	1 (1.7)
Last alcohol status prior to index date	None/Never	166 (43.1)	25 (40.3)	15 (42.9)	6 (27.3)	5 (23.8)	22 (37.9)
	Current/Ex	219 (56.9)	37 (59.7)	20 (57.1)	16 (72.7)	16 (76.2)	36 (62.1)

RA=Rheumatoid Arthritis, SSc = Systemic Sclerosis, SLE = Systemic Lupus Erythamatosus, SS = Sjögren Syndrome, DM/PM=Dermatomyositis/Polymyositis, CTD=Connective Tissue Disease, Dx=Diagnosis

Table 3. Survival analyses for all-cause mortality (Cox proportional hazards regression)

	N	No. of deaths	HR*	95% CI	p-value (LRT)
Individual CTD groups vs. RA					
RA	385	179	1.000	Reference	
SSc	62	13	0.497	0.282 to 0.879	
SLE	35	8	0.537	0.260 to 1.108	
SS	22	6	0.681	0.301 to 1.543	
DM/PM	21	7	0.621	0.291 to 1.328	
> 1 CTD Dx	58	16	0.586	0.348 to 0.986	0.0314
Other CTD vs. RA					
RA	385	179	1.000	Reference	
Other CTD	198	50	0.600	0.431 to 0.834	0.0024

RA=Rheumatoid Arthritis, SSc = Systemic Sclerosis, SLE = Systemic Lupus Erythamatosus, SS = Sjögren Syndrome, DM/PM=Dermatomyositis/Polymyositis, CTD=Connective Tissue Disease, Dx=Diagnosis, HR = Hazard Ratio, CI=Confidence Interval, *=Adjusted for age

Table 4. Incident cardiovascular comorbidity after index date (Cox proportional hazards regression)

	N	No. of incident diagnoses	HR*	95% CI	p-value (LRT)
Arrhythmia					
RA	303	28	1.000	Reference	
Other CTD	176	12	0.802	0.388 to 1.659	0.552
CHF					
RA	314	38	1.000	Reference	
Other CTD	171	9	0.478	0.224 to 1.020	0.056
IHD					
RA	251	13	1.000	Reference	
Other CTD	148	3	0.492	0.131 to 1.846	0.293
PH					
RA	382	4	1.000	Reference	
Other CTD	193	16	8.316	2.549 to 27.124	<0.001

RA=Rheumatoid Arthritis, CTD=Connective Tissue Disease, CHF=Congestive Heart Failure, IHD=Ischemic Heart Disease, PH=Pulmonary Hypertension, HR = Hazard Ratio, CI=Confidence Interval, *=Adjusted for age and gender

Figure 1. Kaplan-Meier plots comparing survival across CTD-ILD subgroups, adjusted for age at index date and gender (N=583)

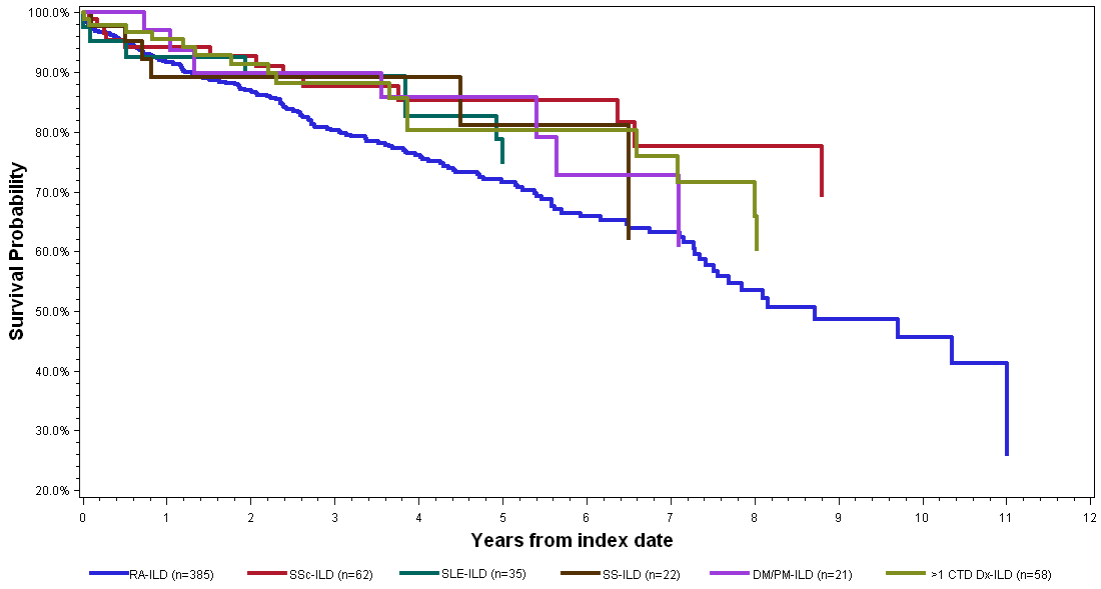
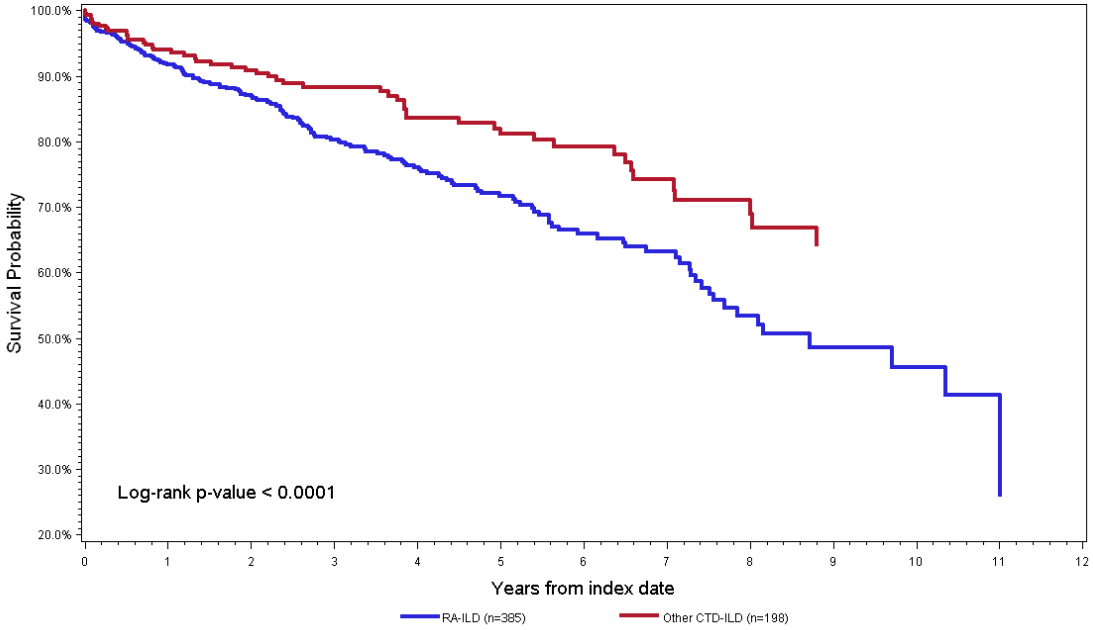


Figure 2. Kaplan-Meier plots comparing survival in RA-ILD vs. Other CTD-ILD, adjusted for age at index date and gender (N=583)



7.3.7 References

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8 Appendices

8.1 Appendix 1. Read diagnosis codes

READ Code	READ Name
ILD of known cause or associated with other diseases	
Extrinsic Allergic Alveolitis (EAA)	
H35..00	Extrinsic allergic alveolitis
H350.00	Farmers' lung
H351.00	Bagassosis
H352.00	Bird-fancier's lung
H352000	Budgerigar-fanciers' lung
H352100	Pigeon-fanciers' lung
H352z00	Bird-fancier's lung NOS
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
H35y000	Cheese-washers' lung
H35y100	Coffee-workers' lung
H35y200	Fish-meal workers' lung
H35y300	Furriers' lung
H35y400	Grain-handlers' disease
H35y600	Sequoiosis (red-cedar asthma)
H35y700	Wood asthma
H35y800	Air-conditioner and humidifier lung
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
Hyu4300	[X]Hypersensitivity pneumonitis due to other organic dusts
Pneumoconioses	
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 [1]
H41z.00	Asbestosis NOS
H42..00	Silica and silicate pneumoconiosis

READ Code	READ Name
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
H440.00	Byssinosis
H441.00	Cannabinosis
H442.00	Flax-dressers' disease
H44z.00	Pneumopathy due to inhalation of other dust NOS
H45..00	Pneumoconiosis NOS
H450.00	Pneumoconiosis associated with tuberculosis
H464200	Chronic pulmonary fibrosis due to chemical fumes
H46z000	Silo-fillers' disease
Hyu4000	[X]Pneumoconiosis due to other dust containing silica
Hyu4100	[X]Pneumoconiosis due to other specified inorganic dusts
Drug / radiation-induced lung disease (DRAD-ILD)	
H4y0.00	Acute pulmonary radiation disease
H4y0000	Acute radiation pneumonitis
H4y0z00	Acute pulmonary radiation disease NOS
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
Hyu4800	[X]Chronic+other pulmonary manifestations due to radiation
ILD associated with other diseases (ILD-ODIS)	
H55..00	Postinflammatory pulmonary fibrosis
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

READ Code	READ Name
H57y000	Pulmonary amyloidosis
H57y100	Lung disease with polymyositis
H57y300	Lung disease with Sjogren's disease
H57y400	Lung disease with systemic lupus erythematosus
H57y500	Lung disease with syphilis
H57yz00	Lung disease with diseases EC NOS
A789900	HIV disease resulting in lymphoid interstitial pneumonitis
N04y012	Fibrosing alveolitis associated with Rheumatoid Arthritis
Idiopathic Interstitial Pneumonia (IIP)	
Idiopathic Pulmonary Fibrosis (IPF)	
H563.00	Idiopathic fibrosing alveolitis
H563.12	Cryptogenic fibrosing alveolitis
H563z00	Idiopathic fibrosing alveolitis NOS
Other potential IIP diagnoses (not used due to sparse no. of cases found)	
H563.11	Hamman - Rich syndrome
H563000	Alveolar capillary block
H564.00	Bronchiolitis obliterans organising pneumonia
H312300	Bronchiolitis obliterans
H58y400	Squamous metaplasia of lung
H560.00	Pulmonary alveolar proteinosis (PAP)
Granulomatous ILD	
H57y200	Pulmonary sarcoidosis
G754.00	Wegener's granulomatosis
AD50.00	Sarcoidosis of the lung
AD53.00	Sarcoidosis of skin
AD51.00	Sarcoidosis of lymph nodes
AD52.00	Sarcoidosis of lung with sarcoidosis of lymph nodes

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02/2009 to 03/2012:	**University of Basel, Department of Pharmaceutical Sciences, Basel Pharmacoepidemiology Unit (BPU), Basel, Switzerland**
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Doctoral thesis:	"A descriptive epidemiological study of Interstitial Lung Disease (ILD) in the United Kingdom general population" (Data source: UK GPRD) Supervised by Prof. Dr. Christoph R. Meier, MSc, PhD

09/1997 to 09/1998:	**London School of Hygiene & Tropical Medicine (LSHTM), University of London, London, UK**
Degree completed:	Master of Science in Epidemiology (MSc)
MSc thesis:	"Antihypertensive Drug Treatment and Depression: A prospective investigation in an elderly population" Analysis of data from a psychiatric sub-study which was 'nested' within the Medical Research Council (MRC) trial of the treatment of hypertension in older adults, conducted between 1982 and 1989. The analysis was conducted with permission of the Institute of Psychiatry, London, and was supervised by Dr. Martin J. Prince.

Undergraduate education

09/1988 to 12/1992:	**University of California, Berkeley, CA, USA**
Degree completed:	Bachelor of Arts (B.A.)

Secondary education

09/1984 to 06/1988:	**Los Altos High School, Hacienda Heights, CA, USA**
Degree completed:	High School Diploma (with Honors)

Abstracts / Poster Presentations / Independent Project Work

1) Amar RK, Jick SS, Rosenberg D, Maher TM, Meier CR. *Epidemiology of the Pneumoconioses in the UK General Population***.** Accepted for poster presentation at the 27th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE), Chicago, USA, 14-17 August 2011.

2) Amar RK, Jick SS, Rosenberg D, Maher TM, Meier CR. *Drug-/Radiation-Induced Interstitial Lung Disease in the UK General Population: Incidence, Drug Use, and Characteristics at Diagnosis***.** Accepted for poster presentation at the 27th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE), Chicago, USA, 14-17 August 2011.

3) http://www.henet.ch/ebph. Swiss-based interdisciplinary project: Evidence-based Public Health (EBPH). Collaboration with the Swiss Ministry of Health (Bundesamt für Gesundheit (BAG)) and co-author of 1st release of EBPH Guidelines and Curriculum 1999-2000.

Publications & Submitted Manuscripts

1) Amar RK, Jick SS, Rosenberg D, Maher TM, Meier CR. **Incidence of the Pneumoconioses in the U.K. general population between 1997 and 2008**. *Respiration* 2012 Jun 7. [Epub ahead of print]

2) Amar RK, Jick SS, Rosenberg D, Maher TM, Meier CR. **Drug-/radiation-induced interstitial lung disease in the United Kingdom general population: Incidence, all-cause mortality, and characteristics at diagnosis.** *Respirology* 2012 May 7. [Epub ahead of print]

3) Amar RK, Jick SS, Rosenberg D, Maher TM, Meier CR. **Interstitial lung disease in patients with connective tissue disease: A retrospective cohort study of incident cardiovascular comorbidity and all-cause mortality using the U.K. General Practice Research Database**. Submitted to and under review by *Rheumatology*

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Skills & Other Information

- Sound knowledge of and practical experience using Good Clinical Practice (GCP)
- Excellent understanding of the principles of epidemiology, clinical trials methodology, and biostatistics
- Academic and on-the-job experience using the following statistical packages: STATA, SAS, and SPSS (advanced knowledge).
- On-the-job experience using Oracle Clinical & Remote Data Capture (OC/RDC), Oracle Adverse Event Reporting System (AERS)
- Advanced knowledge of MS Word, Excel, PowerPoint, and Access