

Is occupational asbestos exposure an under-recognised cause of idiopathic pulmonary fibrosis?

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A thesis presented for the degree of
Doctor of Philosophy

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I, Carl Jonathan Reynolds confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

The question of whether occupational asbestos exposure is an under-recognized cause of idiopathic pulmonary fibrosis arises because it is clinically plausible, epidemiologically plausible, and consistent with fibre studies and case-control data. This thesis examines the question by means of a literature review and a novel hospital based case-control study, the idiopathic pulmonary fibrosis job exposures study (IPFJES).

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Abbreviations

- **IPF** Idiopathic pulmonary fibrosis.
- **MUC5B** Mucin 5B gene.

Chapter 1

Introduction to thesis

1.1 Occupational asbestos exposure as an underrecognised cause of idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrotic lung disease which in 2012 was the recorded cause of death for c.4000 people in England and Wales. Its incidence, currently around 7.5/100,000 person-years, has increased by 5% pa since 2000.[1] The pathophysiology of IPF is complex, the outcome of host susceptibility factors, epithelial injury, and a dysregulated repair process. Several gene polymorphisms which result in a vulnerable alveolar epithelium have been characterized; they include abnormalities in mucin genes (eg MUC5B), surfactant protein genes, and telomerase genes (eg TERT and TERC).[2][3][4] The median age of onset is 70 years and the condition is more common in men (M:F ratio 1.6), manual workers, and those living in industrial areas[1], patterns that are not unique to the UK.[3] The prognosis is poor, with a median survival of three years.[5][6]

These epidemiological distributions of IPF are consistent with a long-latency response to occupational dust exposure; in particular, the incidence of IPF correlates strongly (if ecologically) with historic asbestos use.[7] Mineralogical studies support the concept of asbestosis-IPF misclassification by revealing high fibre burdens in the lung tissue of patients diagnosed with ‘IPF’ and

revision of the diagnosis to ‘asbestosis’.[8][9][10][11]

Identification of occupational asbestos fibre exposure as an under-recognised cause of IPF is important to improve our understanding of the aetio-pathophysiology of IPF and the accuracy of prognostic information. It would have implications for compensation and impact on the current restrictions on individual treatment. Importantly, it would inform evidence-based workplace exposure policies in the UK and internationally, particularly in the many countries with continuing high levels of asbestos use.

1.2 Aims and objectives

My overall aim is to characterize and measure asbestos exposure as an occupational determinant of IPF; additionally, I will determine host-exposure interactions mediated by candidate susceptibility polymorphisms (in particular MUC5B promoter polymorphism rs35705950).

My specific research questions are:

1. Does a dose-response relationship exist for occupational asbestos exposure and IPF?
2. Does the presence of asbestos exposure modify the association between IPF and rs35705950?

Chapter 2

Data sources

- For the literature review and meta-analysis of occupational exposures in IPF I consider all published IPF case-control studies reporting on occupational exposures.
- For the mortality analysis I use data obtained from the Office of National Statistics, Health and Safety Executive, and the World Health Organisation Mortality Database.
- Brief reviews of asbestos exposure assessment and genetic susceptibility in IPF rely on the published literature.
- Primary case-control data collected during my PhD as part of the idiopathic pulmonary fibrosis job exposures study (IPFJES) is used to analyze asbestos exposure in IPF. (?include navaratum case control jobs data that was shared)

2.1 Outline of thesis

This chapter (Chapter 1) describes the problem studied, aims and objectives, and approach. Chapter 2 is a literature review and meta-analysis of IPF case-control studies that report on occupational exposure. Chapter 3 is an analysis of IPF and asbestos related disease mortality data. Chapter 4 is a review of asbestos exposure assessment methodology. Chapter 5 is a review of genetic susceptibility in IPF. Chapter 6 describes the idiopathic

pulmonary fibrosis job exposures study including results and analysis arising from it. Chapter 7 concludes the thesis by summarising it and suggesting future work.

Chapter 3

Literature review and meta-analysis: how much IPF is attributable to occupational exposures?

3.1 Introduction

Idiopathic pulmonary fibrosis (IPF) is a diagnosis of exclusion. It is made in the presence of a usual interstitial pneumonitis (UIP) pattern on high resolution CT scan or biopsy. The diagnosis requires that known causes of interstitial lung disease (such as drug toxicity, connective tissue disease, domestic, and occupational or environmental exposures) be excluded.[12]

Attributing a disease process to a specific exposure can be difficult. Disease processes are frequently complex or multifactorial, depending on the interaction of genetic and environmental components. Well-studied and relatively frequent entities such as chronic obstructive pulmonary disease, ischaemic heart disease and diabetes lend themselves to epidemiologic investigation, delineating the major risk factors for disease and their relative contributions to risk at the population level. IPF presents an additional challenge to attribution; because of its relative infrequency, epidemiologic study of the disease

is largely limited to case-control studies.[13] Studying specific occupational exposures also presents its own challenges; co-exposure is common, occupational hygiene data is frequently limited and self-reported exposure is prone to recall bias.

I identified several review articles of the epidemiology of interstitial lung disease that do not necessarily focus on IPF and only briefly mention occupational factors (e.g. Ley2013[3]). Here I consider review articles that specifically deal with occupational factors in IPF and cite the case-control studies used.

Turner-Warwick (1998) discusses potential difficulties in establishing attribution and causality in IPF. She observes that there is variation in clinical practice with respect to the standard applied to exclude IPF; some clinicians exclude IPF when exposure to a potential cause is identified, others only when there is clear exposure to an established cause. She explains that diagnosis based on radiologic and clinical findings, and not on lung biopsy or bronchioalveolar lavage, may result in initiating agents for disease being overlooked. Further, that exposures such as asbestos, silica, coal, graphite, hard metal, and avian proteins, may result in disease that can not be differentiated from IPF.[14]

Reviewing the epidemiology of IPF and case-control studies to date Hubbard (2001) describes the association of IPF with occupational exposures to metal and wood and estimates that 10% of IPF cases may be due to occupational metal exposure and 5% of cases to wood.[15]

Taskar and Coultas (2006) review and carry out a meta-analysis of six case-control studies investigating environmental and occupational exposures in IPF. They report population attributable risk percentages for agriculture and farming (20.8%), livestock (4.1%), wood dust (5%), metal dust (3.4%), stone/sand/silica (3.5%), and smoking (49.1%).[16]

Gulati and Redlich's (2015) review of exposures causing usual interstitial pneumonia highlights that asbestosis may appear indistinguishable from IPF and summarises previous case-control studies but did not pool studies to perform a meta-analysis.[17]

I sought to identify and meta-analyze all IPF case-control studies dealing with occupational exposures.

3.2 Method

Pubmed, embase, and google scholar search engines were searched for combinations of the terms ‘idiopathic pulmonary fibrosis’, ‘occupation’, ‘case-control study’ and synonyms. When relevant papers were identified papers referenced and papers citing the paper were reviewed. Medline ranker[18] and bespoke pubmed ‘mining’ techniques[19] were also used.

Two investigators independently reviewed and abstracted data for five exposure categories common to the identified case-control studies: “vapors, gases, dusts, and/or fumes (VGDF)”, “metal dust”, “wood dust”, “silica dust”, and “agricultural dust”. We calculated PAF as follows: $PAF = pc(OR - 1)/OR$, where pc is the proportion of cases exposed and OR is the risk estimate.

We calculated pooled OR and pooled PAF for occupational exposures using fixed effects models and random effects models in Stata. When there was results of the models differed substantively, we used the results of the fixed effects model, which were more conservative. The pooled PAF relied on the ratio of attributable cases to all cases underlying each risk estimate.

3.3 Results

We found (as of May 2017) 14 case-control studies looking at occupational exposures in IPF (Table 3.1) the most recent review article covers only eight of them. Associations with metal, wood, silica, and agricultural dust were reported. [20][21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31]

43 risk estimates from 14 publications (2027 IPF cases in total) were used. Each exposure category was assessed with 6-11 risk estimates (Table 3.2).

Table 3.1: Summary of IPF case-control studies investigating occupational exposures

Reference (n cases)	OR; 95% CI					PAF %					Case Definition	Exposure Measure
	vgdf*	metal	wood	ag	si	vgdf*	metal	wood	ag	si		
Scott 1990(40)	1.3; 0.8, 2.0	11.0; 2.3, 52.0	2.9; 0.9, 9.9	10.9; 1.2, 96.0	1.6; 0.5, 4.8	17	12	10	12	15	clinical assessment, CXR, pulmonary function	questionnaire
Iwai 1994(86)		1.3; 1.1, 1.6		3.0; 1.3, 7.4							clinical assessment, CXR or CT, pul- monary function	questionnaire
Iwai 1994(615)	2.0; 1.2, 3.1										autopsy	job group
Hubbard 1996(218)		1.7; 1.1, 2.7	1.7; 1.0, 2.9		1.8; 1.0, 3.1	10	6				clinical assessment, CXR or CT, pul- monary function	questionnaire and telephone interview
Mullen 1998(15)	2.4; 0.7, 8.4		3.3; 0.4, 25.8		11; 1.1, 115	23		7		20	clinical assessment, lung biopsy or CT	questionnaire
Baumgartner 2000(248)		2.0; 1.0, 4.0	1.6; 0.8, 3.3	1.6; 1.0, 2.5	3.9; 1.2, 12.7		5	3	7	3	clinical assessment, lung biopsy or BAL, CT	telephone inter- view
Hubbard 2000(22)		1.1; 0.4, 2.7				5					death certificate diag- nosis	job group
Miyake 2005(102)		9.6; 1.7, 181.1	6.0; 0.3, 112.4		1.8; 0.5, 7.0	26	11	4		11	clinical assessment, lung biopsy or BAL, CT	questionnaire
Gustafson 2007(140)	1.1; 0.7, 1.7	0.9; 0.5, 1.6	1.2; 0.7, 2.2		1.4; 0.7, 2.7	6		3		10	pulmonary fibrosis of unknown aetiology + requiring LTOT	questionnaire
Garcia-Sancho Figueroa 2010(97)	1.2; 0.8, 1.9				9						clinical assessment, CT +/- lung biopsy	questionnaire
Garcia-Sancho 2011(100)	2.8; 1.5, 5.5				5						clinical assessment, CT +/- lung biopsy	questionnaire
Awadalla 2012(201)		1.6; 0.7, 3.6	2.7; 1, 16.8	1.3; 0.7, 2.0	1.1; 0.5, 2.7		6	7	7	13	clinical assessment, CT, pulmonary func- tion	questionnaire
Paolucci 2013 (ab- stract only)(65)		2.8; 1.1, 7.2			2.0; 0.9, 4.4		9	2		22	clinical assessment and CT	questionnaire
Koo 2017(78)	2.7; 0.7, 10.9	5.0; 1.4, 18.2	2.5; 0.5, 12.3		1.2; 0.4, 3.8	35	22	5		27	clinical assessment, CT +/- lung biopsy	interview

Table 3.2: Pooled estimates of occupational contributions to IPF (based on 12 case-control studies)

Exposure	Risk estimates (n)	Pooled OR (95% CI)	Pooled PAF (95% CI)
VGDF*	8	1.6 (1.3-1.9)	14 (12-17)
Metal dust	10	1.4 (1.3-1.7)	8 (6-10)
Wood dust	11	1.7 (1.3-2.2)	4 (3-5)
Agricultural dust	6	1.8 (1.0-3.1)	8 (5-10)
Silica dust	9	1.7 (1.3-2.3)	7 (5-9)

3.4 Discussion

tables above will need updating because of gremlins

Our results support the case for a proportion of IPF cases being attributable to occupational exposures.

Pooled ORs were significantly elevated for VGDF, metal dust, wood dust, agricultural dust, and silica dust; the pooled PAF estimates by category ranged from 4-23%. This is an important finding for an otherwise idiopathic disease which carries significant morbidity and mortality; identifying causal occupational agents would permit remediation and prevention.

Associations between IPF and wood, metal, and agricultural dust were previously reported in a meta-analysis of six case-control studies by Taskar and Coultas. [16] While our findings are similar we found a smaller effect size for agricultural exposure and a large effect size for non-specific vapours, gases, dust, and fumes (VGDF), see Table 3.2.

Funnel plot asymmetry using Egger’s test, which may be due to publication bias, was present for VGDF ($p = 0.04$) and metal dust ($p = 0.03$) but not for wood dust ($p = 0.09$), silica dust ($p = 0.2$), and agricultural dust ($p = 0.6$). However, the number of studies included is small and funnel plot asymmetry may be due to chance rather than bias.

There are several limitations to the meta-analysis that arise from the case-control studies included.

Several studies [20] [32] [24] [26] [28] used population controls but do not provide details on participation rates. Participation rates can be low for community controls; a recent UK case-control study investigating prothrombotic factors in IPF reported a response rate of 28% for community controls. [33] This approach is vulnerable to non-responder bias. One study[34] used employee occupational records and death certificates from pension-fund records for a single company and was only able to locate the occupational records for 40% of cases and 38% of controls.

Nearly all studies relied on self-reported exposures rather than life time oc-

cupational histories to assess exposure; an approach that is prone to recall bias and does not permit examination of dose-response relationships.

Reliance of self-reported exposures also means that studies are potentially vulnerable to confounding as a result of co-exposure. For example, several studies have described strong associations between metal work and IPF and specify sheet metal workers[21][20][34], a group who are frequently exposed to dust containing asbestos fibres[35] and who in a recent UK study, had the highest risk of mesothelioma.[36]

Case definitions and sources for cases varied between studies. For example Scott (1990)[20] used a case definition which included a chest radiograph showing bilateral interstitial shadowing whereas most other studies relied on high resolution CT. Four studies used mortality data [21][37][26][34] to identify cases and one study[26] used a national register of patients receiving oxygen therapy. Differences in healthcare coverage and coding practices can result in selection bias.[38]

3.5 Conclusion

The observed excess risk could represent disease misclassification of pneumoconiosis or hypersensitivity pneumonitis, but this is unlikely to fully explain the observed effects. Our analysis supports an etiologic role for occupational exposures in IPF, potentially explaining up to 23% of the burden of disease and highlighting a role for workplace exposure reduction in disease prevention.

Chapter 4

Mortality analysis: do mortality trends support an occupational cause?

4.1 Introduction

The incidence of Idiopathic pulmonary fibrosis (IPF) has been increasing at a rate of 5% per annum since 2000. By definition, the diagnosis of IPF is not made in the presence of an identifiable cause. However, the distribution of the disease in the population (more common in men, manual workers, and those living in more industrial areas of the country) suggests a causal contribution from an occupational or environmental source.

It is hypothesised that a proportion of Idiopathic Pulmonary Fibrosis (IPF) cases are due to occult environmental or occupational exposures to asbestos dust. This would be expected to result in a spatio-temporal association between IPF, Mesothelioma, and Asbestosis mortality patterns coinciding with asbestos exposure. It would also be expected to produce a birth cohort effect

Our aim was to examine trends in IPF, Mesothelioma, and Asbestosis mortality data for evidence of cohort effect and association.

4.2 Method

Regional age and sex stratified mortality data for IPF, Mesothelioma, and Asbestosis were obtained for England and Wales from the Office of National Statistics for the period 1974–2012. Data were age-standardised and visualised using the Python Pandas data analysis library and matplotlib.

4.3 Results

IPF mortality continues to rise. Female:Male is approximately 1:1.6. There are more IPF deaths in the North West and South East of England. IPF mortality does appear to correlate with mesothelioma mortality (Figure 4.1). There is evidence of a cohort effect with age-specific IPF death rates increasing in successive cohorts, most clearly seen from age 60 (Figure 4.2). While overall rates were higher for men but there were not marked sex differences in cohort mortality trends.

4.4 Discussion

icd coding chat

This is the discussion. Duis ultrices tempor sem vitae convallis. Pellentesque lobortis risus ac nisi varius bibendum. Phasellus volutpat aliquam varius. Mauris vitae neque quis libero volutpat finibus. Nunc diam metus, imperdiet vitae leo sed, varius posuere orci.

4.5 Conclusion

Conclusions: The birth cohort effect we observed is consistent with a proportion of IPF cases being due to an occupational or environmental exposure with latency and further research is needed.

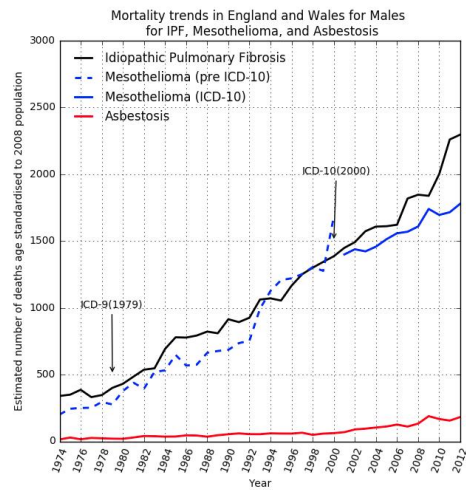


Figure 4.1: IPF, mesothelioma, and asbestosis mortality trends

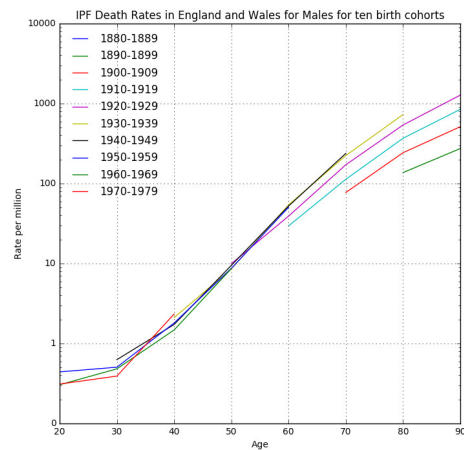


Figure 4.2: IPF male birth cohorts

Chapter 5

Asbestos exposure assessment: can it be done?

5.1 Introduction

Asbestos related respiratory disease is initiated by inhalation of asbestos fibres. In the UK clinically significant asbestos exposure is largely occupational and, as a result of asbestos control legislation, historic.

Occupational asbestos exposure can be assessed quantitatively by sampling ambient air at a workplace and calculating a fibre count using microscopy. Alternatively, because inhaled asbestos fibres persist in the lung they can be sampled by lung biopsy, bronchoalveolar lavage, or at autopsy.

Historic workplace measurements are a valuable resource for assessing exposure but are limited in several ways. Measurements are not available for many occupations, where measurements are available they are dependant on working practices and measurement technique at the time of assessment do not necessarily generalize well.

Measurement of asbestos fibres in lung tissue by means of biopsy or bronchoalveolar lavage is invasive and both procedures carry the risk of serious complication including death. Additionally, the biopersistence of asbestos fibres is variable, counts are sensitive to techniques used, and establishing

appropriate references ranges is challenging.[39]

Modern validated quantitative exposure reconstruction methods integrate historic workplace measurements with simulated workplace measurements and an individuals recollection of job processes he or she has carried out during their working life.[40]

Finally, job-exposure matrices (JEMs) are widely used in occupational epidemiology studies to assess exposure to potential hazards. These assign levels of exposure to health hazards on the basis of job title.

The asbestos exposure assessment literature is large and recognised to be at risk of bias as a result of its economic importance to powerful industrial and medicolegal actors[41].

We critically review different means of asbestos exposure assessment and consider their clinical and research utility.

5.2 Method

We searched pubmed and google scholar for combinations and synonyms of “asbestos”, “exposure assessment”, together with terms for modes of assessment including “lung biopsy”, “bronchoalveolar lavage”, “exposure reconstruction”, and “job-exposure matrix”.

5.3 Results

5.3.1 LUNG BIOPSY AND BRONCHOALVEOLAR LAVAGE

The first report of fibrosis of the lung due to asbestos dust[42] included a description of the post mortem microscopic appearances of the lungs which showed abundant asbestos fibres in areas of fibrosis.

The demonstration of asbestos fibres on lung biopsy in the context of pulmonary fibrosis is clearly supportive of the diagnosis of asbestosis. However,

a failure to demonstrate fibres can not be used to rule out asbestos exposure because fibres, particularly chrysotile fibres, may be cleared from the lung and counting methods have a significant false-negative rate.[39]

Despite this recent 2014 Helsinki guidelines[43] and UK Royal College of Pathologist guidelines appear to suggest that a clear history of substantial occupational asbestos exposure is insufficient for diagnosis and that the absence of asbestos bodies or fibre counts above a certain threshold might be used to rule out a the diagnosis. The shortcomings of such an approach highlighted above are also described by responses to the Helsinki guideline.[44][45][46]

As alluded to previously lung biopsy also carries significant health risks, particularly for patients who already have compromised lung function. Therefore it can not be justified solely on medico-legal grounds.[??] Therefore, the clinical utility of lung biopsy and bronchoalveolar lavage is limited to ruling in asbestosis when a suggestive exposure history and radiology are lacking.

In a research context lung biopsy and bronchoalveolar lavage have provided valuable population level insights. Lung biopsy asbestos fibre counts have been examined in a UK case-control study where mesothelioma cases were compared with lung cancer controls. Fibre counts were found to be higher in groups with greater occupational risk (as defined by PMR), providing additional support for the pre-eminence of an occupational history.[36][??] In a follow up study asbestos fibre counts from unselected surgically treated pneumothorax patients were used to demonstrated that population amphibole burden is falling and is proportional to mesothelioma mortality.[47]

A similar correlation with occupational exposure history, overall downward trend in fibre counts, and a significant false negative rate has been observed in a recent Belgian study of patients undergoing bronchoscopy with bronchoalveolar lavage sampling for asbestos fibre quantification.[??]

5.3.2 HISTORIC WORKPLACE MEASUREMENTS

Occupational hygienists have recorded a large numbers of workplace measurements of asbestos in different settings, at different times, using a variety of different means. These measurements reside in national databases such as the HSE National Exposure Database[48], and EV@LUTIL[49], in the published literature, and in unpublished company records.

The use of different means of making workplace assessments resulting in difficulties with respect to the accuracy and comparability of measurements has been highlighted. For example, instruments that count particles rather than asbestos fibres have been used and there is no established conversion factor.[50] Phase contrast microscopy has also been used which is less sensitive than scanning electron microscopy, which is in turn less sensitive than transmission electron microscopy and energy-dispersive x-ray analysis.[??]

Where era and task specific workplace exposure data matching a particular patient occupational history is available and readily identifiable it is a valuable means of assessing exposure history. Unfortunately, this is a rare occurrence.

Measurements have found greater utility in a research setting where they can help to quantify risk and inform regulatory policy and compliance in specific workplace settings, for example, in car mechanics[51] or skilled craftsmen.[52]

5.3.3 EXPOSURE RECONSTRUCTION

Sahmel et al[53] propose a seven-step framework (see Figure 5.1) which they use to enumerate and critique exposure reconstruction approaches.

Reconstruction techniques may be quantitative, semi-quantitative, or qualitative. Quantitative exposure reconstruction bases exposure estimates on data from similar (historic or current) exposure scenarios or simulation studies. Semi-quantitative exposure reconstruction bases exposure estimates on exposure data matrices (using a job-exposure matrix) and/or exposure determinants (using an exposure model). Qualitative exposure reconstruction bases exposure estimates on the expert judgement of an industrial hygienist

and self reported exposures.

Examples of quantitative asb historic studies Examples of simulate asb studies (advantage that can bring modern measurment techniques to bear)

semiquantitative techniques often called jems

[54]

cummulative retrospective exposure assessment correlates with asbestos lung burden analysis[55]

[56]

The paper describes a potentially valuable exposure assessment method for risk stratifying asbestos exposed workers to optimize mesothelioma screening efforts. The exposure assessment model is logical and the validation data is compelling. Theoretically the model would result in a more granular estimation of exposure than alternative estimation methods relying on job-title alone. The approach is limited by the relatively small number of industry-specific data points used for validation which is unavoidable because of the scarcity of exposure measurement data.

[56]

[55]



Figure 5.1: Seven step framework for exposure reconstruction

5.3.3.1 Job-exposure matrices

[57][58] [59] pros/cons jems [60] source of error jems

what are jems

asbestos examples

what are their strenghts and weakness

research and clinical utility

5.3.3.2 Proportional mortality ratios for pleural mesothelioma

One recent novel JEM[36] assigned risk of exposure using occupational mortality statistics for pleural mesothelioma. Because pleural mesothelioma in men is nearly entirely attributable to occupational asbestos exposure, pleural mesothelioma is rapidly fatal, and death certificates record occupation in addition to cause of death, the proportional mortality ratio for pleural mesothelioma (number of deaths due to pleural mesothelioma/total number of deaths) can serve as proxy for average asbestos exposure in a particular occupation.

? stick in table of PMRs

add ‘validation’ thingy with lung bx [gilham etc]

5.3.3.3 Exposure modelling approaches

what are exposure model approaches

what are their strenghts and weakness

research and clinical utility

asbestos examples

Exposure modelling approaches typically modify existing measurement data on the basis of exposure determinant knowledge.

A common conceptual framework for this is the source-receptor model (link a pic).

source receptor model e.g [??] ?smith

Temporal trends seen in the limit of detection (LOD) data in exposure databases tend to track regulatory controls and can be used to estimate historic exposure levels in the absence of data by interpolation.[54]

5.3.3.4 Self-reported exposure

what are self reported exposures

strengths and weakness

research and clinical utility

[61] good overview of shortcomings of this approach.

5.4 Discussion

guidelines IIRAC ANT

Attribution, specifically the required threshold of asbestos exposure (as assessed by various means) that must be crossed before it is possible to say that, for example, scarring of the lung with an usual interstitial pneumonia pattern in an individual patient is caused by asbestos exposure, carries medico-legal in addition to scientific importance has not been well established for several assessment methodologies.

jems don't take account of variation in job tasks

include ANT on attribution from parkes

[53] point out several important considerations for the use of historical in-

dustrial hygiene measurements. Job or tasks for which there was a contemporaneous exposure concern were more likely to be subject to regulatory exposure control and sampled to demonstrate compliance.

[62] can be an impossible task exposure assessment methods limited inter-rater agreement, reliability, precision vs accuracy

[63] quality criteria for exposure assessment

[64]

overview of comparative studies [61]

5.5 Conclusion

Chapter 6

Genetic susceptibility in IPF and MUC5b: MUC5b + environmental insult = IPF?

6.1 Introduction

Third, advances in our understanding of IPF susceptibility now permit study of host-exposure interactions. The minor-allele of the rs35705950 SNP in the mucin 5B gene was found to be present in 38% of IPF patients but just 9% of controls.[65] The polymorphism results in excess MUC5B protein in the airway, impaired clearance of inhaled substances and a chronic inflammatory burden on the alveolar surface.[65] The association is allele dose-dependent, has been replicated in independent cohorts, and appears to confer improved survival.[3][65][66] Two large GWASs have confirmed the observed associations of IPF with MUC5B and other loci.[67][68]

6.2 Method

Vivamus consectetur, velit in congue lobortis, massa massa lacinia urna, sollicitudin semper ipsum augue quis tortor. Donec quis nisl at arcu volutpat

ultrices. Maecenas ex nibh, consequat ac blandit sit amet, molestie in odio. Morbi finibus libero et nisl dignissim, at ultricies ligula pulvinar.

C

6.3 Results

6.4 Discussion

This is the discussion. Etiam sit amet mi eros. Donec vel nisi sed purus gravida fermentum at quis odio. Vestibulum quis nisl sit amet justo maximus molestie. Maecenas vitae arcu erat. Nulla facilisi. Nam pretium mauris eu enim porttitor, a mattis velit dictum. Nulla sit amet ligula non mauris volutpat fermentum quis vitae sapien.

6.5 Conclusion

This is the conclusion to the chapter. Nullam porta tortor id vehicula interdum. Quisque pharetra, neque ut accumsan suscipit, orci orci commodo tortor, ac finibus est turpis eget justo. Cras sodales nibh nec mauris laoreet iaculis. Morbi volutpat orci felis, id condimentum nulla suscipit eu. Fusce in turpis quis ligula tempus scelerisque eget quis odio. Vestibulum et dolor id erat lobortis ullamcorper quis at sem.

Chapter 7

Idiopathic pulmonary fibrosis job exposures study (IPFJES): Is occupational asbestos exposure an under-recognised cause of IPF?

7.1 Introduction

My study will be a multi-centre, hospital-outpatient, incident case-control study. Participants will be recruited from a UK network of six confirmed centres. Cases will be men who present, between 07.2017 and 07.2019, with a new diagnosis of IPF consistent with standard criteria[69]; they will be identified monthly by the MDT coordinator of participating centres.[70]

For each case, four controls, frequency-matched on age, will be randomly selected from incident outpatient attendances (not confined to respiratory) who do not have a diagnosis of IPF and are from the hospital as the case. Monthly lists of outpatient attendances will be obtained using the patient administration systems of participating centres. 120 cases and 480 controls will be recruited over two years with four participants enrolled and interviewed

per day.

Eligible participants will be contacted by telephone and invited to participate. An interviewer will collect data on demographics, lifetime occupational history, hobbies, family medical history, and smoking using a structured web-based questionnaire designed by us to collect lifetime occupational histories. This approach will facilitate coding, allow input validation, and permit questions to be tailored to pre-specified conditions. The questions will be developed in collaboration with an international expert in asbestos exposure measurement, Dr John Cherrie of the IOM. Participants will be invited to provide a venous blood sample for genetic analysis.

Cases and controls will be genotyped using a panel of 15 pre-defined candidate susceptibility SNPs including rs35705950. Genotyping will be undertaken using Q-PCR and Taqman assays on DNA isolated from whole blood samples.

For the primary analysis unconditional logistic regression will be used to analyse ‘any’ vs ‘no’ asbestos exposure and categories of cumulative exposure adjusting for age and smoking status. Prior data[36] indicate that the probability of exposure among controls is 0.29. If the true OR for disease in exposed subjects relative to unexposed subjects is 2.0, I will need to recruit 94 case patients and 376 control patients to be able to reject the null hypothesis that this odds ratio equals 1 with $\beta = 0.2$ and $\alpha = 0.05$ [71]; my planned sample size includes a margin for model stability and incomplete data.[72]

Secondary (exploratory) analysis will investigate gene-environment interaction. The global minor allele frequency of MUC5B rs35705950 is 0.05.[73] With an estimated prevalence of IPF of 20/100000[1] and with ORs 2.0 for asbestos exposure and 6.8 for rs35705950[65], 113 cases would be required to detect a minimum interaction OR of 4.0.[74] While I acknowledge that this exploratory analysis will have the power to detect only a large effect size it seems a valuable opportunity to examine an unexplored area in IPF research.

7.2 Method

In tincidunt viverra dolor, ac pharetra tellus faucibus eget. Pellentesque tempor a enim nec venenatis. Morbi blandit magna imperdiet posuere auctor. Maecenas in maximus est.

7.3 Results

These are the results. Curabitur vulputate nisl non ante tincidunt tempor. Aenean porta nisi quam, sed ornare urna congue sed. Curabitur in sapien justo. Quisque pulvinar ullamcorper metus, eu varius mauris pellentesque et. In hac habitasse platea dictumst. Pellentesque nec porttitor libero. Duis et magna a massa lacinia cursus.

7.4 Discussion

possibility of missed chronic HP [75]

7.5 Conclusion

This is the conclusion to the chapter. Nulla sed condimentum lectus. Duis sed tempor erat, at cursus lacus. Nam vitae tempus arcu, id vestibulum sapien. Cum sociis natoque penatibus et magnis dis parturient montes, nascetur ridiculus mus.

Chapter 8

Conclusion

8.1 Thesis summary

In summary, pellentesque habitant morbi tristique senectus et netus et malesuada fames ac turpis egestas. Nunc eleifend, ex a luctus porttitor, felis ex suscipit tellus, ut sollicitudin sapien purus in libero. Nulla blandit eget urna vel tempus. Praesent fringilla dui sapien, sit amet egestas leo sollicitudin at.

8.2 Future work

chronic hp

Appendix 1: IPF epidemiology code

IPF epidemiology

Appendix 2: IPFJES study documentation

IPFJES study documentation

References

- 1 Navaratnam V, Fleming K, West J *et al.* The rising incidence of idiopathic pulmonary fibrosis in the uk. *Thorax* 2011;**66**:462–7.
- 2 Maher TM. Idiopathic pulmonary fibrosis: Pathobiology of novel approaches to treatment. *Clin Chest Med* 2012;**33**:69–83. doi:10.1016/j.ccm.2011.11.002
- 3 Ley B, Collard HR. Epidemiology of idiopathic pulmonary fibrosis. *Clinical epidemiology* 2013;**5**:483.
- 4 Spagnolo P, Grunewald J, Bois RM du. Genetic determinants of pulmonary fibrosis: Evolving concepts. *The Lancet Respiratory Medicine* 2014;**2**:416–28.
- 5 Hubbard R, Johnston I, Britton J. Survival in patients with cryptogenic fibrosing alveolitis a population-based cohort study. *CHEST Journal* 1998;**113**:396–400.
- 6 Vancheri C, Failla M, Crimi N *et al.* Idiopathic pulmonary fibrosis: A disease with similarities and links to cancer biology. *Eur Respir J* 2010;**35**:496–504. doi:10.1183/09031936.00077309
- 7 Barber C, Wiggans R, Young C *et al.* UK asbestos imports and mortality due to idiopathic pulmonary fibrosis. *Occup Med* 2015;kqv142.
- 8 Monso E, Tura JM, Marsal M *et al.* Mineralogical microanalysis of idiopathic pulmonary fibrosis. *Arch Environ Health* 1990;**45**:185–8. doi:10.1080/00039896.1990.9936714
- 9 Monsó E, Tura J, Pujadas J *et al.* Lung dust content in idiopathic pulmonary fibrosis: A study with scanning electron microscopy and energy dispersive x ray analysis. *Br J Ind Med* 1991;**48**:327–31.
- 10 Glazer C, Maier L. Occupational interstitial lung disease. *Eur Respir Monograph* 2009;**46**:265–86.
- 11 Ghio A, Sangani R, Roggli V. Expanding the spectrum of particle-and fiber-associated

- interstitial lung diseases. *Turk Toraks Derg* 2014;**15**:1–8.
- 12 Travis WD, Costabel U, Hansell DM *et al.* An official american thoracic society/european respiratory society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *American journal of respiratory and critical care medicine* 2013;**188**:733–48.
- 13 Reynolds CJ, Blanc PD. Organising pneumonia and other uncommon interstitial disorders. In: *Parkes' occupational lung disorders, fourth edition*. 2018.
- 14 Turner-Warwick M. In search of a cause of cryptogenic fibrosing alveolitis (cfa): One initiating factor or many? *Thorax* 1998;**53**:S3–9.
- 15 Hubbard R. Occupational dust exposure and the aetiology of cryptogenic fibrosing alveolitis. *Eur Respir J* 2001;**18**:119s–21s.
- 16 Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? *Proc Am Thorac Soc* 2006;**3**:293–8.
- 17 Gulati M, Redlich CA. Asbestosis and environmental causes of usual interstitial pneumonia. *Current opinion in pulmonary medicine* 2015;**21**:193–200. doi:10.1097/MCP.0000000000000144
- 18 Fontaine J-F, Barbosa-Silva A, Schaefer M *et al.* MedlineRanker: Flexible ranking of biomedical literature. *Nucleic acids research* 2009;**37**:W141–6. doi:10.1093/nar/gkp353
- 19 Reynolds C, De Matteis S, Cullinan P *et al.* Pubmed mining for occupational idiopathic pulmonary fibrosis papers. 2017.
- 20 Scott J, Johnston I, Britton J. What causes cryptogenic fibrosing alveolitis? A case-control study of environmental exposure to dust. *BMJ* 1990;**301**:1015.
- 21 Iwai K, Mori T, Yamada N *et al.* Idiopathic pulmonary fibrosis. epidemiologic approaches to occupational exposure. *Am J Respir Crit Care Med* 1994;**150**:670–5. doi:10.1164/ajrccm.150.3.8087336
- 22 Hubbard R, Lewis S, Richards K *et al.* Occupational exposure to metal or wood dust and aetiology of cryptogenic fibrosing alveolitis. *The Lancet* 1996;**347**:284–9.
- 23 Mullen J, Hodgson MJ, DeGraff CA *et al.* Case-control study of idiopathic pulmonary fibrosis and environmental exposures. *J Occup Environ Med* 1998;**40**:363–7.
- 24 Baumgartner KB, Samet JM, Coultas DB *et al.* Occupational and environmental risk factors for idiopathic pulmonary fibrosis: A multicenter case-control study. collaborating centers. *Am J Epidemiol* 2000;**152**:307–15.
- 25 Miyake Y, Sasaki S, Yokoyama T *et al.* Occupational and environmental factors and

- idiopathic pulmonary fibrosis in japan. *Ann Occup Hyg* 2005;**49**:259–65.
- 26 Gustafson T, Dahlman-Höglund A, Nilsson K *et al.* Occupational exposure and severe pulmonary fibrosis. *Respir Med* 2007;**101**:2207–12.
- 27 García-Sancho Figueroa MC, Carrillo G, Pérez-Padilla R *et al.* Risk factors for idiopathic pulmonary fibrosis in a mexican population. a case-control study. *Respir Med* 2010;**104**:305–9.
- 28 García-Sancho C, Buendía-Roldán I, Fernández-Plata MR *et al.* Familial pulmonary fibrosis is the strongest risk factor for idiopathic pulmonary fibrosis. *Respiratory medicine* 2011;**105**:1902–7. doi:10.1016/j.rmed.2011.08.022
- 29 Awadalla NJ, Hegazy A, Elmetwally RA *et al.* Occupational and environmental risk factors for idiopathic pulmonary fibrosis in egypt: A multicenter case-control study. *Int J Occup Environ Med* 2012;**3**:107–16.
- 30 Paolocci G, Nicolici V, Folletti I *et al.* Risk factors for idiopathic pulmonary fibrosis in southern europe: A case-control study. 2013.
- 31 Koo J-W, Myong J-P, Yoon H-K *et al.* Occupational exposure and idiopathic pulmonary fibrosis: A multicentre case-control study in korea. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2017;**21**:107–12. doi:10.5588/ijtld.16.0167
- 32 Hubbard R, Johnston I, Coultas DB *et al.* Mortality rates from cryptogenic fibrosing alveolitis in seven countries. *Thorax* 1996;**51**:711–6.
- 33 Navaratnam V, Fogarty AW, McKeever T *et al.* Presence of a prothrombotic state in people with idiopathic pulmonary fibrosis: A population-based case-control study. *Thorax* 2014;**69**:207–15. doi:10.1136/thoraxjnl-2013-203740
- 34 Hubbard R, Cooper M, Antoniak M *et al.* Risk of cryptogenic fibrosing alveolitis in metal workers. *The Lancet* 2000;**355**:466–7.
- 35 Welch LS, Michaels D, Zoloth SR. The national sheet metal worker asbestos disease screening program: Radiologic findings. national sheet metal examination group. *Am J Ind Med* 1994;**25**:635–48.
- 36 Rake C, Gilham C, Hatch J *et al.* Occupational, domestic and environmental mesothelioma risks in the british population: A case-control study. *Br J Cancer* 2009;**100**:1175–83. doi:10.1038/sj.bjc.6604879
- 37 Pinheiro GA, Antao VC, Wood JM *et al.* Occupational risks for idiopathic pulmonary fibrosis mortality in the united states. *Int J Occup Environ Health* 2008;**14**:117–23.
- 38 Caminati A, Madotto F, Cesana G *et al.* Epidemiological studies in idiopathic pul-

- monary fibrosis: Pitfalls in methodologies and data interpretation. *European respiratory review : an official journal of the European Respiratory Society* 2015;**24**:436–44. doi:10.1183/16000617.0040-2015
- 39 De Vuyst P, Karjalainen A, Dumortier P *et al.* Guidelines for mineral fibre analyses in biological samples: Report of the ers working group. european respiratory society. *The European respiratory journal* 1998;**11**:1416–26.
- 40 Cherrie JW, Schneider T. Validation of a new method for structured subjective assessment of past concentrations. *Ann Occup Hyg* 1999;**43**:235–45.
- 41 Nemery B, Nuyts V, Nackaerts K. Quantifying asbestos in lung tissue: What debate? *The European respiratory journal* 2017;**49**. doi:10.1183/13993003.00861-2017
- 42 Cooke WE. FIBROSIS of the lungs due to the inhalation of asbestos dust. *British medical journal* 1924;**2**:147–140.2.
- 43 Wolff H, Vehmas T, Oksa P *et al.* Asbestos, asbestosis, and cancer, the helsinki criteria for diagnosis and attribution 2014: Recommendations. *Scandinavian journal of work, environment & health* 2015;**41**:5–15. doi:10.5271/sjweh.3462
- 44 Hammar SP, Abraham JL. Commentary on pathologic diagnosis of asbestosis and critique of the 2010 asbestosis committee of the college of american pathologists (cap) and pulmonary pathology society’s (pps) update on the diagnostic criteria for pathologic asbestosis. *American journal of industrial medicine* 2015;**58**:1034–9. doi:10.1002/ajim.22512
- 45 Baur X, Frank AL, Budnik LT *et al.* Collegium ramazzini: Comments on the 2014 helsinki consensus report on asbestos. *American journal of industrial medicine* 2016;**59**:591–4. doi:10.1002/ajim.22595
- 46 Baur X, Weitowitz H-J, Budnik LT *et al.* Asbestos, asbestosis, and cancer: The helsinki criteria for diagnosis and attribution. critical need for revision of the 2014 update. *American journal of industrial medicine* 2017;**60**:411–21. doi:10.1002/ajim.22709
- 47 Gilham C, Rake C, Hodgson J *et al.* Past and current asbestos exposure and future mesothelioma risks in britain: The inhaled particles study (tips). *International Journal of Epidemiology* 2018.
- 48 Burns DK, Beaumont PL. The hse national exposure database–(NEDB). *The Annals of occupational hygiene* 1989;**33**:1–14.
- 49 Orlowski E, Audignon-Durand S, Goldberg M *et al.* EV@LUTIL: An open access database on occupational exposures to asbestos and man-made mineral fibres. *American journal of industrial medicine* 2015;**58**:1059–74. doi:10.1002/ajim.22498
- 50 Peto J. Problems in dose response and risk assessment: The example of asbestos. In:

Epidemiology and quantitation of environmental risk in humans from radiation and other agents. Springer 1985. 175–85.

51 Blake CL, Dotson GS, Harbison RD. Assessment of airborne asbestos exposure during the servicing and handling of automobile asbestos-containing gaskets. *Regulatory toxicology and pharmacology : RTP* 2006;**45**:214–22. doi:10.1016/j.yrtph.2006.04.007

52 Williams PRD, Phelka AD, Paustenbach DJ. A review of historical exposures to asbestos among skilled craftsmen (1940-2006). *Journal of toxicology and environmental health Part B, Critical reviews* 2007;**10**:319–77. doi:10.1080/10937400601034191

53 Sahmel J, Devlin K, Paustenbach D *et al*. The role of exposure reconstruction in occupational human health risk assessment: Current methods and a recommended framework. *Critical reviews in toxicology* 2010;**40**:799–843. doi:10.3109/10408444.2010.501052

54 Chung DA, Yang RR, Verma DK *et al*. Retrospective exposure assessment for occupational disease of an individual worker using an exposure database and trend analysis. *Journal of occupational and environmental hygiene* 2015;**12**:855–65. doi:10.1080/15459624.2015.1072630

55 Rasmuson JO, Roggli VL, Boelter FW *et al*. Cumulative retrospective exposure assessment (rea) as a predictor of amphibole asbestos lung burden: Validation procedures and results for industrial hygiene and pathology estimates. *Inhalation toxicology* 2014;**26**:1–13.

56 Cherrie JW, McElvenny D, Blyth KG. Estimating past inhalation exposure to asbestos: A tool for risk attribution and disease screening. *International journal of hygiene and environmental health* 2018;**221**:27–32. doi:10.1016/j.ijheh.2017.09.013

57 Oyen SC van, Peters S, Alfonso H *et al*. Development of a job-exposure matrix (asbjem) to estimate occupational exposure to asbestos in australia. *The Annals of occupational hygiene* 2015;**59**:737–48. doi:10.1093/annhyg/mev017

58 Peters S, Vermeulen R, Portengen L *et al*. SYN-jem: A quantitative job-exposure matrix for five lung carcinogens. *The Annals of occupational hygiene* 2016;**60**:795–811. doi:10.1093/annhyg/mew034

59 Ahrens W, Jöckel KH, Brochard P *et al*. Retrospective assessment of asbestos exposure—I. case-control analysis in a study of lung cancer: Efficiency of job-specific questionnaires and job exposure matrices. *International journal of epidemiology* 1993;**22 Suppl 2**:S83–95.

60 Orlowski E, Pohlabeln H, Berrino F *et al*. Retrospective assessment of asbestos exposure—II. at the job level: Complementarity of job-specific questionnaire and job exposure matrices. *International journal of epidemiology* 1993;**22 Suppl 2**:S96–105.

61 Gramond C, Rolland P, Lacourt A *et al*. Choice of rating method for assessing occu-

- pational asbestos exposure: Study for compensation purposes in france. *Am J Ind Med* 2012;**55**:440–9. doi:10.1002/ajim.22008
- 62 Burstyn I. The ghost of methods past: Exposure assessment versus job-exposure matrix studies. *Occup Environ Med* 2011;**68**:2–3. doi:10.1136/oem.2009.054585
- 63 Burdorf A, Heederik D. Applying quality criteria to exposure in asbestos epidemiology increases the estimated risk. *The Annals of occupational hygiene* 2011;**55**:565–8. doi:10.1093/annhyg/mer042
- 64 Teschke K, Olshan AF, Daniels JL *et al.* Occupational exposure assessment in case-control studies: Opportunities for improvement. *Occup Environ Med* 2002;**59**:575–93; discussion 594.
- 65 Seibold MA, Wise AL, Speer MC *et al.* A common muc5b promoter polymorphism and pulmonary fibrosis. *N Engl J Med* 2011;**364**:1503–12. doi:10.1056/NEJMoa1013660
- 66 Peljto AL, Zhang Y, Fingerlin TE *et al.* Association between the muc5b promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. *JAMA* 2013;**309**:2232–9.
- 67 Fingerlin TE, Murphy E, Zhang W *et al.* Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. *Nat Genet* 2013;**45**:613–20. doi:10.1038/ng.2609
- 68 Noth I, Zhang Y, Ma S-F *et al.* Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: A genome-wide association study. *Lancet Respir Med* 2013;**1**:309–17. doi:10.1016/S2213-2600(13)70045-6
- 69 Raghu. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management, author=Raghu, Ganesh and Collard, Harold R and Egan, Jim J and Martinez, Fernando J and Behr, Juergen and Brown, Kevin K and Colby, Thomas V and Cordier, Jean-François and Flaherty, Kevin R and Lasky, Joseph A and others. *Am J Respir Crit Care Med* 2011;**183**:788–824.
- 70 NICE. Idiopathic pulmonary fibrosis: The diagnosis and management of suspected idiopathic pulmonary fibrosis. 2013.<https://www.nice.org.uk/guidance/cg163>
- 71 Dupont WD, Plummer WD. Power and sample size calculations: A review and computer program. *Control Clin Trials* 1990;**11**:116–28.
- 72 Agresti A. Building and applying logistic regression models. *Categorical Data Analysis, Second Edition* 2007;211–66.
- 73 Cariaso M, Lennon G. SNPedia: A wiki supporting personal genome annotation, in-

terpretation and analysis. *Nucleic Acids Res* 2012;**40**:D1308–12. doi:10.1093/nar/gkr798

74 Gauderman WJ. Sample size requirements for association studies of gene-gene interaction. *Am J Epidemiol* 2002;**155**:478–84.

75 Morell F, Villar A, Montero M-Á *et al.* Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: A prospective case-cohort study. *Lancet Respir Med* 2013;**1**:685–94. doi:10.1016/S2213-2600(13)70191-7