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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January 2018

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).

Acknowledgements

I am grateful to Zeinab, Ada, and Rosa for putting up with me.

I am grateful to Paul, Chris, and Sara for their supervision.

I am grateful to the partcipants, to Rupa and all of the principle investigators and their teams for making the study happen.

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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 underecognised 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 aetiopathophysiology 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?

1.3 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 suceptibility 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)

1.4 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 suceptibility 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 2

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

2.1 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 hygeine 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.

2.2   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 a relevant papers was 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.

2.3   Results

We found (as of May 2017) 15 case-control studies looking at occupational exposures in IPF 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] [32] [33] [34]

40 risk estimates from 12 publications (1326 IPF cases in total) were used (Table 3.1)[20] [22] [23] [24] [25] [26] [27] [29] [30] [31] [32] [34]

Three studies were not used, one because data was not collected on the proportion of cases with specific occupational exposures[21], one because of methodological differences in exposure assignment[28], and one because if reported data for pulmonary fibrosis rather than IPF.[33]

Each exposure category was assessed with 6-11 risk estimates (Table 3.2).

Table 2.1: Summary of IPF case-control studies investigating occupational exposures

Reference (n cases)	OR; 95% CI					PAF %				
	vgdf*	metal	wood	ag	si	vgdf*	metal	wood	ag	si
Scott 1990(40)[?]	1.3; 0.8, 2.0	11.0; 2.3, 52.4	2.9; 0.9, 9.9	10.9; 1.2, 96.0	1.6; 0.5, 4.8	17	12	10	12	5
Hubbard 1996(218)[?]		1.7; 1.1, 2.7	1.7; 1.0, 2.9				10	6		
Mullen 1998(15)[?]	2.4; 0.7, 8.4		3.3; 0.4, 25.8		11; 1.1, 115	20		7		20
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	2
Hubbard 2000(22)[?]		1.1; 0.4, 2.7					5			
Miyake 2005(102)[?]	5.6; 2.1, 17.9	9.6; 1.7, 181.1	6.0; 0.3, 112.4	0.6; 0.2, 1.9	1.8; 0.5, 7.0	26	11	4	0	
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	0	3		3
Garcia-Sancho Figueroa 2010(97)[?]	1.2; 0.8, 1.9					9				
Garcia-Sancho 2011(100)[?]	2.8; 1.5, 5.5					50				
Awadalla 2012 men (95)[?]		1.6; 0.7, 3.6	2.7; 1.1, 6.8	1.0; 0.4, 2.3	1.1; 0.5, 2.7		6	9	0	1
Awadalla 2012 women (106)[?]			4.3; 0.8, 22.1	3.3; 1.2, 10.1				6	14	
Paolocci 2013 soft wood (abstract only)(65)[?]		2.8; 1.1, 7.2	1.1; 0.4, 3.3		2.0; 0.9, 4.4		9	0		11
Paolocci 2013 hard wood (abstract only)(n/a)[?]			0.9; 0.3, 2.8	8				0		
Koo	2.7;	5.0;	2.5;		1.2;	35	22	5		5

Chapter 3

Discussion

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 remidiation and prevention.

Associations between IPF and wood, metal, and agricultural dust were previouly 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 assymetry 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] [35] [24] [27] [30] 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 commumnity controls. [36] This approach is vulnerable to non-responder bias. One study[25] 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 occupational 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][25], a group who are frequently exposed to dust containing asbestos fibres[37] and who in a recent UK study, had the highest risk of mesothelioma.[38]

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][28][27][25] to identify cases and one study[27] used a national register of patients recieving oxygen therapy. Differences in healthcare coverage and coding practices can result in selection bias.[39]

3.1 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 preven-

tion.

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.
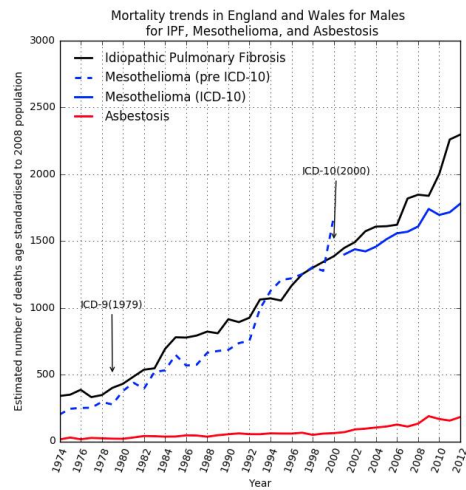
Figure 4.1: IPF, mesothelioma, and asbestosis mortality trends
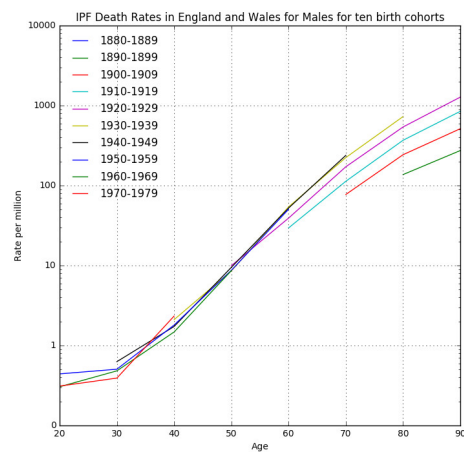
Figure 4.2: IPF male birth cohorts

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Chapter 5

Historic 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; they 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 biopersistance of asbestos fibres is variable, counts are sensitive to techniques used, and establishing

appropriate references ranges is challenging.[40]

Expert assessment and exposure modelling approaches 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.[41]

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.

Finally, self-reported exposures are a subjects direct report of what they have been exposed to, these are usually elicited by questionnaire or at interview.

The asbestos exposure assessment literature presents difficulties for review because it is large and recognised to be at risk of bias as a result of its economic importance to powerful industrial and medicolegal actors[42].

Here we critically review different means of historic 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". When a relevant papers was identified, papers referenced, and papers citing, the paper were reviewed.

5.3   Results

5.3.1   Lung biopsy and bronchoalveolar lavage

The first report of fibrosis of the lung due to asbestos dust[43] 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.[40]

Despite this recent 2014 Helsinki guidelines[44] and UK Royal College of Pathologists 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 the diagnosis. The shortcomings of such an approach highlighted above are also described by responses to the Helsinki guideline.[45][**???**][46][47]

Lung biopsy carries significant health risks, particularly for patients who already have compromised lung function and it can not be justified solely on medico-legal grounds.[46] 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.[38][48] 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.[49]

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 broncheoalvelolar lavage sampling for asbestos fibre quantification.[50]

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[51], and EV@LUTIL[52], in the published literature, and in unpublished company records.

The use of different means of making workplace assessments results in difficulties with respect to the accuracy and comparability of measurements. For example, instruments that count particles rather than asbestos fibres have been used and there is no established conversion factor.[53] Phase contrast microscopy has also been used which is less sensitive that scanning electron microscopy, which is in turn less sensitive than transmission electron microscopy and energy-dispersive x-ray analysis.[54]

Where era and task specific workplace exposure data matching a particular patient occupational history is available and readily deniable it is a valuable means of assessing exposure history. Unfortunately, in practice measurements are usually limited to the subset of jobs thought to be potentially harmful "high" exposure jobs at the time of measurement. As awareness of the sources and harm of asbestos exposure has developed overtime the available data, until the use of asbestos was banned in the UK, is also skewed to more recent times.[55][56]

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[57] or skilled craftsmen.[58]

5.3.3 Exposure reconstruction

Sahmel et al[56] 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.[56]

5.3.3.1 Job-exposure matrices

Several job-exposure matrices that deal with asbestos have been reported. Pannett et al's 1985 job-exposure matrix for use in population studies in England and Wales[59] found good agreement between job-title assigned categories of exposure (none, low, moderate, high) for asbestos and direct review of the original occupational history by an expert.

Rake et al[38] assigned categories risk of exposure (low, medium, high) 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. This approach has been validated in the same cohort by amphibole fibre counts.[48]

DOM-JEM[60] was developed for use in population based multi-centre lung

Step 1: Establishing the Goals of the Exposure Reconstruction

Step 2: Organizing and Ranking Available Exposure Information

Step 3: Identifying Key Data Gaps in the Available Exposure Information

Step 4: Selecting the Best Approach to Reconstructing Exposures

Step 5: Incorporating Probabilistic Methods into the Reconstruction Process

Step 6: Conducting an Uncertainty Analysis for the Results of the Reconstruction

Step 7: Validating the Reconstructed Estimates of Exposure

Figure 5.1: Seven step framework for exposure reconstruction

cancer case-control study. It assigns job titles one of three categories of asbestos exposure (no exposure, low exposure, high exposure) based on the consensus of three independent expert raters. DOM-JEM showed poor agreement with expert assessment ($\kappa = 0.17$) but less heterogeneity. In a study applying DOM-JEM to the Netherlands Cohort Study (NCS) DOM-JEM showed poor agreement with expert assessment (K = 0.29).[61]

The Finish Information System on Occupational Exposure (FINJEM)[62] covers exposure to 84 different agents, including asbestos, for 311 jobs across 9 periods spanning 1945-2015. Era-specific estimates of the mean level of asbestos exposure are available for 27 jobs based on expert assessment and measurement data; the exact details of the grounds for estimates are kept in a proprietary FINJEM database which is not freely available. FINJEM showed poor agreement with expert assessment of asbestos exposure ($\kappa = 0.23$) but reasonable identification of mesothelioma risk when evaluated using the NCS.[61][63]

AsbJEM[64] was developed in Australia by an expert panel of three industrial hygienists using all available exposure data. It is based on FINJEM and provides quantitative estimates of annual exposure for 224 occupations across three time periods spanning 1943 to 2004. It also showed poor agreement with expert assessment of asbestos exposure ($\kappa = 0.10$)

SYN-JEM[65] describes a JEM developed for four carcinogens. It provides quantified asbestos exposure estimates based on 27958 personal measurements (spanning 1971-2009), a mixed effects statistical model, and a priori categorical assessment of exposure (none, low, high). Cherrie et al[66] point out that SYN-JEM provides little contrast in the modelled exposure level between categories as the geometric mean for low jobs was 0.061 fibres/ml and for high jobs 0.074 fibres/ml and that there are wide variations in regional estimates that are difficult to explain.

JEMS are generally taken to be superior to direct questions about exposures because they are cheaper, have greater validity, and are less vulnerable to differential recall. This is because recall of occupations is not influenced by disease status, coding of occupation is blind to case-control status, and translation of codes into exposure is standardized and can not be influence

by disease status of a subject.[67][68][69]

Orlowski et al[70] compared two JEMs with a structured job specific questionnaire (SQ) in a lung cancer case-control study. They found that agreement between the JEMs and the SQ was poor ($\kappa = 0.23 - 0.27$) and suggested that the sources of error for JEMs were loss of information due to the use of job codes as surrogates for job task descriptions and the insufficiency of published data on occupational asbestos exposure.

JEMs are not routinely used in clinical practice because they are not usually available or accessible for specific patients. In a research setting they are frequently helpful though in addition to the strengths and weaknesses outlined about the desirability of reusing an existing JEM vs developing a study specific JEM must be considered.

5.3.3.2 Exposure modelling approaches

Exposure modelling approaches modify existing measurement data on the basis of knowledge of the determinants of exposure. They may be viewed as the formalization of professional decision criteria used by hygienists in their assessment of workplace exposures.[55]

A common conceptual framework for this is the source-receptor model source receptor model[71][55] whereby inhalation exposure is considered in terms of an exposure source, a pathway from source to receptor, and the receptor. The model is then used to propose modifying factors such as activity emission potential, substance emission potential, localized control, worker behavior, surface contamination and respiratory protection.[71].

In the hands of some hygienists assessment of historic asbestos exposure based on interview can correlate well with amphibole fibre counts.[72] By extension, exposure modelling approaches, using industrial hygienist methods, might be expected to be useful. Exposure modelling approaches make strong intuitive sense; it is known that there is significant within-worker and between-worker variability in occupational exposures[73] and, for example, room size and ventilation have been empirically shown to affect the concen-

tration of airborne chemical exposures.[74] Further, mathematical exposure models that take account of known exposure modifying factors to estimate past exposures have shown a good correlation with measured values.[41]

A quantified validated historic asbestos exposure model[66] has recently been developed and proposed as a means of for risk stratifying asbestos exposed workers to optimize mesothelioma screening efforts. The approach has the advantage, compared with job-exposure matrices, of providing a more granular quantified exposure assessment, sensitive to the exposure circumstances of the individual. However, the approach is limited by the fact that the individual must recall that they must recall their exposure circumstances which due to the latency of asbestos related disease may have occurred over 30 years ago. The approach is also limited by the relatively small number of industry-specific data points used for validation, though is unavoidable because of the scarcity of exposure measurement data.

Exposure modelling approaches to assessing asbestos exposure have research and clinical utility notwithstanding the limitations outlined above together with the requirement that assessors be appropriately trained.

5.3.3.3 Self-reported exposure

Self-reported exposures are a subjects direct report of what they have been exposed to. Typically this is elicited by asking about a specific exposure via questionnaire or interview. Differential recall of self-reported exposures according to disease status is a concern but few studies have found evidence of this and it appears to be less of an issue when prompted responses, rather than volunteered, responses about occupational exposures are used.[75]

Most studies comparing self-reported exposures to industrial hygiene measurements have found significant associations but with wide variation in the proportions of variance explained by the self reports. This is not surprising given that it is known there is significant within-worker and between-worker variability in occupational exposures.[68][73]

Studies comparing self-reported exposures to expert assessment find highly

variable levels of agreement ($\kappa - 0.05 - 0.94$) with a median $\kappa 0.6$. In two studies comparing self-reported exposures with JEMs, self-reported exposures were more sensitive and of similar or worse specificity.[68]

Self-reported exposures have been shown to be more accurate for easily sensed exposures such as solvents with a strong smell, dusts with larger particle sizes, and vibrations that can be felt. Providing a reference point, for example using well known machines from a workplace to gauge noise category also improves accuracy.[68]

Self-reported exposures have clinical utility in that they can suggest or support consideration of an occupational cause for disease. Ideally such self-reports are combined with the clinicians knowledge of the likely occupational exposures given the occupational history and other available data to strengthen or weaken the case as appropriate. Similarly, they have utility in a research setting where they may augment other means of assessment.

5.4 Discussion

The accuracy of historic asbestos exposure assessment, by any means, is limited by the paucity of occupational asbestos measurement data, measurement technique limitations, within and between worker exposure variability, and participant recall. There does not exist a universally agreed "gold standard" against which to evaluate methods. Accurate quantified assessment of historic exposure, where evidence is scarce, may be an impossible task.[76]

Nonetheless, clinically, historic asbestos exposure assessments must be made for attribution. Specifically, to inform whether the required threshold of asbestos exposure (as assessed by various means) has been crossed so it is possible to say that, for example, scarring of the lung with an usual interstital pneumonia pattern in an individual patient is caused by asbestos exposure. This carries medicolegal in addition to scientific importance and has not been well established by any assessment method.

In the context of mesothelioma case-control studies fibre-counts do at least provide an objective means of assessing historic asbestos exposure against

which other means can be compared. It is encouraging that industrial hygienist assessment and assessment using job title and PMR correlates strongly with fibre counts.[69][48] Further and more generally, it is encouraging that estimates from explicit asbestos exposure modelling systems such as Cherrie et al's[66], show good correlation with measurement data.

5.5   Conclusion

Quantitative estimates of historic occupational asbestos exposures will generally have high uncertainty. However, less precise measures, such as relative difference in exposure among epidemiological groups may be quite certain even though the numerical estimates are only approximate. This is invaluable in studies examining aetiological hypothesis.[55]

Chapter 6

Genetic susceptibility in IPF and MUC5b: MUC5b + enivornmental 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.[77] The polymorphism results in excess MUC5B protein in the airway, impaired clearance of inhaled substances and a chronic inflammatory burden on the alveolar surface.[77] The association is allele dose-dependent, has been replicated in independent cohorts, and appears to confer improved survival.[3][77][78] Two large GWASs have confirmed the observed associations of IPF with MUC5B and other loci.[79][80]

6.2 Method

6.2.1 DNA Extraction

We extracted DNA from collected 10ml EDTA blood samples using a GE
Healthcare Nucleon BACC3 Genomic DNA Extraction Kit (see appendix 2
for IPFJES DNA Extraction Protocol).
(add detail on principles)

6.2.2 Genotyping

We used a QuantStudio TM 7 Flex Real-Time PCR system with a TaqMan
SNP genotyping assay for MUC5b rs35705950 to genotype samples (see ap-
pendix 2 for IPFJES Genotyping Protocol). (add detail on principles)

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 in-
terdum. 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-regcognised 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[81]; they will be identified monthly by the MDT coordinator of participating centres.[82]

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[38] 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 $\alpha = 0.05$[83]; my planned sample size sample size includes a margin for model stability and incomplete data.[84]

Secondary (exploratory) analysis will investigate gene-environment interaction. The global minor allele frequency of MUC5B rs35705950 is 0.05.[85] With an estimated prevalence of IPF of 20/100000[1] and with ORs 2.0 for asbestos exposure and 6.8 for rs35705950[77], 113 cases would be required to detect a minimum interaction OR of 4.0.[86] 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 [87]

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 male-
suada 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

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