

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

Carl Jonathan Reynolds

A thesis presented for the degree of
Doctor of Philosophy

Supervised by:
Professor Paul Cullinan
Dr Chris Barber

Imperial College London, UK
January 2018

Except where otherwise noted, content in this thesis is licensed under a
Creative Commons Attribution 4.0 License
(<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted
use, distribution, and reproduction in any medium, provided the original
work is properly cited. Copyright 2018, Carl Reynolds.

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 participants, to Rupa and all of the principle investigators and their teams for making the study happen.

Table of Contents

Abstract	i
Acknowledgements	ii
List of figures	iii
List of tables	iv
Abbreviations	v
1 Introduction to thesis	1
1.1 Occupational asbestos exposure as an underrecognised cause of idiopathic pulmonary fibrosis	1
1.2 Aims and objectives	2
1.3 Data sources	2
1.4 Outline of thesis	3
2 Literature review and meta-analysis	4
2.1 Introduction	4
2.2 Method	5
2.3 Results	6
2.4 Conclusion	6
3 Mortality analysis	8
3.1 Introduction	8
3.2 Method	9
3.3 Results	9
3.4 Discussion	10
3.5 Conclusion	10

4	Asbestos exposure assessment	12
4.1	Introduction	12
4.2	Method	13
4.3	Results	13
4.4	Discussion	13
4.5	Conclusion	13
5	Genetic susceptibility in IPF	14
5.1	Introduction	14
5.2	Method	14
5.3	Results	15
5.4	Discussion	15
5.5	Conclusion	15
6	Idiopathic pulmonary fibrosis job exposures study (IPFJES)	16
6.1	Introduction	16
6.2	Method	17
6.3	Results	18
6.4	Discussion	18
6.5	Conclusion	18
7	Conclusion	19
7.1	Thesis summary	19
7.2	Future work	19
	Appendix 1: Some extra stuff	20
	Appendix 2: Some more extra stuff	21
	References	22

List of figures

Figure 4.1 This is an example figure . . .	pp
Figure x.x Short title of the figure . . .	pp

List of tables

Table 5.1 This is an example table . . .	pp
Table x.x Short title of the figure . . .	pp

Abbreviations

jam

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?

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 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.

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 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 2

Literature review and meta-analysis

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]

There are many review articles of the epidemiology of interstitial lung disease that do not necessarily focus on IPF and only briefly mention occupational factors. We selected review articles that specifically deal with occupational factors in IPF and cite the case-control studies and case-reports identified.

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.[13]

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.[14]

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%).[15]

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.[16]

2.2 Method

Background: Optimal strategies to extract relevant content from Pubmed for occupational lung disease topics are not clearly defined and the utility of mining techniques has not been assessed. Aims and objectives: To evaluate, given a ‘seed’ of known relevant papers (here 12 occupational IPF case-control studies), the use of relative citation ratio (RCR)[1], jaccard similarity(JS)[2] and coverage(C) to identify additional relevant papers. Methods: We used the python programming language and the Pubmed application programming interface to extract all papers citing the ‘seed’ papers and to calculate and sort by RCR, JS, and C. Full analysis online.[3] Results: Papers citing ‘seed’ papers sorted by RCR, JS, and C. Table 1 and Figure 1. Conclusions: Pubmed mining techniques can help to identify additional relevant papers.

2.3 Results

We found (as of May 2017) 14 case-control studies looking at occupational exposures in IPF (Table \ref{metatable1}); the most recent review article covers only eight of them. Associations with metal, wood, silica, and agricultural dust were reported. [17][18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28]

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.

In all, 43 risk estimates from 14 publications (2027 IPF cases in total) were used. Each exposure category was assessed with 6-11 risk estimates. Pooled OR s were significantly elevated for each category; the pooled PAF estimates by category ranged from 4-14% (Table \ref{metatable2}). We found funnel plot asymmetry using Egger’s test, which may be due to publication bias, for VGDF ($p = 0.04$) and metal dust ($p = 0.04$) but not for wood dust ($p = 0.1$), 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. ## Discussion

2.4 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 14% of the burden of disease and highlighting a role for workplace exposure reduction in disease prevention.

Chapter 3

Mortality analysis

3.1 Introduction

Mortality from Idiopathic Pulmonary Fibrosis in England and Wales by birth cohort

Introduction and objectives: 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. This would be expected to produce a cohort effect. Our aim was to examine trends in IPF mortality data for evidence of such an effect.

The recent publication of the INPULSIS1, INPULSIS2, and ASCEND trials mean that meaningful treatment for patients with IPF beyond palliation or lung transplantation is an emergent possibility. But for a history of asbestos exposure, IPF and Asbestosis may produce a clinically identical picture with progressive breathlessness and a Usual

Interstitial Pneumonia on CT or histopathologic examination. A history of asbestos exposure may be easily missed and several authors have hypothesised that a proportion of IPF may be due to occult asbestos exposure. New

antifibrotic treatments for IPF throw the question of whether or not a proportion of IPF is due to occult asbestos exposure into sharp focus; patients known to have Asbestos Exposure are currently not considered to be candidates for antifibrotic treatments and it may be timely to revisit this. These data show national and regional correlations, and marked sex differences, which are supportive of the hypothesis that a proportion of IPF is due to Occult Asbestos Exposure and provide motivation for further studies in this area.

Background: It is hypothesised that a proportion of Idiopathic Pulmonary Fibrosis (IPF) cases are due to occult environmental or occupational exposures to asbestos dust. Aims and objectives: To investigate a possible association between IPF, Mesothelioma, and Asbestosis mortality consistent with asbestos exposure. To visualise agestandardised annual mortality trends for IPF, Mesothelioma, and Asbestosis for men and women.

3.2 Method

Methods: Age and sex stratified mortality data for IPF 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.

We present new data obtained from the Office of National Statistics for England and Wales on the annual number of deaths due to IPF, Mesothelioma, and Asbestos for the period 1974–2012 broken down by age, sex, and region.

3.3 Results

Results: There is evidence of a cohort effect with age-specific IPF death rates increasing in successive cohorts, most clearly seen from age 60. Overall rates were higher for men but there were not marked sex differences in cohort mortality trends (data not shown).

Results: IPF mortality continues to rise. Female:Male is approximately 1:1.6.

Figure 3.1 shows a figure.

Figure 3.2 shows a figure.

3.4 Discussion

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.

3.5 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.

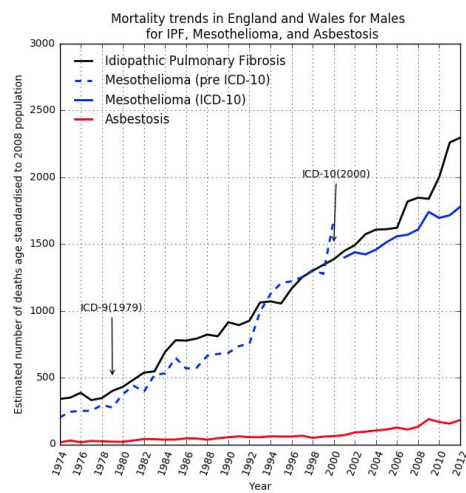


Figure 3.1: IPF, mesothelioma, and asbestosis mortality trends

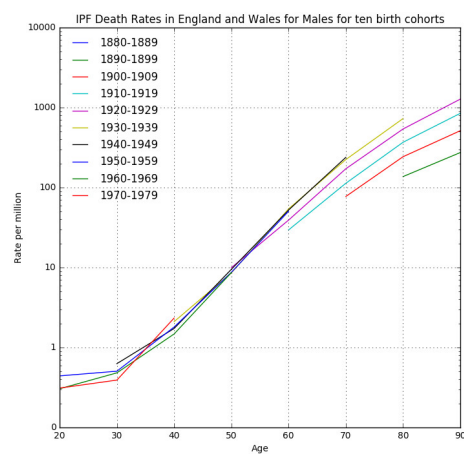


Figure 3.2: IPF male birth cohorts

Chapter 4

Asbestos exposure assessment

4.1 Introduction

In addition to its epidemiological and clinical plausibility there are several additional reasons why study of this area is needed. First, most previous work relied on self-reported workplace exposure information, an approach that is open to recall bias and deals poorly with confounding; for example, studies have described strong associations between metal work and IPF and specify sheet metal workers[18][17][29], a group who are frequently exposed to dust containing asbestos fibres[30] and who in a recent UK study, had the highest risk of mesothelioma.[31] Lifetime occupational histories are more accurately recalled than self-reported workplace exposures and can be combined with measures such as proportionate mortality (PMR) estimates and job-process assessments to minimize recall bias and more accurately characterise cumulative exposures. [32][33][34][31] This allows too the examination of ‘exposure-response’ relationships, entirely lacking in the published literature.

4.2 Method

Donec imperdiet, lectus vestibulum sagittis tempus, turpis dolor euismod justo, vel tempus neque libero sit amet tortor. Nam cursus commodo tincidunt.

4.3 Results

These are the results. In vitae odio at libero elementum fermentum vel iaculis enim. Nullam finibus sapien in congue condimentum. Curabitur et ligula et ipsum mollis fringilla.

4.4 Discussion

4.5 Conclusion

This is the conclusion to the chapter. Quisque nec purus a quam consectetur volutpat. Cum sociis natoque penatibus et magnis dis parturient montes, nascetur ridiculus mus. In lorem justo, convallis quis lacinia eget, laoreet eu metus. Fusce blandit tellus tellus. Curabitur nec cursus odio. Quisque tristique eros nulla, vitae finibus lorem aliquam quis. Interdum et malesuada fames ac ante ipsum primis in faucibus.

Chapter 5

Genetic susceptibility in IPF

5.1 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.[35] The polymorphism results in excess MUC5B protein in the airway, impaired clearance of inhaled substances and a chronic inflammatory burden on the alveolar surface.[35] The association is allele dose-dependent, has been replicated in independent cohorts, and appears to confer improved survival.[3][35][36] Two large GWASs have confirmed the observed associations of IPF with MUC5B and other loci.[37][38]

5.2 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

5.3 Results

5.4 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.

5.5 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 6

Idiopathic pulmonary fibrosis job exposures study (IPFJES)

6.1 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[39]; they will be identified monthly by the MDT coordinator of participating centres.[40]

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[31] 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 $\alpha = 0.05$ [41]; my planned sample size sample size includes a margin for model stability and incomplete data.[42]

Secondary (exploratory) analysis will investigate gene-environment interaction. The global minor allele frequency of MUC5B rs35705950 is 0.05.[43] With an estimated prevalence of IPF of 20/100000[1] and with ORs 2.0 for asbestos exposure and 6.8 for rs35705950[35], 113 cases would be required to detect a minimum interaction OR of 4.0.[44] 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.

6.2 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.

6.3 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.

6.4 Discussion

This is the discussion. Curabitur gravida nisl id gravida congue. Duis est nisi, sagittis eget accumsan ullamcorper, semper quis turpis. Mauris ultricies diam metus, sollicitudin ultricies turpis lobortis vitae. Ut egestas vehicula enim, porta molestie neque consectetur placerat. Integer iaculis sapien dolor, non porta nibh condimentum ut.

6.5 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 7

Conclusion

7.1 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.

7.2 Future work

There are several potential directions for extending this thesis. Lorem ipsum dolor sit amet, consectetur adipiscing elit. Aliquam gravida ipsum at tempor tincidunt. Aliquam ligula nisl, blandit et dui eu, eleifend tempus nibh. Nullam eleifend sapien eget ante hendrerit commodo. Pellentesque pharetra erat sit amet dapibus scelerisque.

Vestibulum suscipit tellus risus, faucibus vulputate orci lobortis eget. Nunc varius sem nisi. Nunc tempor magna sapien, euismod blandit elit pharetra sed. In dapibus magna convallis lectus sodales, a consequat sem euismod. Curabitur in interdum purus. Integer ultrices laoreet aliquet. Nulla vel dapibus urna. Nunc efficitur erat ac nisi auctor sodales.

Appendix 1: Some extra stuff

Add appendix 1 here. Vivamus hendrerit rhoncus interdum. Sed ullamcorper et augue at porta. Suspendisse facilisis imperdiet urna, eu pellentesque purus suscipit in. Integer dignissim mattis ex aliquam blandit. Curabitur lobortis quam varius turpis ultrices egestas.

Appendix 2: Some more extra stuff

Add appendix 2 here. Aliquam rhoncus mauris ac neque imperdiet, in mattis eros aliquam. Etiam sed massa et risus posuere rutrum vel et mauris. Integer id mauris sed arcu venenatis finibus. Etiam nec hendrerit purus, sed cursus nunc. Pellentesque ac luctus magna. Aenean non posuere enim, nec hendrerit lacus. Etiam lacinia facilisis tempor. Aenean dictum nunc id felis rhoncus aliquam.

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 Turner-Warwick M. In search of a cause of cryptogenic fibrosing alveolitis (cfa): One initiating factor or many? *Thorax* 1998;**53**:S3–9.

14 Hubbard R. Occupational dust exposure and the aetiology of cryptogenic fibrosing alveolitis. *Eur Respir J* 2001;**18**:119s–21s.

15 Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? *Proc Am Thorac Soc* 2006;**3**:293–8.

16 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

17 Scott J, Johnston I, Britton J. What causes cryptogenic fibrosing alveolitis? A case-control study of environmental exposure to dust. *BMJ* 1990;**301**:1015.

18 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

19 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.

20 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.

21 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.

22 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.

23 Gustafson T, Dahlman-Höglund A, Nilsson K *et al.* Occupational exposure and severe pulmonary fibrosis. *Respir Med* 2007;**101**:2207–12.

24 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.

25 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

26 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.

27 Paolocci G, Nicolic V, Folletti I *et al.* Risk factors for idiopathic pulmonary fibrosis in southern europe: A case-control study. 2013.

28 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

29 Hubbard R, Cooper M, Antoniak M *et al.* Risk of cryptogenic fibrosing alveolitis in metal workers. *The Lancet* 2000;**355**:466–7.

30 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.

31 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

32 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.

33 Bourgkard E, Wild P, Gonzalez M *et al.* Comparison of exposure assessment methods in a lung cancer case-control study: Performance of a lifelong task-based questionnaire for asbestos and pahs. *Occup Environ Med* 2013;**70**:884–91. doi:10.1136/oemed-2013-101467

34 Cherrie JW, Schneider T. Validation of a new method for structured subjective assessment of past concentrations. *Ann Occup Hyg* 1999;**43**:235–45.

35 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

36 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.

37 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

38 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

39 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.

40 NICE. Idiopathic pulmonary fibrosis: The diagnosis and management of suspected idiopathic pulmonary fibrosis. 2013.<https://www.nice.org.uk/guidance/cg163>

41 Dupont WD, Plummer WD. Power and sample size calculations: A review and computer program. *Control Clin Trials* 1990;**11**:116–28.

42 Agresti A. Building and applying logistic regression models. *Categorical Data Analysis, Second Edition* 2007;211–66.

43 Cariaso M, Lennon G. SNPedia: A wiki supporting personal genome annotation, interpretation and analysis. *Nucleic Acids Res* 2012;**40**:D1308–12. doi:10.1093/nar/gkr798

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