

IPF JES


Idiopathic Pulmonary Fibrosis Job Exposures Study

A case-control study to investigate whether occupational asbestos exposure is an under-recognized cause of idiopathic pulmonary fibrosis (IPF) using an interview to measure previous asbestos exposure and a blood test to investigate genetic susceptibility.

**Version 0.4
May 2, 2017**

MAIN SPONSOR: Imperial College London
FUNDERS: Wellcome Trust (201291/Z/16/Z)
STUDY COORDINATION CENTRE: Imperial College London
IRAS reference: 203355

Protocol authorised by:

Name & Role	Date	Signature
Carl Reynolds, Chief Investigator	May 2, 2017	

Study management group

Chief Investigator: Carl Reynolds

Co-investigators: Paul Cullinan, Chris Barber, Sara De Matteis

Statistical Supervisor: Cosetta Minelli

Statistician: Carl Reynolds

Study Management: Paul Cullinan, Chris Barber, Sara De Matteis, Carl Reynolds

Study Coordination Centre

For general queries, supply of study documentation, and collection of data, please contact:

Dr Carl Reynolds

carl.reynolds@imperial.ac.uk

07737 904 807

National Heart and Lung Institute

Room G39 Emmanuel Kaye Building

1b Mansrea Road, London, SW3 6LR

Clinical Queries

Clinical queries should be directed to Dr Carl Reynolds who will direct the query to the appropriate person.

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office

Imperial College London & Imperial College Healthcare NHS Trust

2nd Floor Medical School Building

St Marys Hospital Praed Street London W2 1NY

Tel: 020759 41862

Funder

Wellcome Trust (Ref 201291/Z/16/Z)

This protocol describes the Idiopathic Pulmonary Fibrosis Job Exposures Study (IPF JES) and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator. This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Contents

Study Summary	6
1 Introduction	7
1.1 Background	7
2 Study objectives	8
3 Study design	8
3.1 Study outcome measures	8
4 Participant entry	9
4.1 Pre-registration evaluations	9
4.2 Sampling	9
4.3 Inclusion criteria	9
4.4 Exclusion criteria	9
4.5 Withdrawal criteria	9
5 Adverse events	10
5.1 Definitions	10
5.2 Reporting Procedures	10
5.2.1 Non serious AEs	10
6 Assessment and follow up	11
7 Statistics and data analysis	11
8 Regulatory issues	11
8.1 Ethics approval	11
8.2 Consent	11
8.3 Confidentiality	12
8.4 Indemnity	12
8.5 Sponsor	12
8.6 Funding	12
8.7 Audits and inspections	12
9 Study management	12
10 Publication policy	12
Appendices	13
Appendix A Research outputs	13
Appendix B Supplementary figures and tables	14
Appendix C Study flow chart and Gannt chart	17
Appendix D Study Information Sheet for Health Care Professionals	20
Appendix E Participant Information Sheet	22
Appendix F Participant consent form	27

Appendix G Hospital specialist cover letter (control recruitment)	29
Appendix H GP cover letter	31
Appendix I Study standard operating procedure	33

Key words

Idiopathic pulmonary fibrosis, asbestos, case-control study

Study Summary

Title: Idiopathic Pulmonary Fibrosis Job Exposures Study (IPF JES).

Design: Hospital case-control study.

Aim: To characterize and measure asbestos exposure as an occupational determinant of IPF.

Outcome measures: 1. Association between asbestos exposure and IPF estimated using logistic regression for any vs no asbestos exposure and categories of cumulative exposure and adjusting for age and smoking status. 2. Gene-environment interaction (for MUC5B rs35705950 and asbestos exposure) odds ratio.

Population: Male patients with a new diagnosis of IPF and age-matched controls who have a new outpatient clinic appointment during the study period.

Eligibility: Meets population definition, able to give informed consent, has never worked outside of the UK.

Duration: Three years.

1 Introduction

1.1 Background

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/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 areas¹, 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-recognized 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. Details of how the proposed research will inform government policy and change working practices are provided in Appendix A.

In preparing this protocol, I examined mortality trends in England and Wales for IPF and asbestos-related diseases. UK age-standardized mortality rates from 1974 to 2012 continued to rise with marked sex and regional variations, consistent with occupational exposure being an under-recognized cause of IPF.¹² I analysed European age-standardised mortality rates for mesothelioma and IPF for 27 countries for which data was available and found a positive correlation ($r = 0.51$, $p = 0.007$). I collated 13 case-control studies of IPF and occupational dust exposure; eight reported significant associations with metal dust exposure^{13,14,15,16,17,18}, four with wood dust^{19,20,18,21} and two with stone dust.^{22,23}

Finally, I analysed the limited occupational information in a recent case-control study, designed to examine the role of thrombosis in IPF.¹ Using an approach from a large mesothelioma study based on proportional mortality ratios²⁴ I estimated the odds ratio (OR) associated with ever having had a job with probable asbestos exposure was 2.8 (95% CI: 1.42-5.75, $p = 0.001$) adding further weight to the argument that occupational asbestos exposure in IPF should be properly investigated. Supplementary figures and a table of previous case-control studies are provided in Appendix B.

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^{14,13,16}, a group who are frequently exposed to dust containing asbestos fibres²⁵ and who in a recent UK study,

had the highest risk of mesothelioma.²⁴ 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.^{26 27 28 24 29} This allows too the examination of 'exposure-response' relationships, entirely lacking in the published literature.

Second, all but two studies^{14 21} used community controls. While this is generally desirable, hospital controls are preferred in circumstances when acceptable community control participation rates cannot be achieved, case acquisition is incomplete, or recall bias is an issue. Recent participation rates for community controls in UK studies of IPF have been as low as 28%;³⁰ and a recent US series estimated that the ante-mortem diagnosis of IPF was missed in 20% of cases.³¹ Further, the use of community controls for hospital cases risks significant information mismatch on exposures. While hospital controls are less representative of the base population, their use does not prevent a study from being either scientifically valid or generalizable³² as is well demonstrated by a recent influential UK hospital case-control study which found that exposure to metal fume predisposed to infectious pneumonia.³³

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.³⁴ The polymorphism results in excess MUC5B protein in the airway, impaired clearance of inhaled substances and a chronic inflammatory burden on the alveolar surface.³⁴ The association is allele dose-dependent, has been replicated in independent cohorts, and appears to confer improved survival.^{34 35} Two large GWASs have confirmed the observed associations of IPF with MUC5B and other loci.^{36 37}

I propose a new case-control study that systematically collects lifetime occupational histories to derive exposure risk using formal asbestos exposure assessment. I will also collect IPF susceptibility genotypes to permit me, uniquely, to examine exposure-response relationships, latency periods and genotype-exposure interactions.

2 Study 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?

3 Study design

3.1 Study outcome measures

Primary outcome Association between asbestos exposure and IPF estimated using logistic regression for any vs no asbestos exposure and categories of cumulative expo-

sure and adjusting for age and smoking status.

Secondary outcome Gene-environment interaction odds ratio (for MUC5B rs35705950 and asbestos exposure)

4 Participant entry

4.1 Pre-registration evaluations

Pre-registration evaluation will include screening for eligibility using inclusion and exclusion criteria.

4.2 Sampling

Cases and controls will be frequency matched on age categories.

4.3 Inclusion criteria

- Cases
 - Male
 - New diagnosis of IPF between February 2017 and October 2019
- Controls
 - Male
 - New outpatient department attendee between February 2017 and October 2019

4.4 Exclusion criteria

- Cases
 - Unable to give informed consent
 - Ever worked outside of the UK
- Controls
 - Unable to give informed consent
 - Ever worked outside of the UK

4.5 Withdrawal criteria

Research participants will be withdrawn from the study upon their request or if for any reason they are unable to complete the study interview.

5 Adverse events

5.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- Is life-threatening refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.2.1 Non serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, relapse and death due to IPF, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Imperial College London where in the opinion of the Chief Investigator, the event was:

- related, ie resulted from the administration of any of the research procedures; and
- unexpected, ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs:

Email: carl.reynolds@imperial.ac.uk

Please send SAE forms to:

National Heart and Lung Institute
Room G39 Emmanuel Kaye Building
1b Mansrea Road, London, SW3 6LR
Tel: 07737 904 807

6 Assessment and follow up

Research participants will complete an interview and a blood test. The study will end when analysis of the last research participant is complete.

7 Statistics and data analysis

For the primary analysis 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 indicate that the probability of exposure among controls is 0.63. If the true OR for disease in exposed subjects relative to unexposed subjects is 1.5, I will need to recruit 460 case patients and 460 control patients to be able to reject the null hypothesis that this odds ratio equals 1 with $\beta = 0.2$ and $\alpha = 0.05$; my planned sample size includes a margin for model stability and incomplete data.

Secondary (exploratory) analysis will investigate gene-environment interaction. The global minor allele frequency of MUC5B rs35705950 is 0.05. With an estimated prevalence of IPF of 20/100000 and with ORs 1.5 for asbestos exposure and 6.8 for rs35705950, 460 cases would be required to detect a minimum interaction OR of 5.0.

8 Regulatory issues

8.1 Ethics approval

The Chief Investigator has obtained approval from the Research Ethics Committee via IRAS. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 Consent

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons will be respected. In these cases the participant will be withdrawn from the study and their data and samples destroyed. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 Funding

The Wellcome Trust are funding the research.

8.7 Audits and inspections

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9 Study management

The day-to-day management of the study will be co-ordinated through Dr Carl Reynolds.

10 Publication policy

All research findings will be published in accordance with the Wellcome Trust and Imperial College London open access publication policies.

Appendix A Research outputs

There will be three main outputs of the study:

1. Data from the study, including anonymised raw data, will be communicated to the wider academic community, and policy-makers, by publication and presentation at national and international respiratory and epidemiology meetings.
2. Data from the study will inform HSE and policy decisions with respect to work place dust control; we are collaborating with Andrew Darnton who works at HSE specialising in mesothelioma and other asbestos related diseases.
3. Data from the study will inform policy decisions with respect to the use of anti-fibrotic treatments in patients with asbestosis. We will establish good working relations with NICE and the NHS England Specialist Respiratory Clinical Reference Group to communicate our findings. NHS patients with IPF due to occult occupational asbestos exposure may be entitled to compensation and our work may lead to reconsideration of current restrictions on disease modifying anti-fibrotic therapies for patients with asbestosis.

An estimated 125 million people around the world work in environments in which they are exposed to asbestos, and at least 107,000 people die from occupational exposure to asbestos every year³⁸. Understanding the role of asbestos exposure in idiopathic pulmonary fibrosis is an important data point for disease prevention policy measures.

Appendix B Supplementary figures and tables



Figure 1: ONS data. Idiopathic Pulmonary Fibrosis, Mesothelioma, and Asbestosis mortality trends for England and Wales 1974-2012. A corrective factor provided by HSE has been applied to pre-ICD 10 Mesothelioma deaths (dashed line). https://github.com/drcjar/pypf/blob/master/notebooks/pypf_analysis.ipynb



Figure 2: ERS Whitebook data. Age standardised mortality rate per 100,000 for 27 European Union member countries (data not available for Greece). Pearson correlation coefficient = 0.51, $p = 0.007$. https://github.com/drcjar/pyypf/blob/master/notebooks/ERS_whitebook_ipf_meso.ipynb

Summary of case-control studies of occupational dust exposure in IPF by Carl Reynolds

Ref	Country	Cases (N)	Findings	Notes (including source of cases and controls, measure of exposure used, and response rates)
Scott 1990	UK	40	Occupational exposures to metal dust ((OR 10.97, 95%CI 2.3-52.4, p<0.001), wood dust (OR 2.94, 95%CI 0.87-9.9), p = 0.08), and stone/sand (OR 1.59, 95%CI 0.52-4.79) are associated with IPF	Community controls, questionnaire asking directly about exposures, response rate was 87% for cases and 60% for controls.
Iwai 1994	Japan	1311	The IPF rate more than doubled (p <0.01) among subjects engaged in occupations that exposed them to dust or organic solvents	Cases and controls selected from the "Annals of the Pathology Autopsy Cases in Japan" (APACJ) during a 12-yr period (1974-85). The "longest or last" job (according to Japanese Standard Job Category) was exposure measure.
Iwai 1994	Japan	86	Higher odds ratio was noted among metal production workers and miners compared with healthy and hospital control subjects (1.37 and 1.34, respectively, p < 0.01)	Hospital controls. Questionnaire asking directly about exposures.
Hubbard 1996	UK	218	Occupational exposures to metal dust (OR 1.68, 95% CI 1.07-2.65, p = 0.024), wood dust (OR 1.71, 95% CI 1.01-2.92, p = 0.048), and are associated with CFA	Community controls. 92% of eligible cases and 68% of controls returned completed questionnaires and each case had an average of 2.6 controls. Telephone interviews were completed for 76% of cases and for an average of 2.5 controls per case. Exposure response relations (odds ratio per work year of exposure) were OR 1.11, 95% CI 1.06-1.16, p = 0.001 for metal dust and OR 1.12, 95% CI 1.02-1.24 for wood dust.
Mullen 1998	USA	17	Occupational exposure to any dust (OR 2.37, 95% CI 0.67-8.44), asbestos (OR 6.77, 95% CI 0.57-90.7), and silica (OR 11, 95% CI 1.05-115) was associated with ILD	Cases and controls from community clinic, postal questionnaire. 17 of 35 cases contacted (37.7%) and 94 of 290 controls contacted (32.4%) responded to the questionnaire.
Hubbard 2000	UK	55	Direct relation between duration of exposure and the risk of CFA (OR per 10 years of exposure 1.71, 95%CI 1.09-2.68, p=0.02)	Case and controls selected from death certificates held in pension-fund records of employees working for Rolls-Royce Plc at five UK sites. Lifetime occupational data were obtained from individual employment records held by the company for each employee and, and each job was coded according to whether it involved work with meta. Occupational records were located for 40% of cases and 38% of controls.
Baumgartner 2000	USA	248	Occupational exposure to metal dust (OR = 2.0, 95% CI: 1.0, 4.0), stone cutting/polishing (OR = 3.9, 95% CI: 1.2, 12.7), stone cutting/polishing (OR = 3.9, 95% CI: 1.2, 12.7), and vegetable dust/animal dust (OR = 4.7, 95% CI: 2.1, 10.4) are associated with IPF	Community controls, telephone interview asking directly about exposures, 91% of cases and 81% of controls were interviewed.
Miyake 2005	Japan	102	Occupational exposure to metal dust (OR 9.55, 95%CI 1.68-181.12) is an independent risk factor for IPF	Hospital controls. Questionnaires covered "type of job held for the longest period of time" and exposure to 13 specific occupational agents. A full occupational history was not requested.
Gustafson 2007	Sweden	140	Occupational exposure to birch dust (OR 2.7, 95% CI 1.3-5.65) and hardwood dust (OR 2.7, 95% CI 1.14-6.52) are associated with IPF	Community controls, postal questionnaire which asked directly about occupational exposures e.g "Have you ever been exposed to asbestos?"
Pinheiro 2008	USA	84010	Mortality odds ratios were raised for people working in "Wood buildings and mobile homes" (MOR 5.3, 95% CI 1.2-23.8), "Metal mining"(MOR 2.2, 95% CI 1.1-4.4), and "Fabricated metal products"(MOR 1.7, 95% CI 1.0-3.1)	Cases and controls were identified from 1993 to 2003 mortality data and assigned to either the 'exposed' or the 'unexposed' group on the basis of their industry code.
Garcia-Sancho	Mexico	100	Occupational exposure to dusts, smokes, gases or chemicals was associated with IPF (OR 2.4, 95% CI, 1.4-4.0, p = 0.001)	Community controls. A trained interviewer visited every home and administered a structured questionnaire.
Awadalla 2012	Egypt	201	Occupational exposure to wood dust for men (OR 2.71 (1.01-7.37, 95% CI)) and animal feeds, products, and dust (OR 1.78 (1.01-3.13) 95% CI) and insecticides/pesticides (1.04-72.17, 95% CI) for women.	Case response rate was 91%. Age (\pm 3 yrs), sex, residence, and smoking status matched hospital controls were selected from patients admitted with respiratory disease other than IPF with a 93% response rate. Occupational questions focused on the type of job held for longest period of time during the subjects work life and years of exposure. Questions about exposure to 11 specific occupational and environmental agents were also asked.
Ekstrom 2014	Sweden	171	Smoking has dose related association with increased risk of severe IPF, occupational exposures increase risk	Used the same study design and dataset as Gustafson 2007

Appendix C Study flow chart and Gantt chart

IPF Job Exposures Study (IPF JES) Flow Chart



IPF Job Exposures Study (IPF JES) 36-Month Gannt Chart



Appendix D Study Information Sheet for Health Care Professionals

IPF Job Exposures Study (IPF JES)

Previous studies have found associations between occupational metal, stone, and wood dust exposures and IPF but have not looked specifically at quantitative asbestos exposure.

The question of whether job exposures such as asbestos exposure are important in causing a proportion of cases of IPF arises because:

- classical asbestosis looks very like IPF
- the trends of IPF and asbestos use in the UK are closely aligned; while this does not prove causation it is consistent with a link
- it would explain, at least in part, why the disease is more common in men from certain parts of the country
- men who have worked with wood or metals would commonly be exposed also to asbestos
- *preliminary* analysis of occupational data for cases and controls obtained from a recent IPF study shows that the odds ratio associated with ever having had a job where asbestos exposure is likely (using a definition from a large mesothelioma case-control study) is 2.8 (95% CI: 1.42-5.75, $p = 0.001$)

Knowing whether there is a link between job exposures such as asbestos and some cases of IPF would help to better understand the causes of IPF; would change approaches to its current treatment; would have important implications for compensation; and would help to prevent the disease in parts of the world where asbestos is still used widely.

We will be recruiting male patients with a new IPF diagnosis (consistent with 2011 ATS/ERS criteria) made between 1/02/2017 and 1/10/2019.

Study details This study will recruit men with new diagnoses of IPF (cases) from a network of UK hospitals. For purposes of comparison a group of men of the same age attending the same hospitals at about the same time for other conditions (controls) will be recruited, in a ratio of 1:1; the total number of participants will be 920.

Cases and controls will be invited to give details, through a telephone interview, of all the jobs they have had since leaving school. These jobs will be scored for the likelihood of their incurring exposure to asbestos; the techniques for doing this are well established. The proportions of so-exposed jobs will be compared between the cases and the controls to investigate whether there is a dose-response relationship for occupational asbestos exposure and IPF.

Participants will also be invited to provide a blood sample to investigate whether asbestos exposure modifies the association between idiopathic pulmonary fibrosis and a MUC5B promoter (rs35705950) polymorphism which is known to confer susceptibility to IPF.

Contact Dr Carl Reynolds / carl.reynolds@imperial.ac.uk / 07737 904 807
National Heart and Lung Institute, Room G39 Emmanuel Kaye Building, 1b Manresa Road, London, SW3 6LR.

Appendix E Participant Information Sheet

Participant Information Sheet

Idiopathic Pulmonary Fibrosis Job Exposure Study (IPF JES)

IPF JES is a research study that aims to discover if workplaces are a cause of idiopathic pulmonary fibrosis (IPF)

The lead researcher is Dr Carl Reynolds, clinical research fellow at Imperial College London.

PART 1

Can you help with a research study?

- We would like to invite you to take part in a research study. Before you decide we would like you to understand why the research is being carried out and what it would involve for you.
- One of our team will go through this information sheet with you and answer any questions you have. This should take about 10–15 minutes.
- Please talk to others about the study if you wish and ask us if anything is not clear.

What is the purpose of the study?

- Idiopathic pulmonary fibrosis (also called IPF) is a disease that causes scarring of the lungs. The scarring damages the air sacs that allow oxygen to be transferred to the blood and transported to vital organs. IPF is a serious illness that causes cough, shortness of breath, and fatigue.
- We don't know what causes IPF but it is becoming more common in England, Scotland and Wales where it affects over 4000 people each year. People who get IPF are usually older than 40; the disease is more common in men and in parts of the country with a history of heavy industry.
- This study will help to find out how much IPF can be attributed to workplace environments in England, Scotland and Wales. This will help us to better understand the causes of IPF, make sure people get the right treatment and compensation they are entitled to, and ensure that the controls at work are right so that we protect workers and prevent disease in the future.



Why have I been chosen?

- The study works by comparing people with IPF (cases) to people who are similar but do not have IPF (controls). Both groups are essential for the study.
- You have been chosen to take part in the study as a **case** if you have a new diagnosis of IPF.
- You have been chosen to take part in the study as a **control** if you do not have IPF but recently had a hospital outpatient appointment and are of a similar age to patients who are newly diagnosed with IPF.

Do I have to take part?

- It is up to you to decide if you want to take part in the research. We will describe the study and go through this information booklet with you.
- If you agree to take part we will ask you to read and sign a consent form.
- You are free to withdraw at any time, without giving a reason. This will not affect any of the care you receive.

Who are the researchers?

The research will be conducted by a team based at Imperial College London, Imperial College Healthcare NHS Hospitals, and Sheffield Foundation Trust NHS Hospitals. The research is funded by the Wellcome Trust. The main investigators are:

- Dr Carl Reynolds, Wellcome Trust Clinical Research Training Fellow, NHLI (Imperial College London). (Chief investigator)
- Professor Paul Cullinan, Professor, Honorary consultant physician (respiratory medicine). Occupational and Environmental Medicine, NHLI (Imperial College London), Royal Brompton Hospital, London. Joint appointment; tenured. (Co-Investigator)
- Dr Chris Barber, Consultant physician (respiratory medicine), Northern General Hospital, Sheffield. (Co-Investigator)
- Dr Sara De Matteis, Clinical Lecturer, NHLI (Imperial College London). (Co-Investigator)

PART 2

What will happen to you if you take part?

- If you agree to take part the researcher will contact you to arrange a telephone interview at a time that is convenient for you.
- The telephone interview will last no longer than one hour.
- During the interview you will be asked questions about

- All of the jobs you have had since leaving school; we may also ask about the jobs of people you have lived with
 - Where you have lived
 - Your lifetime smoking history
- You will be contacted to arrange a blood test to investigate genetic susceptibility to IPF. If possible the blood test will be taken when you next have blood tests to avoid an extra test. If this is not possible it will be arranged at a time and place that is convenient for you. We will cover any reasonable travel expenses incurred due to participation in the study and agreed in advance.
- With your permission, we will write to your GP to inform them that you are participating.
- We will tell you what we find. What we find might not contain any helpful information for you. If we find anything we think is important we will, with your permission, inform your clinical team.

Why are you requesting a blood test?

We want to know if workplace environments are a cause of IPF. We know that for most diseases whether or not a person gets the disease depends both on what they encounter in their environment, and the DNA or genes they are born with.

IPF is a rare disease. It is not a disease that normally runs in families but it is more common in people with certain genetic differences, such as a small change that affects mucus in our airways (called MUC5B rs35705950). The blood test helps us to check if it is workplace environments together with these genetic differences that causes IPF.

What will the result of the blood test mean for me?

If you are found to carry the MUC5B rs3570950 genetic difference it does not mean that you have IPF or that you or your family members will get IPF.

Studies have shown that you are about six times more likely to have IPF if you carry MUC5B rs3570950. However, IPF is rare (fewer than one in 2000 people in the UK are diagnosed with the condition at some time in their life), so the overall risk of IPF for people who carry MUC5B rs3570950 is still very low.

Are there any benefits to taking part?

It is unlikely that the study will help you personally. The information we get from this research may help to understand the causes of IPF, make sure people get the right treatment and compensation they are entitled to, and ensure that the controls on chemicals at work are right so that we protect workers and prevent disease in the future.

Patients with diseases that are discovered to be caused by work might get compensation. Currently, patients with IPF are unlikely to get compensation because it is not known to be caused by work. If we find that workplace environments do cause IPF for some people then this may change for patients in the future.

Are there any risks to taking part?

The greatest risk to you of participation in this study is an inadvertent disclosure of your private identifiable information. To minimize the risk of loss of confidentiality your interview response (and blood sample) will not be labelled with your private identifiable information. Interview response information will be kept encrypted on a computer in a locked office. Blood samples will be stored in a secure facility. You will not be identified in any report or publication of this study or its results.

There is a risk that we will find something that is important to your health. This could be distressing to you. If we find anything that we think could be important to your health we will inform you, and with your permission, your GP and hospital doctors.

The study has been reviewed by the Nottingham 1 Research Ethics Committee.

What will happen when the research is finished?

A summary of the results will be available and we will send you a copy if you request it. Data from the study, including anonymised unprocessed data, will be communicated to the wider academic community, and policy-makers, by publication and presentation at national and international respiratory and epidemiology meetings. Summary data will also be shared with the care teams participating in the study.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers. They will do their best to answer your questions. Their contact details are on the last page of this booklet. If you remain unhappy and wish to complain formally you can do this by contacting the Patient Advice and Liaison Service (PALS).

Appendix F Participant consent form

INFORMED CONSENT FORM FOR SUBJECTS ABLE TO GIVE CONSENT

Idiopathic Pulmonary Fibrosis Job Exposure Study (IPF JES)

Name of Principle Investigator: _____

Please initial box

1. I confirm that I have read and understand the subject information sheet dated _____ version _____ for the above study and have had the opportunity to ask questions which have been answered fully. ☐
2. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from Imperial College London or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to access my records that are relevant to this research. ☐
4. I consent to being contacted by the research team. ☐
5. I consent to my interview being recorded. No ☐ Yes ☐
6. I consent to genetic testing as part of the research. ☐
7. I consent to storage of information and blood samples collected from me for future research. No ☐ Yes ☐
8. I consent to my GP and hospital care teams being informed of my participation in the research and, with my permission, of any clinically significant findings arising from the research. ☐

Name of subject

Signature

Date

Subject's date of birth

Name of person taking consent (if different from Principle Investigator)

Signature

Date

Appendix G Hospital specialist cover letter (control recruitment)

Cons
Speciality
Hospital
Town
Postcode

April 28, 2017

RE: IPF JES

Dear Doctor,

We have randomly selected your clinic on date XX/XX/XXXX as a source of potential controls for IPF JES, a multicentre case-control study to investigate job exposures in IPF. The study involves a short interview to measure historic job exposures and a blood test to investigate susceptibility genetics. I enclose a one-page summary of the study together with the participant information sheet and would be happy to answer any questions you might have. Would you be happy for males attending the clinic aged between X and Y to be approached about the study and provided with an information sheet? We would then hope to enrol them in the study at their next outpatient appointment.

Yours sincerely

Dr Carl Reynolds

A handwritten signature in black ink, appearing to read 'C Reynolds', with a long, sweeping underline that extends to the left.

[IPF JES Consultant Control Letter Version 0.4]

Appendix H GP cover letter

Dr General Practitioner
The Surgery
1 General Practice Lane
Practiveville
London SW1A 2HQ

April 28, 2017

RE: Joe Bloggs, 12/3/34, NHS number XXX-XXX-XX

Dear Doctor,

I am writing to inform you that Mr Bloggs has agreed to participate in IPF JES, a multicentre case-control study to investigate job exposures in idiopathic pulmonary fibrosis (IPF).

The study includes both patients with ('cases') and without ('controls') IPF and involves an interview to measure historic job exposures and a blood test to investigate susceptibility genetics. I will write to inform you (with your patient's consent) if there are any clinically significant findings for your patient.

I enclose the participant information sheet and would be happy to answer any questions you might have.

Yours sincerely

Dr Carl Reynolds

A handwritten signature in black ink, appearing to read 'R Reynolds', with a large, sweeping flourish above the name.

[IPF JES GP Letter Version 0.4]

Appendix I Study standard operating procedure

Standard Operating Procedure for case and control recruitment and exposure assessment in the Idiopathic Pulmonary Fibrosis Job Exposure Study (IPF JES)

Contents

1 Scope and applicability	1
2 Introduction	1
3 Recruitment	2
3.1 Recruitment of cases	2
3.2 Recruitment of controls	2
4 Exposure assessment	5
5 Introduction	5
6 Occupational history	5
7 Residential history	7
8 Cohabitation history	7
9 Smoking history	7
10 mMRC dyspnoea questions	8
11 Drug and medical history	8
12 Family history	8
13 Asbestos exposure history	8
14 (for cases only) how were you diagnosed	9
15 Ethnicity	9
16 Thank-you and updates	9
17 Venepuncture, sample storage, transportation, and processing	9
18 Unique research IDs	9

1 Scope and applicability

The purpose of this SOP is to describe the instructions for the enrolment of cases and controls, exposure assessment, and genetic testing in the IPF JES.

2 Introduction

The objective of IPF JES is to characterize and measure job exposures as an occupational determinant of Idiopathic Pulmonary Fibrosis (IPF). This will be achieved through a case-control study in which historic job exposures are measured using a validated semi-structured interview. A blood test will also be obtained to investigate interaction between job exposures and IPF genetic susceptibility factors.

3 Recruitment

3.1 Recruitment of cases

See figure 1

Cases will be recruited from male patients with a new diagnosis of IPF made during the study period within the research network.

All clinic patients who meet the case inclusion criteria will be provided with a participant information sheet and participant job history sheet. Patients will be enrolled into the study, blood will be drawn, and a case-report form will be completed. The case-report form and blood samples will be placed into a pre-paid Royal Mail container and put in a postbox. Inclusion and exclusion criteria will be checked as part of enrolment.

The central research team will be updated monthly with details of the number of eligible patients attending clinic, the number of eligible patients approached to participate in the study, and the number of patients agreeing to participate in the study.

Recruitment of cases from a centre stops when the agreed centre target is met or the agreed centre recruitment period ends.

3.2 Recruitment of controls

See figure 2

Controls will be recruited from male patients with a new outpatient department attendance at the same hospital or trust that the cases originate from. Controls will be frequency matched on age to 5-year bands (e.g 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85+). The overall ratio of cases to controls will be 1:1.

A control clinic will be randomly selected (from all clinics, not limited to respiratory) at each centre. Paediatric clinics and gynaecological clinics will be excluded. This may be achieved by randomly sampling a list of all clinics, by randomly sampling a list of outpatient locations and a time of the week, or by other means. The central research team will provide support for this activity.

The local research team will write to the lead clinician for the selected clinic to obtain permission to recruit patients to the study. If permission is refused then the process is repeated until a lead clinician agrees. Once agreement is obtained this clinic will be the source clinic for all controls at that centre for the duration of the study.

Potential controls will be invited to participate in the study and provided with a patient information sheet when they attend the outpatient department. Patients will be enrolled into the study, blood will be drawn, the participant will be provided with a job history sheet, and a case-report form will be completed. The case-report form and blood samples will be placed into a pre-paid Royal Mail container and put in a postbox. Inclusion and exclusion criteria will be checked as part of enrolment.

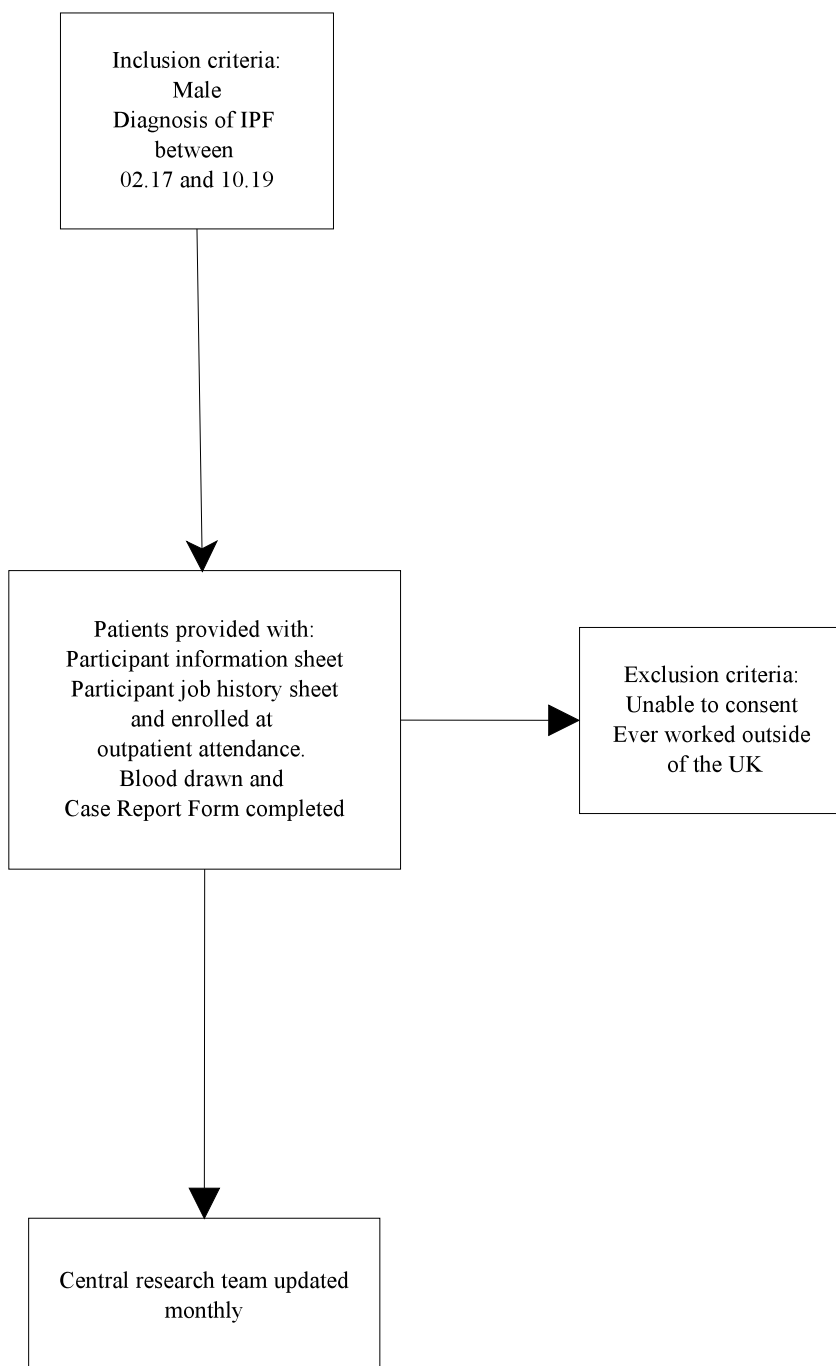


Figure 1: Case recruitment

The central research team will be updated monthly with details of the number of eligible patients attending clinic, the number of eligible patients approached to participate in the study, and the number of patients agreeing to participate in the study.

Recruitment of controls from a centre stops when recruitment of cases stops and one control for each case has been recruited or the agreed centre recruitment period ends.

4 Exposure assessment

The exposure assessment is carried out by the central research team by means of a computer-assisted telephone interview.

5 Introduction

Hello, my name is **name of researcher**. I am a doctor/nurse/research assistant calling as part of the IPF Job Exposure Study. Is this **name of participant**?

I would like to ask you some questions about the jobs you have had, where you have lived, and smoking. I would also like to record this call for our research if that's ok with you.

Your answers will help us to understand the causes of IPF, make sure people get the right treatment, and ensure that controls of exposures at work are right so that we protect workers and prevent disease in the future.

The interview should take about 30 minutes. Is now a good time to talk?

6 Occupational history

I want you to think about all of the jobs you've had. I know this can be hard, we'll try one at a time.

Do you remember the first job that you had after school?

1. What was the name of your job? (we record SOC2000 job title and map SOC90)
2. What did you do in this job? (we record free text but also have a drop down of activities associated with asbestos exposure)
3. What was the name of the company (if applicable)? (we record name and SIC code, we possibly link to open corporates company house record)
4. What did the company make (if applicable)? (we record free text but also have a drop down of asbestos containing products)
5. In what sort of working area did you spend most of your time? e.g Office, In the Open, Workshop, Construction Site, Factory (Light Industry), Heavy Industry (eg. Power Station), Hospital, School/University, Warehouse, On Location, various buildings, Shop, At Home, Ship/Ship yard, Other (specify)
6. Did you work full time? (if not specify average hours per week)
7. Did you work all year round (if not specify months of the year)

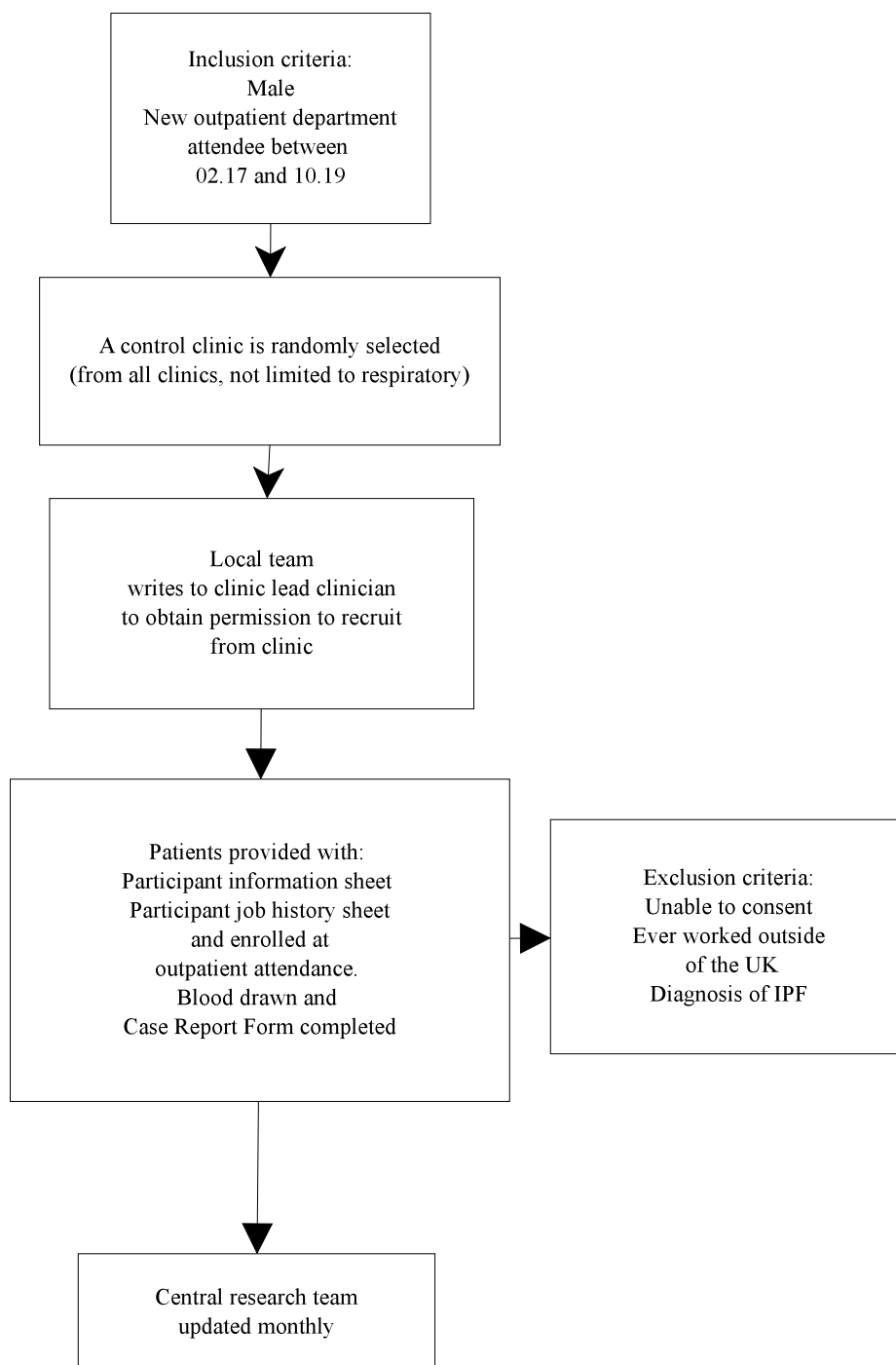


Figure 2: Control recruitment

SOC90	Occupation	PMR
541	Coach & vehicle body builders	528.18
534	Metal plate workers, shipwrights, riveters	416.64
532	Plumbers, heating & ventilating engineers	388.67
570	Carpenters & joiners	382.34
896	Construction & related operatives	359.23
311	Building inspectors	317.83
520	Production fitters (electrical/electronic)	300.15
521	Electricians, electrical maintenance fitters	264.12
893	Electrical, energy, boiler & related	252.09
533	Sheet metal workers	245.71
301	Engineering technicians	232.22
506	Floorers, floor coverers, carpet fitters	232.05
913	Mates to metal/electrical & related fitters	230.89
211	Mechanical engineers	217.44
571	Cabinet makers	215.36

Table 1: Standard Occupational Classification 1990 code, Occupation, and Mesothelioma Proportional Mortality Ratio (PMR) for the top 15 significant (95% CI does not include 100) PMRs. HSE data.

8. Do you remember how old you were or what year you started the job?
9. Do you remember how old you were or what year you finished the job?
10. Do you remember what job you had next?

(1 through 10 repeats until lifetime occupational history is complete. Standard occupational classification is used to code occupations)

Any reported contact with asbestos or 'trigger' products (HSE list), industries (construction, factory work, power station work, other heavy industry, ships or ship yards), jobs (see Table 1), and job processes prompts an asbestos exposure history (see later) to be taken.

References

- 1 V Navaratnam, KM Fleming, J West, CJP Smith, RG Jenkins, A Fogarty, and RB Hubbard. The rising incidence of idiopathic pulmonary fibrosis in the uk. *Thorax*, 66(6):462–467, 2011.
- 2 Toby M Maher. Idiopathic pulmonary fibrosis: pathobiology of novel approaches to treatment. *Clin. Chest Med.*, 33(1):69–83, Mar 2012. doi: 10.1016/j.ccm.2011.11.002. URL <http://dx.doi.org/10.1016/j.ccm.2011.11.002>.
- 3 Brett Ley and Harold R Collard. Epidemiology of idiopathic pulmonary fibrosis. *Clinical epidemiology*, 5:483, 2013.
- 4 Paolo Spagnolo, Johan Grunewald, and Roland M du Bois. Genetic determinants of pulmonary fibrosis: evolving concepts. *The Lancet Respiratory Medicine*, 2(5):416–428, 2014.
- 5 Richard Hubbard, Ian Johnston, and John Britton. Survival in patients with cryptogenic fibrosing alveolitis a population-based cohort study. *CHEST Journal*, 113(2):396–400, 1998.
- 6 C. Vancheri, M. Failla, N. Crimi, and G. Raghu. Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology. *Eur. Respir. J.*, 35(3):496–504, Mar 2010. doi: 10.1183/09031936.00077309. URL <http://dx.doi.org/10.1183/09031936.00077309>.
- 7 CM Barber, RE Wiggans, C Young, and D Fishwick. Uk asbestos imports and mortality due to idiopathic pulmonary fibrosis. *Occup. Med.*, page kqv142, 2015.
- 8 E. Monso, J. M. Tura, M. Marsal, F. Morell, J. Pujadas, and J. Morera. Mineralogical microanalysis of idiopathic pulmonary fibrosis. *Arch. Environ. Health*, 45(3):185–188, 1990. doi: 10.1080/00039896.1990.9936714. URL <http://dx.doi.org/10.1080/00039896.1990.9936714>.
- 9 E Monsó, JM Tura, J Pujadas, F Morell, J Ruiz, and J Morera. Lung dust content in idiopathic pulmonary fibrosis: a study with scanning electron microscopy and energy dispersive x ray analysis. *Br. J. Ind. Med.*, 48(5):327–331, 1991.
- 10 CS Glazer and L Maier. Occupational interstitial lung disease. *Eur Respir Monograph*, 46:265–286, 2009.
- 11 Andrew Ghio, Rahul Sangani, and Victor Roggli. Expanding the spectrum of particle-and fiber-associated interstitial lung diseases. *Turk Toraks Derg*, 15:1–8, 2014.
- 12 C Reynolds, C Barber, and P Cullinan. S3 idiopathic pulmonary fibrosis, mesothelioma, and asbestosis mortality trends for england and wales: Is asbestos exposure associated with ipf? *Thorax*, 69(Suppl 2):A4–A5, 2014.
- 13 Jonathan Scott, Ian Johnston, and John Britton. What causes cryptogenic fibrosing alveolitis? a case-control study of environmental exposure to dust. *BMJ*, 301(6759):1015, 1990.

- 14 K. Iwai, T. Mori, N. Yamada, M. Yamaguchi, and Y. Hosoda. Idiopathic pulmonary fibrosis. epidemiologic approaches to occupational exposure. *Am. J. Respir. Crit. Care Med.*, 150(3):670–675, Sep 1994. doi: 10.1164/ajrccm.150.3.8087336. URL <http://dx.doi.org/10.1164/ajrccm.150.3.8087336>.
- 15 Richard Hubbard, Ian Johnston, David B Coultas, and John Britton. Mortality rates from cryptogenic fibrosing alveolitis in seven countries. *Thorax*, 51(7):711–716, 1996.
- 16 Richard Hubbard, Marie Cooper, Marilyn Antoniak, Andrea Venn, Sayeed Khan, Ian Johnston, Sarah Lewis, and John Britton. Risk of cryptogenic fibrosing alveolitis in metal workers. *The Lancet*, 355(9202):466–467, 2000.
- 17 Yoshihiro Miyake, Satoshi Sasaki, Tetsuji Yokoyama, Kingo Chida, Arata Azuma, Takafumi Suda, Shoji Kudoh, Naomasa Sakamoto, Kazushi Okamoto, Gen Kobashi, et al. Occupational and environmental factors and idiopathic pulmonary fibrosis in japan. *Ann. Occup. Hyg.*, 49(3):259–265, 2005.
- 18 Germania A Pinheiro, Vinicius C Antao, John M Wood, and James T Wassell. Occupational risks for idiopathic pulmonary fibrosis mortality in the united states. *Int. J. Occup. Environ. Health*, 14(2):117–123, 2008.
- 19 R Hubbard, S Lewis, K Richards, J Britton, and I Johnston. Occupational exposure to metal or wood dust and aetiology of cryptogenic fibrosing alveolitis. *The Lancet*, 347(8997):284–289, 1996.
- 20 Torbjörn Gustafson, Anna Dahlman-Höglund, Kenneth Nilsson, Kerstin Ström, Göran Tornling, and Kjell Torén. Occupational exposure and severe pulmonary fibrosis. *Respir. Med.*, 101(10):2207–2212, 2007.
- 21 N. J. Awadalla, A. Hegazy, R. A. Elmetwally, and I. Wahby. Occupational and environmental risk factors for idiopathic pulmonary fibrosis in egypt: a multicenter case-control study. *Int J Occup Environ Med*, 3(3):107–116, Jul 2012.
- 22 K. B. Baumgartner, J. M. Samet, D. B. Coultas, C. A. Stidley, W. C. Hunt, T. V. Colby, and J. A. Waldron. Occupational and environmental risk factors for idiopathic pulmonary fibrosis: a multicenter case-control study. collaborating centers. *Am. J. Epidemiol.*, 152(4):307–315, Aug 2000.
- 23 J. Mullen, M. J. Hodgson, C. A. DeGraff, and T. Godar. Case-control study of idiopathic pulmonary fibrosis and environmental exposures. *J. Occup. Environ. Med.*, 40(4):363–367, Apr 1998.
- 24 C. Rake, C. Gilham, J. Hatch, A. Darnton, J. Hodgson, and J. Peto. Occupational, domestic and environmental mesothelioma risks in the british population: a case-control study. *Br. J. Cancer*, 100(7):1175–1183, Apr 2009. doi: 10.1038/sj.bjc.6604879. URL <http://dx.doi.org/10.1038/sj.bjc.6604879>.
- 25 L. S. Welch, D. Michaels, and S. R. Zoloth. The national sheet metal worker asbestos disease screening program: radiologic findings. national sheet metal examination group. *Am. J. Ind. Med.*, 25(5):635–648, May 1994.

- 26 K. Teschke, A. F. Olshan, J. L. Daniels, A. J. De Roos, C. G. Parks, M. Schulz, and T. L. Vaughan. Occupational exposure assessment in case-control studies: opportunities for improvement. *Occup. Environ. Med.*, 59(9):575–93; discussion 594, Sep 2002.
- 27 Eve Bourgkard, Pascal Wild, Maria Gonzalez, Joëlle Févotte, Emmanuelle Penven, and Christophe Paris. 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.*, 70(12):884–891, Dec 2013. doi: 10.1136/oemed-2013-101467. URL <http://dx.doi.org/10.1136/oemed-2013-101467>.
- 28 John W Cherrie and Thomas Schneider. Validation of a new method for structured subjective assessment of past concentrations. *Ann. Occup. Hyg.*, 43(4):235–245, 1999.
- 29 Clare Gilham, Christine Rake, Garry Burdett, Andrew G Nicholson, Leslie Davison, Angelo Franchini, James Carpenter, John Hodgson, Andrew Darnton, and Julian Peto. Pleural mesothelioma and lung cancer risks in relation to occupational history and asbestos lung burden. *Occupational and environmental medicine*, pages oemed–2015, 2015.
- 30 Vidya Navaratnam, Andrew W Fogarty, Tricia McKeever, Norma Thompson, Gisli Jenkins, Simon R Johnson, Gerard Dolan, Maruti Kumaran, Kate Pointon, and Richard B Hubbard. Presence of a prothrombotic state in people with idiopathic pulmonary fibrosis: a population-based case-control study. *Thorax*, 69(3):207–215, Mar 2014. doi: 10.1136/thoraxjnl-2013-203740. URL <http://dx.doi.org/10.1136/thoraxjnl-2013-203740>.
- 31 Craig E Daniels, ES Yi, and Jay H Ryu. Autopsy findings in 42 consecutive patients with idiopathic pulmonary fibrosis. *Eur. Respir. J.*, 32(1):170–174, 2008.
- 32 Kenneth J Rothman, John E J Gallacher, and Elizabeth E Hatch. Why representativeness should be avoided. *Int. J. Epidemiol.*, 42(4):1012–1014, Aug 2013. doi: 10.1093/ije/dys223. URL <http://dx.doi.org/10.1093/ije/dys223>.
- 33 Keith T. Palmer, Jason Poole, Jon G. Ayres, Jonathan Mann, P Sherwood Burge, and David Coggon. Exposure to metal fume and infectious pneumonia. *Am. J. Epidemiol.*, 157(3):227–233, Feb 2003.
- 34 Max A Seibold, Anastasia L Wise, Marcy C Speer, Mark P Steele, Kevin K Brown, James E Loyd, Tasha E Fingerlin, Weiming Zhang, Gunnar Gudmundsson, Steve D Groshong, Christopher M Evans, Stavros Garantziotis, Kenneth B Adler, Burton F Dickey, Roland M du Bois, Ivana V Yang, Aretha Herron, Dolly Kervitsky, Janet L Talbert, Cheryl Markin, Joungjoa Park, Anne L Crews, Susan H Slifer, Scott Auerbach, Michelle G Roy, Jia Lin, Corinne E Hennessy, Marvin I Schwarz, and David A Schwartz. A common muc5b promoter polymorphism and pulmonary fibrosis. *N. Engl. J. Med.*, 364(16):1503–1512, Apr 2011. doi: 10.1056/NEJMoa1013660. URL <http://dx.doi.org/10.1056/NEJMoa1013660>.
- 35 Anna L Peljto, Yingze Zhang, Tasha E Fingerlin, Shwu-Fan Ma, Joe GN Garcia, Thomas J Richards, Lori J Silveira, Kathleen O Lindell, Mark P Steele, James E Loyd, et al. Association between the muc5b promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. *JAMA*, 309(21):2232–2239, 2013.

- 36 Tasha E Fingerlin, Elissa Murphy, Weiming Zhang, Anna L Peljto, Kevin K Brown, Mark P Steele, James E Loyd, Gregory P Cosgrove, David Lynch, Steve Groshong, Harold R Collard, Paul J Wolters, Williamson Z Bradford, Karl Kossen, Scott D Seiwert, Roland M du Bois, Christine Kim Garcia, Megan S Devine, Gunnar Gudmundsson, Helgi J Isaksson, Naftali Kaminski, Yingze Zhang, Kevin F Gibson, Lisa H Lancaster, Joy D Cogan, Wendi R Mason, Toby M Maher, Philip L Molyneaux, Athol U Wells, Miriam F Moffatt, Moises Selman, Annie Pardo, Dong Soon Kim, James D Crapo, Barry J Make, Elizabeth A Regan, Dinesha S Walek, Jerry J Daniel, Yoichiro Kamatani, Diana Zelenika, Keith Smith, David McKean, Brent S Pedersen, Janet Talbert, Raven N Kidd, Cheryl R Markin, Kenneth B Beckman, Mark Lathrop, Marvin I Schwarz, and David A Schwartz. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. *Nat. Genet.*, 45(6):613–620, Jun 2013. doi: 10.1038/ng.2609. URL <http://dx.doi.org/10.1038/ng.2609> .
- 37 Imre Noth, Yingze Zhang, Shwu-Fan Ma, Carlos Flores, Mathew Barber, Yong Huang, Steven M Broderick, Michael S Wade, Pirro Hysi, Joseph Scuirba, Thomas J Richards, Brenda M Juan-Guardela, Rekha Vij, Meilan K Han, Fernando J Martinez, Karl Kossen, Scott D Seiwert, Jason D Christie, Dan Nicolae, Naftali Kaminski, and Joe G N Garcia. Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study. *Lancet Respir Med*, 1(4):309–317, Jun 2013. doi: 10.1016/S2213-2600(13)70045-6. URL [http://dx.doi.org/10.1016/S2213-2600\(13\)70045-6](http://dx.doi.org/10.1016/S2213-2600(13)70045-6) .
- 38 M et al Concha-Barrientos. Selected occupational risk factors. In Ezzati M et al, editor, *Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors*, volume 2, pages 1651–1802. World Health Organization, 2004. URL <http://www.who.int/publications/cra/chapters/volume2/1651-1802.pdf?ua=1> .