IPF-AES

Idiopathic Pulmonary Fibrosis Asbestos Exposure Study

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Protocol authorised by:

Name & Role	Date	Signature

Study management group

Chief Investigator: Carl Reynolds
Co-investigators: Paul Cullinan, Chris Barber

Statistician: Cosetta Minelli
Study Management: Paul Cullinan, Chris Barber, 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 G45 Emmanual 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/Imperial College Healthcare NHS Trust (delete as applicable) 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 IPF-AES study 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

Glossary

Asbestos Asbestos is a mineral fibre with useful insulating properties. Asbestos use is now strictly controlled because of harmful health effects. Historically, construction materials and household goods have been made from asbestos, and widely used, in the United Kingdom.

Idiopathic pulmonary fibrosis Idiopathic pulmonary fibrosis (also called IPF) is a disease that causes scarring of the lungs. The 'idiopathic' part of the name refers to the cause of the disease being unknown.

Key words

Idiopathic pulmonary fibrosis, asbestos, case-control study

Study Summary

Title: Idiopathic Pulmonary Fibrosis Asbestos Exposure Study (IPF-AES).

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 unconditional logistic regression for any vs no asbestos exposure and categories of cumulative exposure and adjusting for age and smoking status. 2. Gene-environment interaction odds ratio (for MUC5B rs35705950 and asbestos exposure).

Population: Male patients with a new diagnosis of IPF and age-matched controls who have a new outpatient 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 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. 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 1974-2012 for 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 very limited occupational information in a recent case-control study, designed to examine the role of thrombosis.[1] Using an approach from a large mesothelioma study[24] 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 fibres[25] 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] 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%;[29] and a recent US series estimated that the ante-mortem diagnosis of IPF was missed in 20% of cases.[30] 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 generalizable[31] as is well demonstrated by a recent influential UK hospital case-control study which found that exposure to metal fume predisposed to infectious pneumonia.[32]

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.[33] The polymorphism results in excess MUC5B protein in the airway, impaired clearance of inhaled substances and a chronic inflammatory burden on the alveolar surface.[33] The association is allele dose-dependent, has been replicated in independent cohorts, and appears to confer improved survival.[3 33 34] Two large GWASs have confirmed the observed associations of IPF with MUC5B and other loci.[35 36]

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 unconditional logistic regression for any vs no asbestos exposure and categories of

cumulative exposure 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 Inclusion criteria

- Cases
  - Male
  - New diagnosis of IPF at MDT 10.16 and 07.19
- Controls
  - Male
  - New outpatient department attendee between 10.16 and 07.19

4.3 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
  - Diagnosis of IPF

4.4 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:

- Results in death
- 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 G45 Emmanual 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 assesment of the last research participant is complete.

7 Statistics and data analysis

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 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 $\alpha = 0.05$; my planned sample size 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. 41 With an estimated prevalence of IPF of 20/100000 and with ORs 2.0 for asbestos exposure and 6.8 for rs35705950, 113 cases would be required to detect a minimum interaction OR of 4.0

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 must 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 should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participants best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. 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/ Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study (delete as applicable)

8.5 Sponsor

Imperial College London/Imperial College Healthcare NHS Trust (delete as applicable) 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.

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 pneumoconiosis, we are collaborating with Dr Toby Maher who has good working relations with the NICE and is chair of the NHS England Specialist Respiratory Clinical Reference Group. 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 year[37]. Understanding the role of asbestos exposure in idiopathic pulmonary fibrosis is an important data point for disease prevention policy measures.

B Supplementary figures and tables

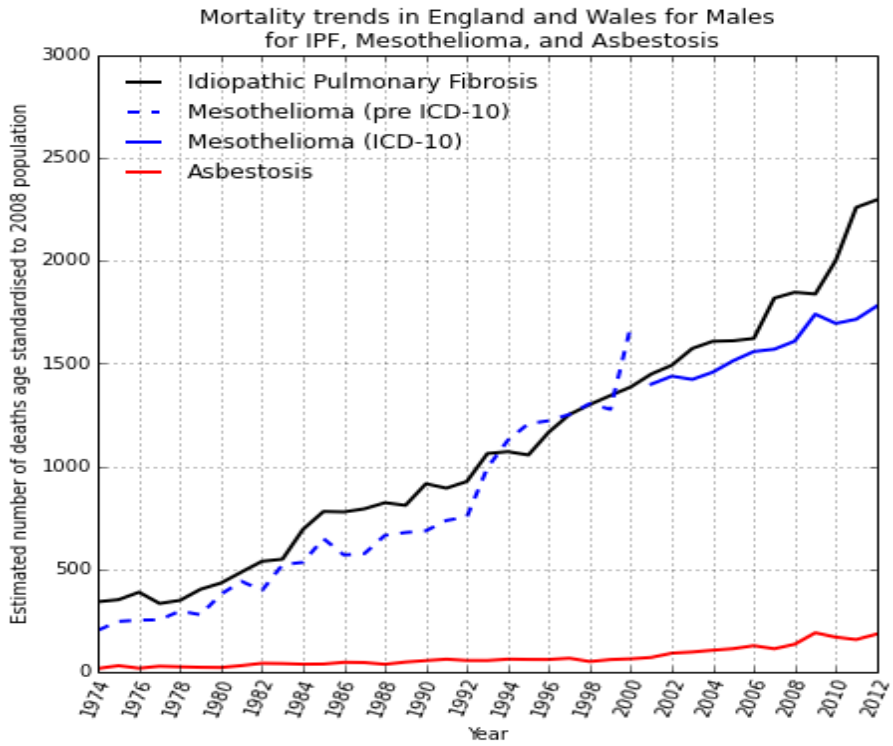


Figure 1: ONS data. Idiopathic Pulmonary Fibrosis, Mesothelioma, and Asbestosis mortality trends for England and Wales 1974-2012. A corrective factor provided by HSE has been applied to pre-ICD 10 Mesothelioma deaths (dashed line). https://github.com/drcjar/pypf/blob/master/notebooks/pypf_analysis.ipynb

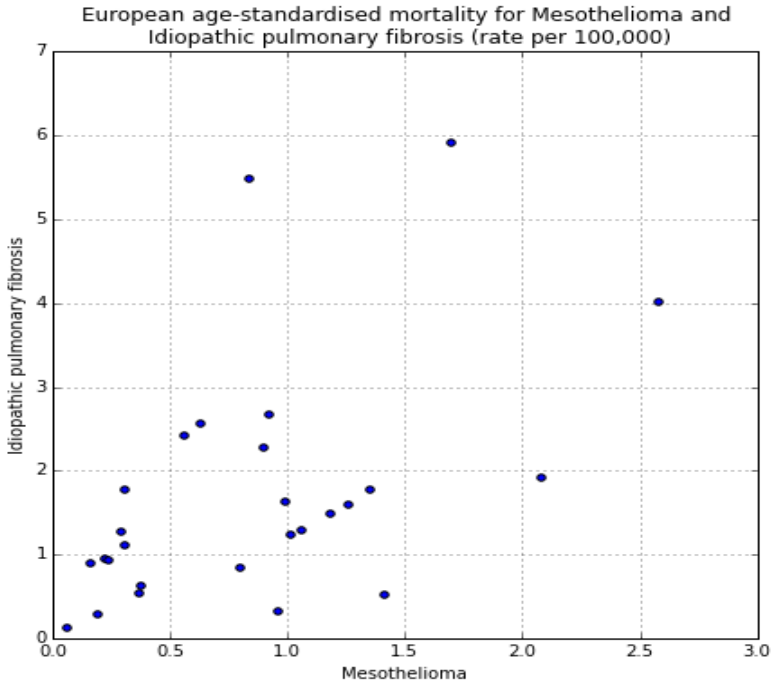


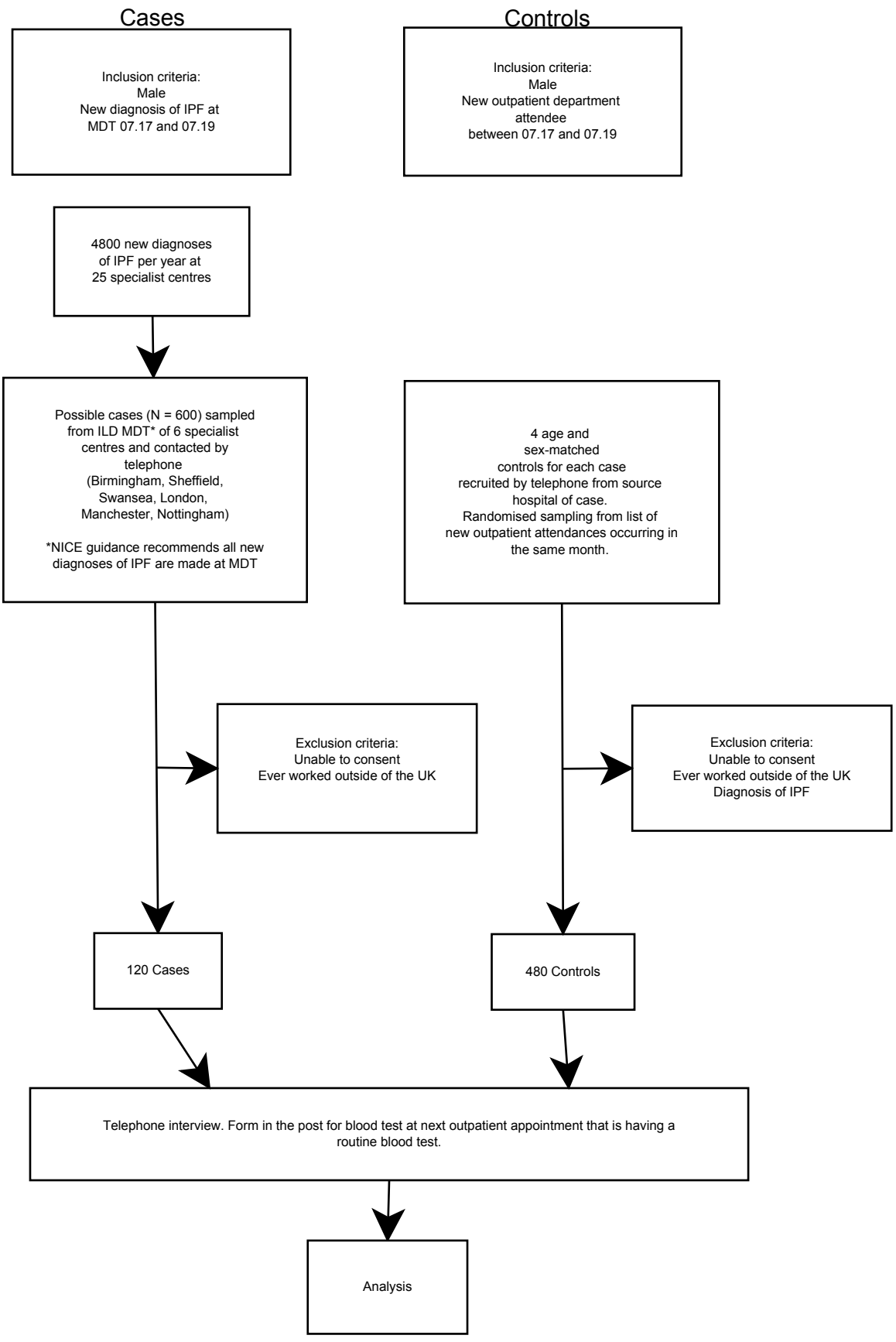
Figure 2: ERS Whitebook data. Age standardised mortality rate per 100,000 for 27 European Union member countries (data not available for Greece). Pearson correlation coefficient = 0.51, p = 0.007. https://github.com/drcjar/pypf/blob/master/notebooks/ERS_whitebook_ipf_meso.ipynb

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

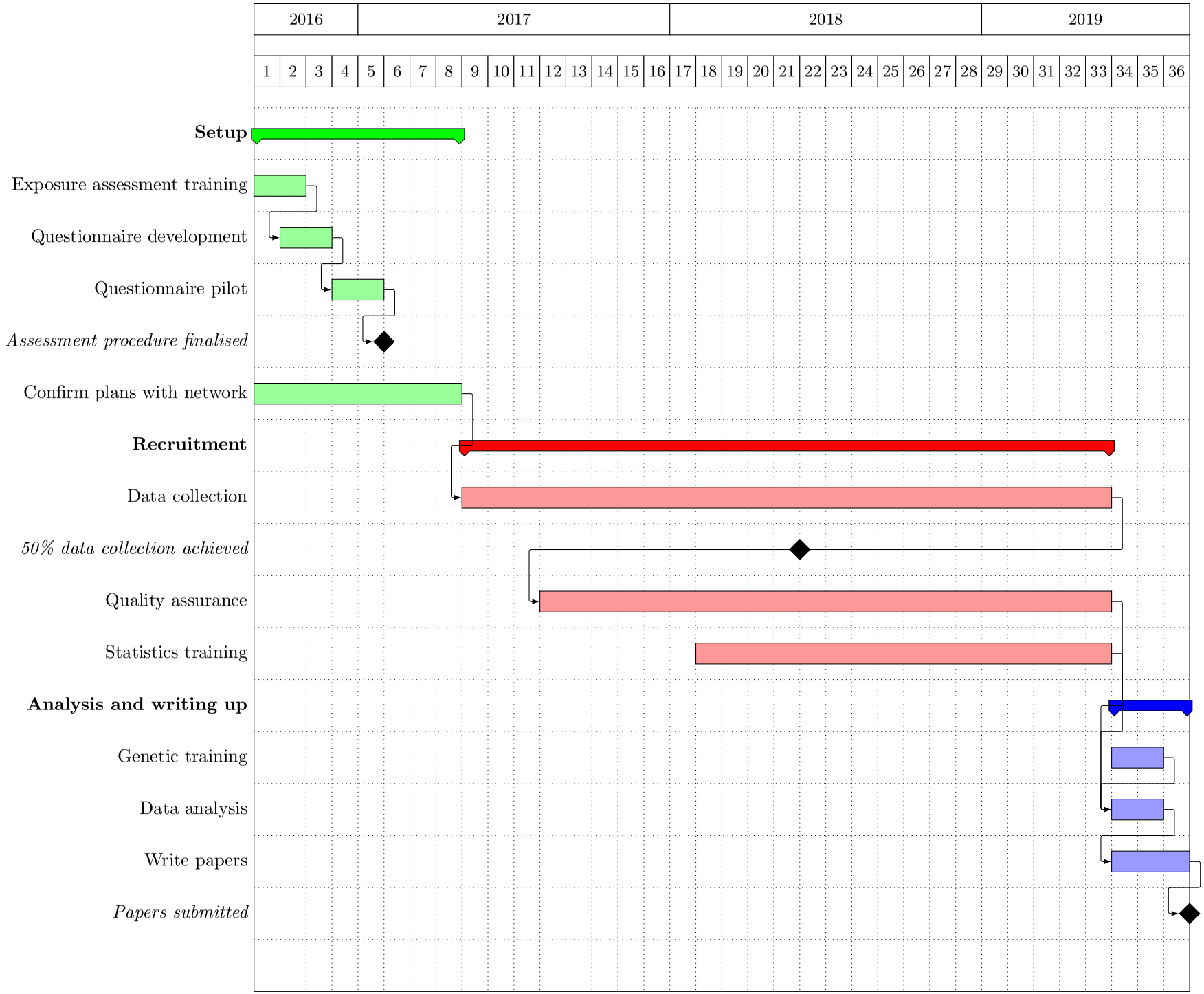
Ref	Country	Cases (N)	Findings	Notes (including source of cases and controls, measure of exposure used, and response rates)
Scott 1990	UK	40	Occupational exposures to metal dust (OR 10.97, 95%CI 2.3-52.4, p<0.001), wood dust (OR 2.94, 95%CI 0.87-9.9), p = 0.08), and stone/sand (OR 1.59, 95%CI 0.52-4.79) 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 "Annuals 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 171, 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 1993-2003 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 (± 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

C Study flow chart and Gannt chart

IPF Asbestos Exposure Study (IPF-AES) Flow Chart



IPF Asbestos Expsosure Study (IPF-AES) 36-Month Gannt Chart



D Participant Information Sheet

Participant Information Sheet

Idiopathic Pulmonary Fibrosis Asbestos Exposure Study (IPF-AES)

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

PART 1

Can you help with a research project?

- 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 the information booklet 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.
- In several ways, IPF resembles asbestosis, the lung-scarring disease caused by inhalation of asbestos fibres at work. Asbestos use is now banned but because there is a long time between breathing in asbestos and disease it is still a significant problem.
- This study will help to find out how much IPF can be attributed to the (past) inhalation of asbestos at work 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 on asbestos dust at work are right so that we protect workers and prevent disease in the future.

LUNGS AT WORK

Imperial College London

Why have I been chosen?

- You have been invited to take part in this study because you have a new diagnosis of IPF ('cases') or because you do not have IPF but recently had a hospital outpatient appointment and are the right age and sex ('controls').
- The study works by comparing 'cases' to 'controls' so both groups are needed.

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, Imperial College London. (chief investigator)
- Professor Paul Cullinan, Professor, Honorary consultant physician (respiratory medicine). Occupational and Environmental Medicine, NHLI (Imperial), Royal Brompton Hospital, London. Joint appointment; tenured. (supervisor)
- Dr Chris Barber, Consultant physician (respiratory medicine), Royal Hallamshire Hospital, Sheffield. (co-supervisor)

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
  - Your medical history including any prescription drugs you are taking
  - Medical problems that run in your family
  - Your lifetime smoking history
  - Contact with dust

- 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.

Are there any benefits to taking part?

We cannot promise that the study will help you, but the information we get from this research will 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 asbestos dust at work are right so that we protect workers and prevent disease in the future.

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 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.

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).

Patient Advice and Liaison Service
Ground floor of the Queen Elizabeth the Queen Mother (QEQM) building,
St Marys Hospital,
South Wharf Road,
London W2 1NY.
Tel: 020 3312 7777
Email: pals@imperial.nhs.uk

What will happen to the information we collect?

The Chief Investigator (Dr Carl Reynolds) will be responsible for ensuring that all the information we collect about you during the study is kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

All the procedures used for handling, processing, storage and destruction of your information will be in compliance with the Data Protection Act 1998. All the information we collect will be encrypted and stored on a password protected computer in a secure building. Blood samples will be stored in a locked fridge in a secure lab. Only members of the research team will have access to the information we collect.

Thank-you for your interest

Please ask if you have questions

Contact

Dr Carl Reynolds / carl.reynolds@imperial.ac.uk / 07737 904 807
National Heart and Lung Institute
Room G45 Emmanual Kaye Building
1b Mansrea Road, London, SW3 6LR

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 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 .

30 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.

31 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 .

32 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.

33 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 .

34 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.

35 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 .

36 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 .

37 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 .