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Original research

What role for asbestos in idiopathic pulmonary fibrosis? Findings from the IPF job exposures case–control study

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ABSTRACT

Background Asbestos has been hypothesised as the cause of the recent global increase in the incidence of 'idiopathic' pulmonary fibrosis (IPF). Establishing this has important diagnostic and therapeutic implications. The association between occupational asbestos exposure and IPF, and interaction with a common (minor allele frequency of 9% in European populations) genetic variant associated with IPF, *MUC5B* rs35705950, is unknown.

Methods Multicentre, incident case–control study. Cases (n=494) were men diagnosed with IPF at 21 UK hospitals. Controls (n=466) were age-matched men who attended a hospital clinic in the same period. Asbestos exposure was assessed at interview using a validated job exposure matrix and a source-receptor model. The primary outcome was the association between asbestos exposure and IPF, estimated using logistic regression adjusted for age, smoking and centre. Interaction with *MUC5B* rs35705950 was investigated using a genetic dominant model.

Results 327 (66%) cases and 293 (63%) controls ever had a high or medium asbestos exposure risk job; 8% of both cases and controls had cumulative exposure estimates ≥ 25 fibre ml⁻¹ years. Occupational asbestos exposure was not associated with IPF, adjusted OR 1.1 (95% CI 0.8 to 1.4; p=0.6) and there was no gene–environment interaction (p=0.3). Ever smoking was associated with IPF, OR 1.4 (95% CI 1 to 1.9; p=0.04) and interacted with occupational asbestos exposure, OR 1.9 (95% CI 1 to 3.6; p=0.04). In a further non-specified analysis, when stratifying for genotype there was significant interaction between smoking and work in an exposed job (p<0.01) for carriers of the minor allele of *MUC5B* rs35705950.

Conclusion Occupational asbestos exposure alone, or through interaction with *MUC5B* rs35705950 genotype, was not associated with IPF. Exposure to asbestos and smoking interact to increase IPF risk in carriers of a common genetic variant, the minor allele of *MUC5B* rs35705950.

Trial registration number NCT03211507.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung disease which in 2016 was the recorded underlying cause of death for approximately 5000 people in England and Wales.¹ The median age of onset is 70 years and the condition is more common

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Idiopathic pulmonary fibrosis (IPF) is more common in older men with a history of manual work; a group for whom, in the UK, occupational asbestos exposure is also common. It is not known if occupational asbestos exposure increases the risk of IPF.

WHAT THIS STUDY ADDS

⇒ We found that a history of occupational asbestos exposure alone is not associated with increased risk of IPF. However, occupational asbestos exposure and smoking do interact to increase IPF risk in carriers of the minor allele of *MUC5B* rs35705950 which has a frequency of around 9% in European populations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests an important role for host susceptibility in IPF pathogenesis. It provides a basis for future gene–environment interaction research and support for a global asbestos ban.

in men (male:female ratio 1.6), manual workers and those living in industrial areas,² patterns that are not unique to the UK.³ The prognosis is poor, with a median survival of 3 years.² The pathophysiology of IPF is complex and believed to be the outcome of epithelial injury, with a dysregulated repair process, in a susceptible host. Several gene polymorphisms which result in a vulnerable alveolar epithelium have been characterised; they include abnormalities in mucin genes (eg, *MUC5B*), surfactant protein genes and telomerase genes (eg, *TERT* and *TERC*).³

Clinical, radiological and histopathological findings in asbestosis and IPF are similar.^{4,5} 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'.^{6,7} *MUC5B*-expressing epithelial cells are the dominant mucous cell type of the honeycomb cysts that characterise the pattern of lung scarring, usual interstitial pneumonia (UIP), seen in both IPF and asbestosis.

The *MUC5B* promoter variant rs35705950 is the strongest common identified risk factor for IPF. The odds of developing pulmonary fibrosis are five

Practice

times higher for individuals carrying one copy of the disease allele, rising to 20 times higher for individuals with two copies, when compared with individuals carrying no copies of the disease allele. The frequency of the disease allele is around 9% in European ancestry populations. The variant increases airway expression of *MUC5B*^{8,9} and is also associated with increased risk of asbestosis, OR 3.5 (95% CI 2.4 to 5.1; $p < 0.001$).¹⁰ Toxicological studies show that asbestos exposure results in production of interleukin-1 beta (IL-1 β), a key proinflammatory cytokine in IPF and a potent stimulus for *MUC5B* expression.¹¹

In the UK, IPF mortality correlates strongly with mesothelioma mortality and lagged historic asbestos imports, ecological patterns that led Barber and his colleagues to hypothesise that 'a proportion of IPF mortality is in fact due to unrecognized asbestos exposure'.¹² Occult occupational asbestos exposure as a cause for otherwise 'idiopathic' pulmonary fibrosis has been an open question for at least 30 years¹³ and is brought to the fore in countries such as Brazil, Russia, India and China which use large quantities of asbestos, and by the continuing global rise in asbestos-related and IPF mortality rates.¹⁴ While occupational dust exposures in IPF have been examined by several previous case-control studies, recently reviewed in a joint American Thoracic Society—European Respiratory Society statement,¹⁵ none has focused on assessment of asbestos exposure. The IPF job exposures study (IPFJES) addresses the question of a role for asbestos exposure in IPF by means of a job exposure matrix based on occupational proportional mortality ratios for pleural mesothelioma,¹⁶ a validated source-receptor model¹⁷ and examination of gene-environment interactions.

METHOD

IPFJES is a multicentre, incident case-control study. Twenty-one hospitals in England, Scotland or Wales were selected on the basis of having a specialist IPF service, geographic dispersion and personal contacts.

Cases were men who were first diagnosed with IPF at a collaborating hospital between 1 February 2017 and 1 October 2019. The study was limited to men to increase power because men more often have occupational asbestos exposure than women. The diagnosis was made at a local multidisciplinary team meeting (MDT) using standard criteria based on clinical features, high-resolution CT and, when necessary, lung biopsy.¹⁸

At each participating hospital, we obtained a list of all outpatient clinics it was possible for the local research team to recruit from and then randomly selected a clinic from that list to serve as source clinic for the recruitment of controls. We did not exclude respiratory or any other clinic. If the clinic selected was unsuitable (it not proving possible to recruit four controls over the course of four clinics), a further random selection was made. As for cases, controls were men who attended the selected outpatient clinics between 1 February 2017 and 1 October 2019. They were frequency-matched to cases on age using five (sometimes 10) year age brackets and recruited in a 1:1 ratio to cases to achieve a predefined recruitment target.

Men unable to give informed consent or who had worked outside the UK for ≥ 1 year (not including work in the armed forces or merchant navy) were excluded from being cases or controls. Participants were recruited by local research teams who completed a case report form and collected a blood sample which were collated centrally.

A trained interviewer (RS or CJR) who was unaware of the case status of participants, administered a structured questionnaire by telephone, using a bespoke web application, to collect

information on lifetime occupations, smoking and dyspnoea (modified Medical Research Council—mMRC—dyspnoea questionnaire).¹⁹ For each occupation, we recorded job title, job tasks, employer and dates of employment. Occupations were automatically coded to a UK standardised occupational classification (SOC90).

Coded jobs were used to assign participants to categories of asbestos exposure risk by means of a job exposure matrix derived from occupational proportional mortality ratios for pleural mesothelioma.¹⁶ For participants who recalled work with asbestos, a detailed assessment of each work task was also recorded to estimate total fibre ml⁻¹ year asbestos exposure using a validated source-receptor model.^{17,20}

Primary and secondary outcome measures were prespecified for the main analysis (clinicaltrials.gov). The primary outcome measure was the association between asbestos exposure and IPF estimated using logistic regression for 'any' versus 'no' asbestos exposure and adjusting for age and smoking status. There were two secondary outcome measures: (1) The dose-response relationship between asbestos exposure and IPF estimated using logistic regression for categories of cumulative exposure and adjusting for age and smoking status. (2) Gene-environment interaction (for *MUC5B* rs35705950 and asbestos exposure) OR.

In a further non-specified analysis, we used multiple logistic regression to investigate gene-environment and gene-environment-environment interactions. We used a dominant rather than additive model in our interaction analysis to avoid model instability arising from the small number of participants with genotype TT.

We undertook further sensitivity analyses to investigate the importance of era by analysing only jobs that ended before 1980, minimum duration in a job by analysing only jobs with a duration of ≥ 5 years and cumulative 'dose' by multiplying duration in a job in years by a risk category weighting (office/low risk industrial 0, medium risk industrial 1, high risk construction/non-construction 2). To investigate the possibility of geographic confounding, we performed a sensitivity analysis restricted to participants who lived within 10 km of their recruiting hospital.

Further details regarding our methods, including details of our power calculation and ethical approval, are provided in the online supplemental file 1.

RESULTS

We recruited 516 cases and 511 controls. Twenty-two cases (4%), and 45 controls (9%) were withdrawn because they no longer wished to take part in the study, they did not respond after we called them on three occasions, or we were notified that they had died before interview. The remaining 960 participants (494 cases, 466 controls) comprise the study sample. Most centres failed to complete the requested screening logs so participation rates are uncertain.

The median year of birth and age was 1943 and 76 years for cases and 1945 and 74 years for controls (table 1). Most participants reported their ethnicity as white. Seventy-six per cent of cases and 70% of controls had ever smoked and only 7% of cases and 8% of controls were from higher professional socioeconomic groups.

All cases had a CT thorax which was reported as showing definite UIP in 266 (54%), possible UIP in 216 (44%) or 'other' in 12 (2%) patients. Nine cases (2%) had a lung biopsy because the CT was non-diagnostic; each of these was reported as compatible

Table 1 Participant characteristics (n=960)

Characteristic	Cases (n=494)	%	Controls (n=466)	%
Median age in years (IQR)	76 (71–81)		74 (69–79)	
Ethnicity				
White	479	97	449	96
Asian/Asian British	11	2	8	2
Black/African	2	0	7	2
Mixed/other	2	0	2	0
Social class*				
1	36	7	39	8
2	57	12	61	13
3	78	16	74	16
4	50	10	51	11
5	94	19	97	21
6	114	23	89	19
7	65	13	55	12
Smoking				
Current smoker	10	2	30	6
Ever smoked	373	76	327	70
Median pack years (IQR)	21 (10–38)		21 (9–36)	
mMRC†				
0	35	7	254	55
1	94	19	65	14
2	165	33	80	17
3	172	35	65	14
4	28	6	2	0
rs35705950 genotype	n=464		n=438	
GG	183	39	336	77
GT	248	53	97	22
TT	33	7	5	1

*Participants were assigned to National Statistics Socio-Economic analytic classes (NS-SEC) provided by the Office of National Statistics on the basis of their occupations. The seven classes used were: 1. higher managerial, administrative and professional occupations; 2. lower managerial, administrative and professional occupations; 3. intermediate occupations; 4. small employers and own account workers; 5. lower supervisory and technical occupations; 6. semi-routine occupations; 7. routine occupations. Further details are provided in the online supplemental file 1.

†mMRC (modified Medical Research Council) dyspnoea scale. 0. not troubled with breathlessness except with strenuous exercise; 1. troubled by shortness of breath when hurrying on the level or walking up a slight hill; 2. walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level; 3. stops for breath after walking about 100 yards or after a few minutes on the level; 4. too breathless to leave the house or breathless when dressing or undressing.¹⁹

with definite UIP. Cases were more breathless than controls as measured by mMRC dyspnoea scale.

Cases and controls had a mean (SD) of 4.6 (2.4) and 4.2 (2.2) jobs, respectively. Median (IQR) duration of a job for cases and controls was 5 (2–13) and 5 (2–14) years, respectively. Three hundred and twenty-six (66%) cases and 292 (63%) controls had ever had a high or medium asbestos exposure risk job (table 2) and did so for a median (IQR) of 25 (8–42) and 20 (6–41) years, respectively. The number of years worked in a medium or high risk job was similar between cases and controls (see figure 1).

A total of 457 asbestos exposed job tasks were recalled in sufficient detail to permit a fibre ml⁻¹ years estimate of exposure for 229 individual participants (122, 25% of cases and 107, 22% controls). Forty (33%) cases and 35 (32%) controls, equating to approximately 8% in each group, had cumulative estimates exceeding 25 fibre ml⁻¹ years.

Table 2 Occupational asbestos exposure in cases and controls (n=960)

Exposure*	Cases (n=494)	%	Controls (n=466)	%
Ever asbestos exposed	327	66	293	63
High-risk non-construction	65	13	51	11
High-risk construction	138	28	126	27
Medium risk industrial	124	25	116	25
Low risk industrial	94	19	97	21
Office	73	15	76	16
Number of patients who recalled working with asbestos (permitting a Fibre ml ⁻¹ year estimate)	22	25	107	23
Median fibre ml ⁻¹ years (IQR)	6 (0–63)		5 (0–60)	
≥100 fibre ml ⁻¹ years	27	5	24	5
≥50 fibre ml ⁻¹ years	34	7	29	6
≥25 fibre ml ⁻¹ years	40	8	35	8

*Categories of occupational asbestos exposure risk were defined on the basis of occupational proportional mortality ratios for mesothelioma¹⁶ and ever asbestos exposed was defined as ever having had a high or medium asbestos exposure risk job. Fibre ml⁻¹ year asbestos exposure estimates were calculated for participants who recalled working with asbestos using a source-receptor model.^{17,20}

Fibre ml⁻¹ years exposure assessments showed reasonable agreement with those made by an independent assessor (JWC) for a validation sample of low, medium and high exposure assessments (see online supplemental figure E2).

Table 3 shows the results of an adjusted multiple regression analysis which confirmed that ever having had a high or medium asbestos exposure risk job was not associated with IPF, OR 1.1 (95% CI 0.8 to 1.4; p=0.6). A history of ever smoking was significantly associated with IPF, OR 1.4 (95% CI 1 to 1.9, p=0.04) and interacted with ever having had a high or medium asbestos exposure risk job, OR 1.9 (95% CI 1 to 3.6; p=0.04).

Nine hundred and two (94%) of the 960 participants were genotyped for *MUC5B* rs35705950 (464 of 494 cases—93%,

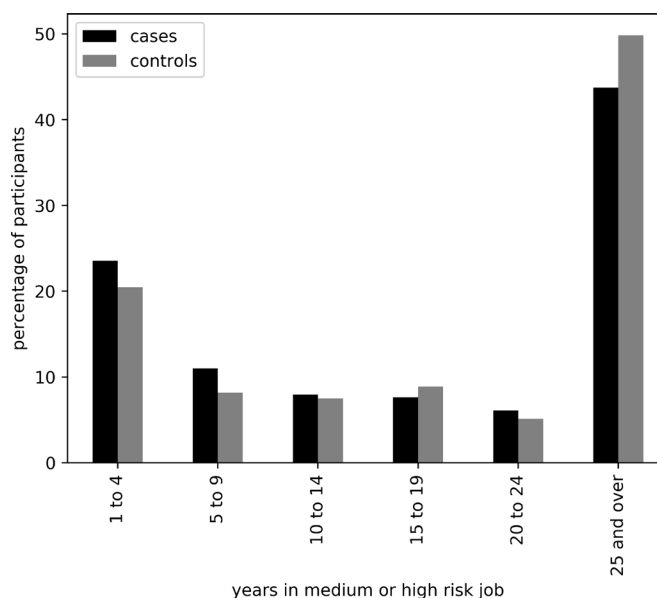


Figure 1 Years spent in medium or high risk jobs for all participants (n=960). A high or medium asbestos exposure risk job was defined on the basis of occupational proportional mortality ratios for mesothelioma.¹⁶

Table 3 Occupational asbestos exposure, smoking and IPF (n=960)

Exposure*	Adjusted OR† (95% CI; p value)
Ever asbestos exposed	1.1 (0.8 to 1.4; 0.60)
High-risk non-construction	0.9 (0.6 to 1.6; 0.8)
High-risk construction	1.1 (0.7 to 1.7; 0.73)
Medium risk industrial	0.9 (0.6 to 1.5; 0.78)
Low risk industrial	0.9 (0.6 to 1.4; 0.57)
Office	1
Ever smoked	1.4 (1 to 1.9; 0.04)
Interaction model (asbestos*smoking)	
Ever asbestos exposed	0.7 (0.4 to 1.2; 0.20)
Ever smoked	1.0 (0.6 to 1.6; 0.83)
Ever asbestos exposed and ever smoked interaction	1.9 (1 to 3.6; 0.04)

*Categories of occupational asbestos exposure risk were defined on the basis of occupational proportional mortality ratios for mesothelioma¹⁶ and ever asbestos exposed was defined as ever having had a high or medium asbestos exposure risk job.

†Adjusted for age, centre and smoking; smoking was not adjusted for when it was the exposure under consideration.

IPF, idiopathic pulmonary fibrosis.

and 438 of 466 controls—94%); 58 participants did not provide a sample. Being heterozygous (GT) had an adjusted OR of 4.7 (95% CI 3.5 to 6.3; $p < 0.001$) for disease while being homozygous (TT) had an adjusted OR of 12.0 (95% CI 4.6 to 31.6, $p < 0.001$). There was no evidence of interaction between *MUC5B* rs35705950 genotype and ever having a high or medium asbestos exposure risk job, adjusted OR 1.3 (95% CI 0.8 to 2.3; $p = 0.3$). In a non-specified analysis, when stratifying for genotype there was a statistically significant interaction between smoking and having ever worked in a high or medium asbestos exposure risk job, adjusted OR for interaction 5.4 (95% CI 1.8 to 15.6; $p = 0.002$) for carriers of the minor allele of *MUC5B* rs35705950 (GT or TT) but not for the wild-type GG, OR 1.3 (0.5 to 2.9, $p = 0.6$) (see [table 4](#))

Further analyses suggested that era, duration of job, cumulative 'dose' and distance from recruiting centre did not alter the observed associations between asbestos exposure and IPF risk. Further details are provided in the online supplemental file 1.

DISCUSSION

We undertook a case-control study to investigate historic occupational asbestos exposure as a potential risk factor for IPF in men. We found that asbestos exposure was common for both cases (66%) and controls (63%) with no significant difference between the two groups. A history of occupational asbestos exposure alone was not associated with increased IPF risk.

We identified a novel significant three-way gene-asbestos-smoking interaction. For individuals carrying the *MUC5B* rs35705950 minor allele, IPF cases were five times more likely than control subjects to report a combined history of cigarette smoking and work for at least 1 year in a high/medium risk asbestos exposure job—a relationship that was not seen with either environmental risk factor alone.

While analyses of interactions between asbestos exposure and *MUC5B* rs35705950, and between occupational asbestos exposure and smoking, were pre-registered; our three-way interaction was not. We were prompted to carry out the analysis after finding a significant interaction between occupational asbestos exposure and smoking, and reading that *MUC5B* rs35705950 predisposes to asbestosis in a paper that came out after the

Table 4 Occupational asbestos exposure, smoking, genotype and IPF; interaction terms and stratified analysis (genotyped participants only, n=902)

Exposure*	Adjusted OR† (95% CI; p value)
Interaction model (asbestos*smoking)	
Ever asbestos exposed	0.6 (0.4 to 1.1; 0.08)
Ever smoked	0.9 (0.6 to 1.5; 0.68)
Ever asbestos exposed and ever smoked interaction	2.2 (1.2 to 4; 0.01)
Interaction model (asbestos*genotype)	
Ever asbestos exposed	1.0 (0.7 to 1.5; 0.84)
Genotype	3.7 (2.4 to 5.8; 0.001)
Ever asbestos exposed and genotype	1.3 (0.8 to 2.3; 0.3)
Interaction model (smoking*genotype)	
Ever smoked	1.29 (0.86 to 1.92; 0.22)
Genotype	3.95 (2.33 to 6.69; 0.001)
Ever smoked and genotype	1.15 (0.62 to 2.13; 0.65)
Stratified interaction model (asbestos*smoking)	
GT or TT	
Ever asbestos exposed	0.4 (0.2 to 1; 0.06)
Ever smoked	0.6 (0.3 to 1.3; 0.2)
Ever asbestos exposed and ever smoked interaction	5.4 (1.8 to 15.6; 0.002)

*Ever asbestos exposed was defined as ever having had a high or medium asbestos exposure risk job, defined on the basis of occupational proportional mortality ratios for mesothelioma.¹⁶ Genotype of *MUC5B* rs35705950, T is the minor allele.

†Adjusted for age±smoking, smoking was not adjusted for when it was considered as an exposure. Centre was not adjusted for in this analysis because numbers were too small for one centre. Analysis limited to the 20 centres which did have sufficient numbers showed that adjusting for centre did not significantly change our results. IPF, idiopathic pulmonary fibrosis.

initiation of our study.¹⁰ The authors posit a common *MUC5B*-driven pulmonary fibrosis endotype. This, together with our knowledge of smoking being a common risk factor for IPF and asbestosis, and of potential mechanisms for asbestos sensing leading to increased *MUC5B* secretion,¹¹ led us to hypothesise a three-way interaction. In a sensitivity analysis, when considering only the 253 of our 464 genotyped cases that had definite UIP, the OR for the three-way interaction was greater still, OR 9.7 (95% CI 2.9 to 32.9; $p < 0.001$) versus 5.4 (95% CI 1.8 to 15.6; $p < 0.002$).

Pulmonary fibrosis is an age-related disease caused, it is assumed, by epithelial injury in individuals with appropriate genetic susceptibility, which may or may not have an identifiable cause.²¹ Polymorphism of the *MUC5B* promoter allele is common (minor allele frequency of 9% in European populations) and a strong genetic risk factor for a range of fibrotic lung diseases including IPF,²² asbestosis,¹⁰ chronic hypersensitivity pneumonitis²³ and rheumatoid arthritis associated interstitial lung disease.²⁴ In keeping with previous findings, the minor allele frequency in our study was significantly higher in IPF cases (34%) than controls (12%) and was strongly associated with disease in an allele dose-dependent fashion. A history of cigarette smoking, another established risk factor in IPF,²⁵ was also significantly more common among cases than controls (76% vs 70%), with an adjusted OR of 1.4. The prevalence of ever smoking was very similar to that reported from other UK studies of IPF.²⁶ Interestingly, there was interaction between ever smoking and occupational asbestos exposure, with an adjusted OR of 1.9. There is evidence from radiographic studies that

smoking increases the attack rate and/or progression rate for asbestosis.²⁷

Given concern that 'occult' asbestosis may be misclassified as IPF^{6,7} and the ecological association between IPF mortality and historic UK asbestos imports,¹² we carried out detailed interviews to examine a potential causative link between MDT-diagnosed IPF and previous occupational asbestos exposure. To avoid sole reliance on patient recall, which is unreliable,²⁸ we used a simple job exposure matrix based on occupational proportional mortality ratios for mesothelioma, and (where possible) a validated source-receptor model. We limited our study to men to increase power because occupational asbestos exposure is more common in men than women.¹⁶ We found that working for at least a year in a high/medium risk asbestos exposure job was common in both cases (66%) and controls (63%) with no significant difference between the two in terms of social class, work duration or cumulative lifetime exposures. These findings were unaffected by adjustment for age, recruiting centre and smoking. Similarly, where an estimate was possible, there were no differences in quantified exposures. These findings indicate that, at least in UK men, there is no overall association between occupational asbestos exposure alone and risk of IPF.

The question of whether some cases should more properly be labelled as asbestosis naturally arises but we note that 8% of both cases and controls had estimated cumulative asbestos exposures in excess of 25 fibre ml⁻¹ years, the Helsinki criteria exposure threshold at which cases of asbestosis may occur.²⁹ Thus, in this generation of British men with interstitial fibrosis, a history of heavy asbestos exposure is common but no more so than in other men attending hospital. Asbestos control measures have significantly reduced exposure in subsequent generations.³⁰

A diagnosis of 'asbestosis' is made in patients with UIP who have had a substantial exposure to asbestos. However, what constitutes a sufficient exposure to cause asbestosis and, in particular, at what level of cumulative exposure the risk of pulmonary fibrosis is more than double the risk in the general population, have not been formally investigated. In this study, the level of asbestos exposure was not different in the cases of UIP from the control group. No case of UIP could therefore be confidently attributed to asbestos exposure and therefore in no case could a diagnosis of asbestosis be logically made.

Prior to our study, seven case-control studies had not found self-reported occupational asbestos exposure to be a significant risk factor in IPF.^{13,31-36} In contrast, Abramson *et al*³⁷ recently published a large IPF case-control study from Australia that did find a significant association, both for self-reported asbestos exposure and cumulative estimates quantified by an asbestos job exposure matrix. Interestingly, although that study reported very low cumulative asbestos exposures in cases (mean 0.23 fibre ml⁻¹ years), a dose-response relationship between exposure and disease was still apparent. Our study found that the median duration of work in a high/medium risk asbestos exposure job for MDT-diagnosed IPF cases was 20 years, with 57% of patients having worked for at least 5 years in a medium risk job or at least 1 year in a high risk job. One in four IPF cases were able to recall previous occupational asbestos exposure, and of these, a third had had an estimated lifetime exposure in excess of 25 fibre ml⁻¹ years.

Genetic susceptibility to IPF is complex, and a limitation of our study was that we were unable to examine gene-environment interactions for the other polymorphisms associated with increased risk of disease. We assessed occupational asbestos exposure in 494 male cases, more than in the largest previous study.³⁷

We chose hospital, rather than population-based controls, as a more valid basis for comparison with hospital diagnosed cases of IPF, being representative of the population who would have been seen in the hospital had they become a case.³⁸ The choice had the added advantage of a higher response rate than would be anticipated for population-based controls; just 28% of community controls responded in a recent UK IPF case-control study³⁹ while hospital controls generally have higher response rates.⁴⁰ Moreover, response rates are associated with socioeconomic status and there is a tendency for more deprived socioeconomic groups to be under-represented and more affluent groups over-represented in population control samples.¹⁶ This risks selection bias, particularly in occupational studies, and the risk is greater with lower response rates.⁴¹ When the response rate is less in lower socioeconomic groups, where the prevalence of exposure to asbestos is greater, the prevalence of exposure in the control group will be lower than the true prevalence, leading to over estimation of the risk of disease associated with the exposure.

The study's design and pre-specified analyses were pre-registered. During the asbestos exposure assessment process, the assessors were unaware of case-status and two validated means of assessing UK asbestos exposure were used, in both groups identically, to permit quantitative and semiquantitative analysis. Our exposure estimates based on job title are very close to those from a recent, UK mesothelioma case-control study using the same method, in which 65% of male general population controls aged 37-79 had ever worked in an occupation at high or medium risk for asbestos exposure.¹⁶ It is well established that men born in the UK in the 1940s, working in the 1960s and 1970s and particularly in the construction industry, had much heavier occupational asbestos exposures than subsequent generations.³⁰ While our estimates of asbestos exposure may appear in disagreement with those for UK participants in a large multicentre lung cancer case-control study (INCO study),⁴² this is explained by the different approach taken. The INCO study reported the percentage of job periods, across all participants (a participant can have more than one job), that were asbestos exposed, which was between 20% and 35% depending on method used, while we defined asbestos exposure for a participant as ever having had a job at medium/high risk. Indeed, when performing a similar job period-level analysis in IPFJES, we found that 1491 of 4192 job periods, or 36%, were exposed.

The estimates derived from the source-receptor model were dependent on participants recalling work with asbestos. While this may be a relatively insensitive measure we do not think it will have introduced any important bias; indeed, since cases were probably more likely to have been questioned about asbestos exposure prior to our study, our estimates may have been biased away from the null. A limitation is that we lack comprehensive data on participation rates. While collaborating hospitals were provided with screening logs and asked to report monthly the number of eligible participants identified, approached and recruited, most found this difficult to organise. Figures from the three centres that did provide detailed participation rates suggest an overall participation rate of approximately 90% for cases and 85% for controls.

Our study is the first to investigate the interaction between established environmental and genetic risk factors for pulmonary fibrosis, a combination of historic occupational asbestos exposure, previous cigarette smoking and a *MUC5B* polymorphism. After stratifying for genotype, we found a significant three-way interaction between having ever smoked and having ever worked for at least a year in a high/medium asbestos exposure risk job (OR 5.4) for carriers of the minor allele of *MUC5B*

rs35705950 (GT or TT). This triple combination of risk factors was present in 32% of the IPF cases who were genotyped. One interpretation of these findings is that in genetically susceptible individuals, chronic exposure to a combination of asbestos fibres and cigarette smoke results in inflammation and epithelial injury sufficient to result in pulmonary fibrosis. This model has biological plausibility since the *MUC5B* promoter variant is associated with overexpression of *MUC5B* leading to mucociliary dysfunction and retention of inhaled particles.^{9,27} In mouse studies, both cigarette smoke and asbestos exposure increase the production of reactive oxygen species that are thought to be important in the pathogenesis of pulmonary fibrosis.⁴³ Asbestos exposure and smoking also activate the NLRP3 inflammasome resulting in increased IL-1 β release, a potent stimulus for increased *MUC5B* expression.^{11 44-46}

Overall, we find no evidence that occupational asbestos exposure alone is associated with IPF. This highlights the inherent difficulties that ILD MDTs face in terms of correctly differentiating patients with IPF and asbestosis; the majority of men in their 70s in the UK who attend hospital with IPF have worked for prolonged periods in high or medium risk asbestos exposure jobs. That such a level of exposure is no more common in men with fibrosis than in others attending hospital suggests that making a diagnosis of asbestosis on the basis of an exposure history alone is, at best, an implicit acknowledgement of host susceptibility.

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Contributors CJR, CB, CM, MM, ANT, JWC, PC made substantial contributions to the design, analysis and interpretation of the work. CJR and RS made substantial contributions to the acquisition of data for the work. All authors contributed to revising the work critically for important intellectual content and approved the final version. CJR is responsible for overall content as guarantor.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by East Midlands - Nottingham 1 Research Ethics Committee REC reference: 17/EM/0021IRAS project ID: 203355. Participants gave informed consent to participate in the study before taking part.

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Online supplement

Ethical approval

The study was approved by the NHS Health Research Authority (IRAS project ID 203355,

REC reference 17/EM/0021) and the sponsor was Imperial College London.

Control clinics

The composition of the control population was as follows:

Centre number (control source clinic)	Cases (N=494)	Controls (N=466)
1 (General Surgery)	42	39
2 (Gastroenterology/Stroke) ¹	13	11
3 (Cardiology)	38	36
4 (Urology)	52	52
5 (Diabetes/Rheumatology) ¹	40	31
6 (Sleep Apnoea)	34	37
7 (Neurology)	15	16
8 (ENT)	40	39
9 (Rheumatology)	31	29
10 (Oncology)	21	73 ²
11 (Urology)	11	11
12 (Haematology)	4	3
13 (Respiratory)	13	14
14 (Cardiology)	20	16
15 (Cardiology)	15	14
16 (Orthopaedics)	39	2 ³
17 (Asthma)	6	6
18 (Hypertension)	15	1 ³
19 (General Surgery)	7	9
20 (Urology)	31	25
21 (Respiratory)	7	2

¹ The control clinic changed at these two sites because of slow recruitment (defined as fewer than four controls recruited over the course of four clinic attendances).

² Controls were over-recruited at the local participating centre to help achieve the recruitment target.

³ Controls were under-recruited because of local research staffing shortage.

The approach of obtaining a list of all outpatient clinics it was possible for the local research team to recruit from and then randomly selecting a clinic from that list to serve as source clinic for the recruitment of controls was taken for two main reasons. Firstly, it is practically convenient to have a single clinic to recruit controls from. There is a single identifiable consultant who can consent to his or her clinic patients being approached and it is easier for the research team to form a relationship with the clinic staff. Secondly, the use of randomisation should, all else being equal, avoid the clinics (and therefore the patients within them) selected being systematically positively or negatively associated with occupational asbestos exposure.

Power calculation

Prior data indicated that the probability of occupational asbestos exposure in UK men aged 37-79 is 0.65.⁽¹⁾ If the true OR for disease in exposed men is 1.5, we calculated we would need to recruit 460 cases and controls, with power of 80% and significance threshold 0.05; our planned sample size included a margin for model stability and incomplete data. In a planned secondary analysis we investigated 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 of 1.5 for asbestos exposure and

of 6.8 for rs35705950, 460 cases would be required to detect a minimum interaction OR of 5.0.

Genotyping

DNA was extracted from whole blood samples using a Nucleon™ BACC3 Genomic DNA Extraction Kit (GE Healthcare). Genotypes of the *MUC5B* SNP rs35705950 were determined using TaqMan assays (Life Technologies, Carlsbad, CA) in 96-well plates, and fluorescence read using a Viia7 Sequence Detection System (Applied Biosystems).

Analysis code

We undertook statistical analyses using Python, SciPy, Statsmodels, and Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Analysis code is available online:

https://github.com/drcjar/ipfies/blob/master/notebooks/8.%20ipfies_paper_analysis.ipynb

Coding socio-economic class

SOC90 coded jobs were also used to assign National Statistics Socio-Economic analytic classes (NS-SEC). The Office of National Statistics provides a lookup to assign each SOC90 code to one of eight classes:

1. Higher managerial, administrative and professional occupations
2. Lower managerial, administrative and professional occupations
3. Intermediate occupations

4. Small employers and own account workers
5. Lower supervisory and technical occupations
6. Semi-routine occupations
7. Routine occupations
8. Never worked and long-term unemployed

We then assigned each individual to a single code by calculating the median code for all of the jobs they had held.

Asbestos job exposure matrix

For all participants SOC90 coded jobs from the lifetime occupational history they provided were used to assign them to one of five main categories based on the highest risk job ever held(1):

1. High-risk non-construction
2. High-risk construction
3. Medium risk industrial
4. Low risk industrial
5. Office

Mapping of SOC90 code to occupational asbestos exposure categories was primarily based on occupational proportional mortality ratios (PMRs) for mesothelioma (see Figure E1). The categorisation was developed by staff who were blind to case-control status. In addition to using PMRs for mesothelioma to assist categorisation they used

knowledge of the details of the details of the job and location.(1) Ever exposed was defined as ever having a medium or high risk asbestos exposure category job.

Figure E1

<i>Job category and occupation</i>	<i>SOC 90 codes & criteria for classification</i>	<i>PMR[†]</i>
Non-construction high risk occupations		128.4
Metal plate worker	533, 534	331.8
Coach & vehicle body builders	541	527.5
Asbestos product manufacturer	Hands-on making asbestos products in regulated industry	139.4
Laggers and electrical, energy, boiler attendants	893 plus 896, 921, 929, 990 further categorised on job title	121.8
Docker, shipbuilding or working on board ship	880, 332, 903 plus 169, 173, 174, 239, 385, 463, 620, 621, 630, 900, 930, 952, 953 further categorised on job title & anyone who spent >50% of time on board ship/in a shipyard	135.2
Navy	"Royal Navy", or equivalent, as employer	125.6
Construction		188.9
Carpenters	570, 920	381.0
Plumbers	532, plus 913 further categorised on job title	361.8
Electricians	521, plus 913 further categorised on job title	259.0
Painters & decorators	507	170.8
Other construction workers	111, 500-506, 509, 885, 886, 895, 896 (if not classified as lagger, above), 921, 923, 924, 929 plus 990 & 913 further categorised on job title	123.0
Medium risk industrial		130.1
Metal working production & maintenance fitters	516 plus 913 further categorised on job title	209.6
Railway worker	881-884, 922	74.2
Chemist or industrial scientist	200, 300-302, 309	159.0
Surveyor or inspector	110, 260, 262, 311	109.7
Metal machining & instrument makers nec.	510-515 517-519	73.0
Electrical & electronic trades nec.	520, 522-529	135.6
Welding, steel erecting & fixing	535-537	173.9
Metal working process operatives	830-844	122.3
Assemblers & routine process operatives	850-869	75.1
Plant & machine operatives nec.	887-892, 894, 897-899	104.8
Low risk industrial		69.4
Motor mechanic	540	47.6
Draughtsmen	310	150.3
Engineers & technologists nec.	210-219	140.6
Stores & warehousemen	440-441	72.4
Armed forces nec.	150-151, 600-601	77.5
Drivers & road transport workers	731, 870-875	49.1
Other industrial not elsewhere classified	113, 153, 171, 304, 348, 396, 531, 542-544, 553, 561, 569, 571, 590, 596, 597, 599, 611, 612, 615, 619, 631, 642, 672, 699, 733, 801, 809, 811, 820, 822, 824, 825, 829, 910, 911-913, 919, 923, 924, 931, 933, 934, 940, 941, 955, 956, 958, 990, 999 nec & anyone spent >75% of time in heavy industry (e.g. power station), factory or warehouse	69.8
Office and other low risk		58.7
	101, 120-127, 130-132, 139, 154, 155, 160, 169, 170, 172-179, 190, 191, 220-224, 230-235, 239-242, 250-253, 260, 261, 270, 271, 290-293, 320, 340-347, 361-363, 370, 371, 380, 381, 383-387, 390, 392, 399-401, 410-412, 420, 421, 430, 450-452, 459-462, 490, 556, 559, 560, 569, 580-582, 592, 594, 595, 598, 610, 619-622, 630, 640-644, 650-652, 659-661, 670, 671, 673, 690, 691, 699, 700-703, 710, 719-722, 730, 732, 790-792, 900-904, 950-956, 958 & nec	

[†] Average PMR using all SOC codes contributing to job category

Figure E1: Classification of job categories with average national mesothelioma PMRs.

Table 2.3.2 in Occupational, domestic and environmental mesothelioma risks in Britain.

(1)

For analysis of categories of exposure participants were assigned to the highest risk category they ever had a job in.

Asbestos exposure assessment using a source receptor model

For participants who recalled carrying out work with asbestos a detailed assessment of each work task was recorded. A fibre.ml⁻¹.year asbestos exposure (AE) estimate was calculated using a source-receptor model. (2)(3)

First we calculated AE for each task as follows:

$$AE = E * H * LC$$

with parameters for the type of asbestos used (substance emission potential, E), what was done with it (activity emission potential, H), and whether there were any local exposure controls, for example wetting (local controls, LC).

AE for each task was then weighted according to the total amount of time spent performing the task and how well ventilated the room the activity was carried out in was (general ventilation parameters, D)(4), to arrive at a task fibre.ml⁻¹.year exposure estimate.

$$\text{fibre.ml}^{-1}.\text{year (job task)} = AE * \text{task_duration} * (\text{task_frequency} / \text{periodicity}) * \text{job_duration} * D$$

Task fibre.ml⁻¹.year exposure estimates were then summed at an individual participant level to provide an overall fibre.ml⁻¹.year estimate. A random sample of five high (top 25% of values), five medium (25-75% centile), and five low (bottom 25% of values) estimates (N=15) were independently assessed by a hygiene assessment expert who was blind to participant case status. The independent assessments tended to be lower than study assessments but there was overall acceptable agreement between assessments assessed using the Bland-Altman method. (see Figure E2)

Figure E2

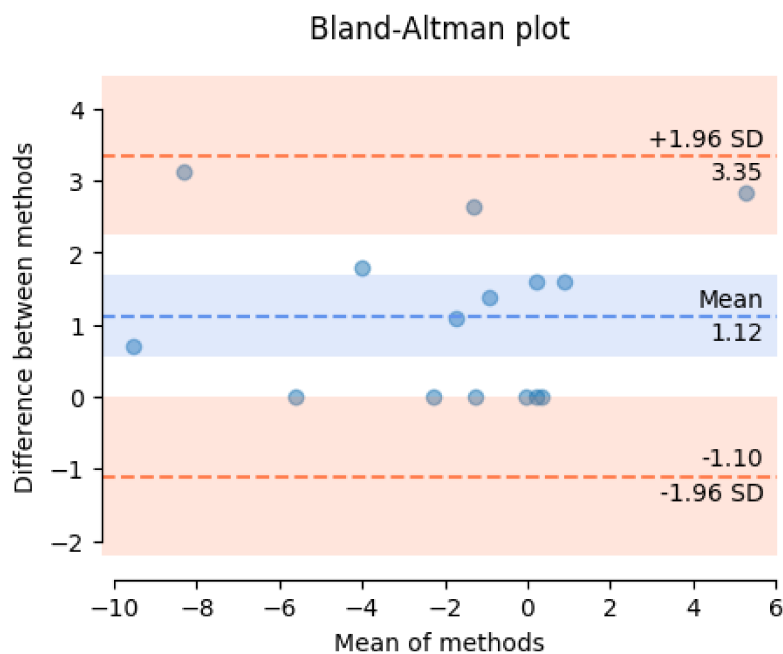


Figure E2: Independent validation of fibre.ml⁻¹.year exposure assessments. A sample of study assessments were repeated independently by an independent assessor. Difference

between methods is study assessment minus the independent assessor assessment.

Mean of methods is the average of the two assessments.

Blinding

Several measures were taken to ensure that, as far as possible, the telephone interviewer was blind to the case status of the research participant. Details of participants, including their case status, were entered into a bespoke web application. The application was used to carry out a telephone interview and by design hid the case status of participants from the interviewer. The interviewer elicited a lifetime occupational history and dynamically assigned a SOC90 code for each job title using the application. Questions regarding asbestos exposure were not asked until the end of the interview unless the participant volunteered working with asbestos. The application of the job exposure matrix and, if the participant recalled asbestos exposure, calculation of the estimated cumulative asbestos exposure was carried out algorithmically using data extracted from the interview application.

Sensitivity analyses

As a result of increasing awareness, and regulation, occupational asbestos exposure was significantly less widespread after 1980.⁽⁵⁾ To investigate whether occupational asbestos exposure might be associated with IPF during this period we performed a sensitivity analysis by only including participants' jobs that ended before 1980. We did not observe a significant association. We also performed sensitivity analyses limiting to jobs that started before 1980, participants born prior to 1965, and considering only jobs before

age 45(6); there was no significant association between asbestos exposure and IPF for these.

Sensitivity analysis (limited to jobs that ended before 1980, N=771)

Exposure*	Adjusted OR† (95%CI;p-value)
ever asbestos exposed	0.9(0.7-1.3;0.66)
high-risk non-construction	1.1(0.6-1.9;0.79)
high-risk construction	1(0.6-1.5;0.84)
medium risk industrial	0.8(0.5-1.3;0.43)
low risk industrial	1(0.6-1.6;0.89)
office	1
ever smoked	1.3(0.9-1.9;0.13)
interaction model (asbestos*smoking)	
ever asbestos exposed	0.6(0.3-1.2;0.14)
ever smoked	1(0.6-1.7;0.98)
ever asbestos exposed and ever smoked interaction	1.7(0.8-3.5;0.15)

*Categories of occupational asbestos exposure risk were defined on the basis of occupational proportional mortality ratios for mesothelioma(1) and ever asbestos exposed was defined as ever having had a high or medium asbestos exposure risk job.

†Adjusted for age, centre, and smoking; smoking was not adjusted for when it was the exposure under consideration.

Sensitivity analysis (limited to jobs that participants spent 5 or more years in, N=957)

Exposure*	Adjusted OR† (95%CI;p-value)
ever asbestos exposed	0.9(0.7-1.2;0.59)
high-risk non-construction	0.7(0.4-1.2;0.2)

high-risk construction	0.9(0.6-1.4;0.77)
medium risk industrial	0.7(0.5-1.1;0.89)
low risk industrial	0.7(0.5-1.1;0.1)
office	1
ever smoked	1.4(1-1.9;0.03)
interaction model (asbestos*smoking)	
ever asbestos exposed	0.7(0.4-1.1;0.11)
ever smoked	1.1(0.7-1.7;0.58)
ever asbestos exposed and ever smoked	1.6(0.9-3;0.12)
interaction	

*Categories of occupational asbestos exposure risk were defined on the basis of occupational proportional mortality ratios for mesothelioma(1) and ever asbestos exposed was defined as ever having had a high or medium asbestos exposure risk job.

†Adjusted for age, centre, and smoking; smoking was not adjusted for when it was the exposure under consideration.

Sensitivity analysis (limited to participants within 10km of the recruiting hospital, N=426)

To investigate the importance of distance from recruiting hospital we estimated participants distance from the hospital by measuring the distance between their registered primary care provider (assumed to approximate residential address) and their recruiting hospital in kilometres(km) using postcode centroid data and Vincenty's formulae, we then analysed participants for whom this distance was less than 10km.

Exposure*	Adjusted OR† (95%CI;p-value)
ever asbestos exposed	1.3(0.8-2;0.37)

high-risk non-construction	1(0.4-2.3;0.96)
high-risk construction	1.1(0.5-2.2;0.86)
medium risk industrial	0.9(0.4-1.9;0.71)
low risk industrial	0.7(0.3-1.5;0.29)
office	1
ever smoked	1.3(0.8-2.1;0.35)
interaction model (asbestos*smoking)	
ever asbestos exposed	1 (0.4-2.4;0.95)
ever smoked	1(0.4-2.3;0.99)
ever asbestos exposed and ever smoked interaction	1.4(0.5-4.1;0.5)

*Categories of occupational asbestos exposure risk were defined on the basis of occupational proportional mortality ratios for mesothelioma(1) and ever asbestos exposed was defined as ever having had a high or medium asbestos exposure risk job.

†Adjusted for age, centre, and smoking; smoking was not adjusted for when it was the exposure under consideration. One centre was excluded from the analysis because it recruited no control participants within 10km.

Cumulative 'dose' based on occupational asbestos exposure (inferred by job title)

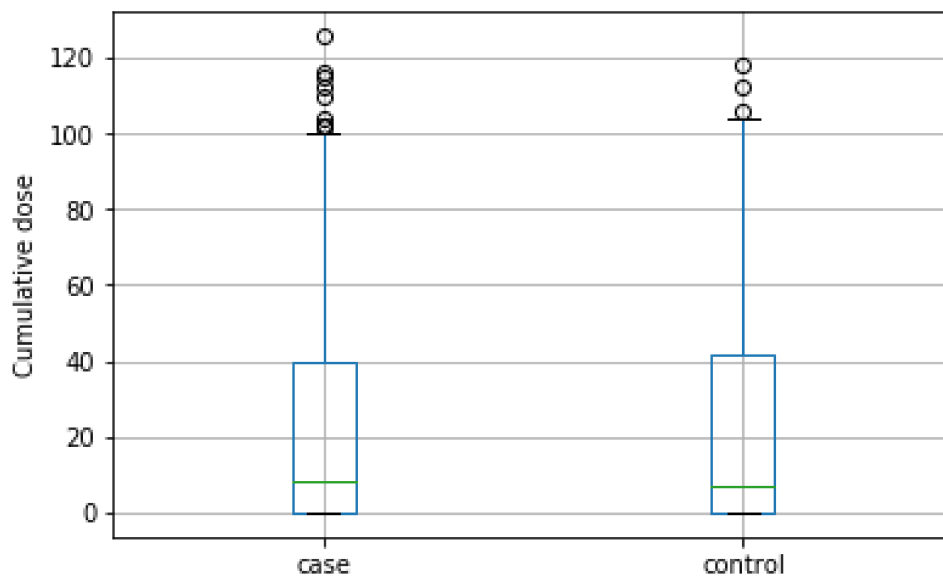
To investigate cumulative 'dose' of exposure based on job title a score was assigned based on asbestos exposure risk category of each job as follows:

- high-risk non-construction : 2
- high-risk construction : 2
- medium risk industrial : 1

- low risk industrial : 0
- office : 0

Scores were then multiplied for each job by the duration in years of the job and then summed at participant level.

	N	mean	std	min	25%	50%	75%	max
cases	494	24	30.6	0	0	8.5	39	126
controls	466	24	30.4	0	0	6.5	42	118



Boxplot of cumulative asbestos exposure estimates (inferred from job title) for cases and controls (N=960)

MUC5B* rs35705950 minor allele frequency for genotyped cases, case subsets, and controls (N)

	IPF	IPF	IPF	IPF asbestos	IPF ≥25	Hospital
	IPF	asbestos	≥25	exposed	fml.yrs	controls
	smoker	exposed	fml.yrs	AND smoker	fml.yrs AND	(438)
	(464)	(352)	(309)	(253)	smoker (30)	

GG	183	135	121	13	94	11	336
GT	248	189	164	21	137	15	97
TT	33	28	24	5	22	4	5
MAF	34	35	34	40	36	38	12

*Genotype of *MUC5B* rs35705950, T is the minor allele. MAF is minor allele frequency (%). fml-yrs is cumulative fibre.ml⁻¹.years of asbestos exposure. Smoker is defined as ever smoked. Ever asbestos exposed is defined as ever having had a high or medium asbestos exposure risk job, defined on the basis of occupational proportional mortality ratios for mesothelioma.(1)

Further information, including the full study protocol, all analysis code, and all other study documentation, is available from the study website <https://ipfjes.org/>

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