



ORIGINAL RESEARCH

Occupational and environmental risk factors for idiopathic pulmonary fibrosis in Australia: case-control study

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ABSTRACT

Introduction Idiopathic pulmonary fibrosis (IPF) is a lung disease of unknown cause characterised by progressive scarring, with limited effective treatment and a median survival of only 2–3 years. Our aim was to identify potential occupational and environmental exposures associated with IPF in Australia.

Methods Cases were recruited by the Australian IPF registry. Population-based controls were recruited by random digit dialling, frequency matched on age, sex and state. Participants completed a questionnaire on demographics, smoking, family history, environmental and occupational exposures. Occupational exposure assessment was undertaken with the Finnish Job Exposure Matrix and Australian asbestos JEM. Multivariable logistic regression was used to describe associations with IPF as ORs and 95% CIs, adjusted for age, sex, state and smoking.

Results We recruited 503 cases (mean±SD age 71±9 years, 69% male) and 902 controls (71±8 years, 69% male). Ever smoking tobacco was associated with increased risk of IPF: OR 2.20 (95% CI 1.74 to 2.79), but ever using marijuana with reduced risk after adjusting for tobacco: 0.51 (0.33 to 0.78). A family history of pulmonary fibrosis was associated with 12.6-fold (6.52 to 24.2) increased risk of IPF. Occupational exposures to secondhand smoke (OR 2.1; 1.2 to 3.7), respirable dust (OR 1.38; 1.04 to 1.82) and asbestos (OR 1.57; 1.15 to 2.15) were independently associated with increased risk of IPF. However occupational exposures to other specific organic, mineral or metal dusts were not associated with IPF.

Conclusion The burden of IPF could be reduced by intensified tobacco control, occupational dust control measures and elimination of asbestos at work.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a lung disease of still poorly defined cause characterised by progressive scarring ultimately causing respiratory failure and death. Despite recent developments in antifibrotic therapy,^{1,2} these new therapies only slow progression and are not curative. Median survival time for IPF is still less than that of many cancers, and was reported as only 2–3 years prior to antifibrotic therapies.³ However, survival is

Key messages**What is the key question?**

- Which occupational and environmental exposures are associated with idiopathic pulmonary fibrosis (IPF) in Australia?

What is the bottom line?

- Occupational exposure to secondhand smoke was associated with a doubling, respirable dust with 1.4-fold and asbestos with 1.6 fold increased risks of IPF; however, occupational exposures to other specific organic, mineral or metal dusts were not associated with IPF. Family history of pulmonary fibrosis was also a strong risk factor.

Why read on?

- The burden of IPF could be reduced by intensified tobacco control, occupational dust control measures and elimination of asbestos at work.

likely to improve by 1–2 years now that these have become the gold-standard treatment for IPF.^{4,5} Although IPF is a relatively rare disease, the public health impact of IPF-related mortality is similar in magnitude to many high priority malignancies including non-Hodgkin's lymphoma, renal cancer and oesophageal cancer.⁶

Since 1990, case-control studies have been conducted in the UK, USA, Japan, Sweden, Egypt, Korea and Italy to assess whether environmental and occupational exposures were associated with 'IPF'.^{7–17} In a meta-analysis of six studies, six exposures were significantly associated with IPF (summary ORs (95% CIs)), including metal dust (2.44 (1.74 to 3.40)), livestock (2.17 (1.28 to 3.68)), stone/sand (1.97 (1.09 to 3.55)), wood dust (1.94 (1.34 to 2.81)), agriculture/farming (1.65 (1.20 to 2.26)) and ever smoking (1.58 (1.27 to 1.97)).¹⁸ A more recent statement from the American Thoracic Society and European Respiratory Society (ATS/ERS) included 15 relevant case-control studies.¹⁹ Pooled ORs were increased for vapours, gas, dust or fumes (VGDF), metal dusts, wood dusts and silica. Individual studies have also found increased risks



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for IPF associated with domestic exposures to mould⁹ and wood fires,⁷ but these findings have not been replicated elsewhere.

Nonetheless the aetiology and pathogenesis of IPF are still not well understood. This means that the identification of risk factors for IPF, especially occupational and environmental exposures, remains critically important. These may at least partly clarify the pathogenesis of this apparently idiopathic disease, and also inform prevention strategies, early diagnosis and screening in at-risk populations and assist in the development of novel therapies.⁶ While there were some estimates of how many Australians have been exposed to occupational carcinogens during their careers,²⁰ not much has been known about other potentially hazardous inhaled agents at work. Assessment of exposure status using only current or last job data could miss earlier exposures with potential long-term effects, and would not account for changes to occupational exposures over time.²¹

Our aim was to identify potential occupational and environmental exposures associated with IPF in Australia.

METHODS

Study design and recruitment

We conducted a case-control study focusing on occupational and environmental risk factors for IPF. Incident or prevalent cases were recruited from the Australian IPF Registry (AIPFR), a national registry of IPF patients which was established by the Lung Foundation Australia in 2012.^{4 22} Respiratory physicians throughout Australia referred to the AIPFR patients who have a clinical diagnosis of IPF. High-resolution chest CT scans and histopathology (in cases where lung biopsy was performed) were collected for expert review. All Registry subjects underwent a multidisciplinary diagnostic review, to confirm the diagnosis of IPF according to the 2011 IPF diagnostic guidelines³—this process has been described in more detail elsewhere.²² The IPF Registry initial questionnaire collected data including patient demographics, smoking, family history, environmental exposures and detailed occupational history. Participants were classified as never smokers, former smokers or current smokers (of at least one cigarette a day for the past year). Family history was considered positive if any member of the immediate family had a history of pulmonary fibrosis (see online supplementary appendix 1 for further details).

Population-based controls were recruited by random digit dialling, frequency matched 2:1 to cases on age, sex and state of residence.

Data collection

Computer-assisted telephone interviews collected data including demographics, smoking, family history, environmental exposures and detailed occupational histories. The specifically trained interviewers administered questions based on those in the AIPFR case questionnaire.

Occupational exposure assessment was conducted using these self-reported occupational histories. Each reported job was coded to the Finnish Job Exposure Matrix (FinJEM)²³ to assign most of the occupational exposures. Participants were considered exposed to an agent in a job if the probability of exposure was greater than 25%.²⁴ Coding of the occupations was originally undertaken by a researcher (SMA) blinded to case-control status and then all codes were checked by the study occupational hygienist (GPB). In addition, asbestos exposures were also estimated using the Australian asbestos JEM (AsbJEM) for combinations of occupation, industry and time period. Time periods were based on changes in Australian asbestos consumption and

legislation: 1943–66, 1967–86, 1987–2003. Any jobs later than 2003 were excluded because of legislative changes.²⁵

All participants provided informed consent.

Sample size

The expected prevalences of occupational exposures were based on the Australian Work Exposure Study (AWES)²⁰: second-hand smoke 24.8% males, 5.8% females; silica 11.6% males, 1.0% females; Wood dust 9.6% males, 0.7% females; and metal (lead) dust 10.7% males, 0.7% females. Based on registry data, we expected 70% of participants to be male and 30% female. Sample size calculations used 80% power and two-sided alpha 0.05 throughout. Given 1:2 matching of cases to controls, we required 299 cases and 598 controls to detect an OR of 2 for silica, wood or metal dust. Similarly to detect OR=1.5 for secondhand smoke, we required 433 cases and 866 controls.

Statistical methods

Characteristics of cases and controls were compared with descriptive statistics including frequencies and proportions, or means and SD. Multivariable logistic regression models were then fitted to estimate OR with 95% CIs comparing exposures between IPF cases and controls, adjusted for a priori confounders of age, sex, state (as a fixed effect) and smoking (never/past/current). In additional analyses, cumulative smoking was fitted in tertiles of packyears. Population attributable fractions (PAFs) were estimated by Levin's formula.²⁶ Population exposures were based on AWES.²⁰ Analysis was conducted in Stata V.15 (StataCorp). P values <0.05 were considered statistically significant.

RESULTS

Description of cases and controls

We recruited 503 cases with a mean±SD age of 71.1±8.5 years. Of the cases, 346 (69%) were male and 147 (31%) female. We recruited 902 controls with a mean±SD age of 70.8±8.4 years. Of the controls, 625 (69%) were male and 277 (31%) female. Age was approximately normally distributed in both cases and controls. State of residence was balanced by design, with most participants recruited from the more populous states of Victoria or New South Wales (online supplementary table S1). Cases had smoked a median of 19.2 (IQR 8.6–34) and controls 13 (2.5–32) pack-years. A comparison of cases and controls for environmental exposures including smoking and home exposures, self-assessed occupational exposures and family history is presented in the left-hand columns of table 1.

Environmental exposures

Adjusted ORs, 95% CIs and p values for 20 environmental exposures are presented in the right-hand columns of table 1. Smoking tobacco ever or in the past was strongly associated with increased risk of IPF. Conversely current tobacco smoking was associated with about a threefold reduction in risk. There was no association with secondhand smoke or pipe smoking. However, self-reported ever smoking marijuana was associated with about a halving of risk after adjustment for age, sex, state and tobacco smoking.

A family history of pulmonary fibrosis was associated with almost a 13-fold increase in risk of IPF, while there did not appear to be any association with a family history of autoimmune disease. Keeping birds (pigeons, parakeets or others) or reporting standing water in the home were associated with halving of the risk of IPF. Exposure to potting mix, soil or compost was associated with a small reduction in risk of IPF in the fully adjusted

Table 1 Comparison of cases and controls for environmental exposures and family history: ORs, 95% CIs and p values

Environmental exposures	Cases (n=503)			Controls (n=902)			Unadjusted ORs	Adjusted ORs		
	Total	Exposed n	%	Total	Exposed n	%		OR	95% CI	P value
Smoking										
Tobacco (ever)	501	352	70.3	902	475	52.7	2.12	2.20*	(1.74 to 2.79)	<0.001
Past tobacco	501	340	67.9	902	412	45.7	2.51	2.61*	(2.06 to 3.29)	<0.001
Current tobacco	501	12	2.4	902	63	7.0	0.33	0.33*	(0.17 to 0.62)	0.001
Secondhand smoke	498	377	75.7	902	663	73.5	1.12	1.03	(0.79 to 1.33)	0.856
Pipe	498	89	17.9	902	137	15.2	1.22	1.05	(0.76 to 1.45)	0.752
Marijuana	497	34	6.8	902	101	11.2	0.58	0.51	(0.33 to 0.78)	0.002
Self-assessed exposures										
Asbestos	484	194	40.1	902	304	33.7	1.32	1.37	(1.08 to 1.74)	0.009
Silica	480	64	13.3	902	176	19.5	0.63	0.61	(0.44 to 0.84)	0.003
Gases/fumes/chemicals	494	242	49.0	902	424	47.0	1.08	1.09	(0.86 to 1.38)	0.465
Dusty environment	499	260	52.1	902	456	50.6	1.06	1.07	(0.85 to 1.36)	0.546
Family history										
Pulmonary fibrosis	490	63	12.9	902	11	1.2	12.0	12.6	(6.52 to 24.2)	<0.001
Autoimmune disease	489	67	13.7	902	113	12.5	1.11	1.12	(0.81 to 1.56)	0.490
Home exposures										
Indoor hot tub	499	15	3.0	902	26	2.9	1.04	1.00	(0.52 to 1.93)	0.994
Water leaks/mould	496	45	9.1	902	90	10.0	0.90	0.91	(0.61 to 1.32)	0.597
Down pillows/duonas	488	178	36.5	902	293	32.5	1.19	1.20	(0.94 to 1.52)	0.138
Pigeons/parakeet/birds	496	43	8.7	902	131	14.5	0.56	0.54	(0.37 to 0.78)	0.001
House/office damp	496	22	4.4	902	38	4.2	1.06	1.07	(0.62 to 1.85)	0.800
Flooding history	499	11	2.2	902	33	3.7	0.59	0.56	(0.28 to 1.13)	0.106
Standing water	498	32	6.4	902	109	12.1	0.50	0.51	(0.34 to 0.77)	0.002
Potting soils/compost	501	62	12.4	902	145	16.1	0.74	0.71	(0.52 to 0.99)	0.040
Reside/work on farm	497	45	9.1	902	106	11.8	0.75	0.78	(0.54 to 1.13)	0.184
Farm animals	496	54	10.9	902	105	11.6	0.93	0.97	(0.68 to 1.39)	0.887

Bold values indicate significant associations (p<0.05)

*Adjusted for age, sex and state; all other OR adjusted for age, sex, state and tobacco smoking (never/past/current).

model. No domestic exposures were associated with increased risk of IPF (table 1). These results did not change when pack-years were fitted to the model (online supplementary table S2).

Occupational exposures

Self-reported exposure to asbestos at work was associated with a 1.4-fold increased risk of IPF. Conversely self-reported silica exposure appeared to be associated with a reduction of risk. Self-reported exposures to gases, fumes, chemicals or a dusty work environment were not associated with IPF. These results were also unchanged when pack-years were fitted to the models (online supplementary table S2).

Seventeen occupational exposures were then assessed using FinJEM. Table 2 shows that secondhand tobacco smoke at work was the most common exposure both in cases (49.4%) and controls (29.1%). Substantial proportions were also exposed to ‘respirable dust’, organic dusts and inorganic mineral dusts, but only relatively small proportions to metal or wood dusts. Secondhand smoke was associated with a twofold and ‘respirable dust’ with a 1.4-fold increased risk of IPF. These results did not change substantially when pack-years were fitted to the models (online supplementary table S3). However, organic dusts,

inorganic mineral dusts including asbestos and quartz, wood and most metal dusts were not associated with IPF in this analysis (table 2). There was a borderline association with cadmium dust, when pack-years were fitted to the models (online supplementary table S3).

Finally occupational asbestos exposure was also assessed using AsbJEM. Cumulative asbestos exposure was divided into four quartiles (see left-hand columns of table 3). The mean±SD asbestos exposure was slightly higher in cases (0.23±0.64 fibre-years/mL) than controls (0.22±0.55 fibre-years/mL), but more of the cases were in the third or fourth quartiles. Cases were thus much more likely than controls to have occupational asbestos exposure, with increasing ORs by quartile (table 3). After adjustment for age, sex, state and smoking, the OR increased from 1.21 in the second, 1.41 in the third to 1.57 in the fourth quartile of exposure. These findings were essentially unchanged, when pack years were fitted to the models (right hand columns of table 3).

Population attributable fractions

Based on the prevalence of occupational exposures in AWES²⁰ and the OR from the FinJEM analysis (above), we estimated that

Table 2 Comparison of cases and controls for occupational exposures assessed by FinJEM: ORs, 95% CIs and p values

Occupational exposures	Cases (n=503)		Controls (n=902)			Unadjusted ORs	Adjusted ORs*			
	Total	Exposed	Total	Exposed			OR	95% CI	P value	
	n	%	n	n	%					
Organic dusts										
Animal dust	479	43	9.0	891	85	9.5	0.94	1.00	(0.67 to 1.49)	0.998
Plant dust	443	14	3.2	858	42	4.9	0.63	0.68	(0.36 to 1.28)	0.229
Wood dust	480	6	1.3	894	17	1.9	0.65	0.69	(0.27 to 1.79)	0.445
Hardwood dust	440	4	0.9	817	14	1.7	0.52	0.51	(0.17 to 1.58)	0.244
Softwood dust	448	4	0.9	829	16	1.9	0.46	0.45	(0.15 to 1.37)	0.159
Inorganic mineral dusts										
Asbestos	397	38	9.6	744	54	7.3	1.35	1.31	(0.84 to 2.07)	0.236
Quartz dust	474	29	6.1	886	42	4.7	1.31	1.28	(0.78 to 2.11)	0.329
Other mineral dusts	473	22	4.7	886	44	5.0	0.93	0.94	(0.55 to 1.61)	0.830
Other dusts										
Secondhand smoke at work	85	42	49.4	203	59	29.1	2.38	2.10	(1.20 to 3.70)	0.010
Respirable dust	422	113	26.8	821	171	20.8	1.39	1.38	(1.04 to 1.82)	0.024
Metal dusts										
Cadmium dust	420	7	1.7	802	6	0.7	2.25	2.41	(0.79 to 7.36)	0.122
Chromium dust	441	6	1.4	797	3	0.4	3.65	3.67	(0.89 to 14.9)	0.070
Iron dust	480	12	2.5	894	24	2.7	0.93	0.91	(0.44 to 1.86)	0.796
Lead dust	386	9	2.3	780	16	2.1	1.14	1.15	(0.49 to 2.66)	0.746
Nickel dust	456	26	5.7	862	37	4.3	1.35	1.41	(0.83 to 2.40)	0.199
Welding dust	449	10	2.2	856	21	2.5	0.91	0.90	(0.41 to 1.97)	0.797
Any metal exposure										
Any metal	480	52	10.8	894	76	8.5	1.31	1.29	(0.85 to 1.87)	0.152

*Adjusted for age, sex, state and tobacco smoking (never/past/current).
FinJEM, Finnish Job Exposure Matrix.

11.6% of IPF could be attributed to secondhand smoke, and 7.6% to respirable dust, but only 0.8% to asbestos.

DISCUSSION

This population-based case and control study using a national registry has found that IPF patients were over twice as likely as controls to have ever smoked or to be former smokers of tobacco. Conversely, current tobacco smoking and marijuana appeared to be associated with reduced risk. Secondhand tobacco smoke was also implicated, with cases being twice as likely as controls to have workplace (but not domestic) exposure. Cases were much

more likely than controls to report a family history of pulmonary fibrosis. Cases were also more likely than controls to have been exposed to respirable dust at work. Both self-reported asbestos exposure and that assessed by an asbestos specific JEM were associated with IPF.

The association of IPF with tobacco smoking has been previously reported and smoking is now a well-recognised cofactor in the development of IPF and other interstitial lung diseases.^{12 13 18 27} We suspect that the apparently protective effect of current smoking found, was because by the time of diagnosis and registration, cases were likely to have been counselled by

Table 3 Associations with occupational asbestos exposure assessed by AsbJEM: ORs, 95% CIs and p values

Asbestos exposure	Quartiles	Fibre-years/mL	Unadjusted ORs			Adjusted ORs			
			ORs	Adjusted ORs	95% CI	P value	OR†	95% CI	P value
Reference group	Q1	≤0.00295	1	1			1		
	Q2	0.00296, ≤0.00425	1.20	1.21	(0.88 to 1.66)	0.233	1.28	(0.90 to 1.80)	0.166
	Q3	0.00426, ≤0.06255	1.39	1.41	(1.03 to 1.93)	0.032	1.46	(1.03 to 2.06)	0.034
	Q4	0.06256 to 8.256	1.55	1.57	(1.15 to 2.15)	<0.001	1.61	(1.14 to 2.27)	0.007

*Adjusted for age, sex, state and tobacco smoking (never/past/current).
†Additionally adjusted for age, sex, state, tobacco smoking (never/past/current) and pack-years.
AsbJEM, asbestos Job Exposure Matrix.

their physicians to cease smoking. Alternatively this finding could have been due to cases who were current smokers being less likely to participate and/or confounded by differences in socioeconomic status between cases and controls.

Although cannabinoids have been shown to have anti-inflammatory effects in animal lungs,²⁸ we doubt that smoking marijuana truly reduced the risk of IPF. The Dunedin multi-disciplinary health and development study of young adults found that marijuana inhalation was associated with higher lung volumes suggesting hyperinflation and increased large airways resistance, but there was little evidence of impaired gas transfer.²⁹ Smoking marijuana is well known by Australian physicians to be associated with bullous lung disease,³⁰ so they might be less likely to diagnose IPF. It is also possible that those cases who smoked marijuana were likely to have smoked less marijuana than tobacco. Further study of respiratory effects of marijuana is necessary.

In addition to rare familial forms of IPF, there are now several genetic risk factors identified for sporadic IPF including polymorphisms of AKAP13, Mucin 5B and desmoplakin,³¹ toll-interacting protein and genes associated with maintenance of telomere length.³² So it is not surprising that we confirmed the importance of family history. However, we did not identify any domestic environmental risk factors for IPF. The apparent protective effects of self reported domestic exposures to birds and standing water would be consistent with the introduction of the 2011 diagnostic criteria for IPF reducing misclassification of hypersensitivity pneumonitis as IPF.

The associations of IPF with secondhand tobacco smoke and respirable dust at work have been previously reported.^{7 10 12} Respirable dust was occupational, inhalatory exposure to particulate matter of any kind, defined in the European Standard and measured with agreed sampling criteria, 50% cut-off point at 4 µm. Unlike some previous studies,^{14–17} we did not find specific associations with wood or most metal dusts. The weak association with cadmium dust was plausible,³³ although this only became significant after adjustment both for smoking and pack-years. The apparent protective effect of self-reported silica exposure was also likely to represent depletion of the case pool by cases with clinically diagnosed silicosis circumstantially rather than IPF. There was no association with quartz dust exposure as more objectively assessed by FinJEM.

Self-reported asbestos exposure is generally considered less accurate than that assessed by a JEM.³⁴ However, it is likely that FinJEM, which is based on Finnish data, might not accurately reflect occupational asbestos exposures in Australia, which has historically had a large mining and manufacturing industry. Thus, we attached more importance to the findings from AsbJEM, which were consistent with a dose response relationship to asbestos. An asbestos related disease screening programme in France found that from the second quartile cumulative exposure was related to increased risk of asbestosis on chest HRCT scans.³⁵ We suspect that some cases called 'IPF' are actually unrecognised asbestosis, in the absence of a thorough occupational history, obvious radiographic evidence of pleural disease and/or sputum examination for asbestos bodies. Nonetheless diagnoses of IPF have been made in the past in asbestos exposed patients.³⁶

The main strength of this study is that we have ascertained cases from a national registry applying then current diagnostic guidelines and recruited population-based controls. The frequency matched design has reduced confounding by age, sex and state of residence. Validated JEMs were applied to estimate occupational exposures, although these were dichotomised.

However, there are also some limitations inherent to the case control design. Although cases were recruited from all states and territories of Australia, some selection bias was likely, because registration was voluntary. While we controlled statistically for confounding by tobacco smoking and pack-years, there remains the possibility of residual confounding by unmeasured factors such as socioeconomic status. Some environmental exposures and family history could only be assessed by self-report, which were subject to recall bias, as cases were more likely to recall these events than were controls. Since cases completed the questionnaires on paper, while controls were interviewed by telephone, the mode of administration could have introduced some bias. It was also possible that some associations were chance findings in the context of multiple comparisons.

The major occupational health policy implications follow from the population attributable fractions. We conclude that 20% of IPF cases could potentially be prevented by tighter control of workplace smoking, dust suppression, and elimination or substitution of asbestos, together with personal protective equipment, when exposure is unavoidable. However, there remains some uncertainty around this estimate, because it is not accurately known how many workers are exposed to respirable dust and in the absence of good population based exposure distribution data, we have deliberately chosen a conservative estimate for the risk associated with asbestos. The ATS/ERS statement estimated somewhat higher pooled PAF of 26% for VGDF, 8% for metal dust, 4% for wood dust and 3% for silica. However, all of the studies on which these estimates were based used self-reported occupational exposures, which may be less accurate.

This finding that such a high proportion of IPF cases are associated with occupational exposures is also extremely important in understanding this otherwise 'idiopathic' disease. We would encourage clinicians to take a thorough occupational history from all patients in whom IPF is suspected. Respirable dust exposure is likely in construction, mining, manufacturing and service industries, such as carpenters, foundry workers and metal workers. Patients are often keen to understand the likely contributors to their disease, and indeed it might be possible that in the early stages, reducing such exposures could lead to amelioration of the disease course. Certainly, these findings are important for families with a strong history of interstitial lung disease, so that currently non-affected family members who may potentially carry a genetic predisposition to IPF ensure active avoidance of potentially critical exposures.

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Contributors MJA conceived and designed the case-control study, interpreted the analysis and wrote the first draft of the paper. TM, SMA and RW analysed and interpreted the data. GPB, SCD, RFH, RW, TJC and EHW conceived and designed the case-control study and interpreted the analysis. IG, PH, SK, YM, PNR, TJC and EHW established the Australian IPF Registry and were involved in acquisition of case data. SR acquired and analysed control data. All authors have revised the paper for important intellectual content and approve this version for publication. MJA and TJC act as guarantors.

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Competing interests MJA holds investigator-initiated grants for unrelated research from Pfizer and Boehringer-Ingelheim. He has undertaken an unrelated consultancy for and received assistance with conference attendance from Sanofi. He has also received a speaker's fee from GSK. IG reports personal fees and non-financial support from Boehringer Ingelheim, personal fees from Roche, Avalyn, Pulmotect and Menarini, grants and non-financial support from Lung Foundation of Australia, grants from NHMRC, outside the submitted work. SK has received personal fees for preparing medicolegal reports for the courts on cases of interstitial lung disease. YM reports non-financial support from Roche and Boehringer Ingelheim, outside the submitted work. PNR reports other from GlaxoSmithKline and Boehringer Ingelheim, outside the submitted work. TJC reports grants and personal fees from Roche, grants, personal fees, non-financial support and other from Boehringer Ingelheim, grants from Actelion, personal fees from Astra Zeneca, grants and personal fees from BMS, and grants from Bayer, outside the submitted work.

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