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Role of diabetes mellitus and gastro-oesophageal reflux in the aetiology of idiopathic pulmonary fibrosis

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Summary
Background: The aetiology of idiopathic pulmonary fibrosis remains poorly understood, but recent studies have suggested that diabetes mellitus and gastro-oesophageal reflux may be risk factors.
Objective: To test possible associations between diabetes mellitus and gastro-oesophageal reflux with idiopathic pulmonary fibrosis in the general population.
Methods: We designed a case–control study in the setting of UK general practices contributing data to The Health Improvement Network primary care database (THIN). We selected patients over 40 years of age with a first diagnosis of idiopathic pulmonary fibrosis, and up to 4 controls per case matched by age, gender, and general practice. We estimated odds ratios for exposure to gastro-oesophageal reflux, gout, hypercholesterolaemia and diabetes mellitus using conditional logistic regression. We explored the role of confounding by smoking habit, socio-economic status, and medication with prednisolone.
Results: Amongst our 920 cases we found increased risks of use of insulin (odds ratio (OR) 2.36; 95% confidence interval (CI) 1.46–3.83) and use of ulcer drugs (OR 2.20; 95% CI 1.88–2.58). These were almost unchanged when we excluded cases and controls who had been prescribed prednisolone. We found no association with hypercholesterolaemia or gout, nor with smoking status or socio-economic status.
Conclusions: The study provides further evidence of an association between idiopathic pulmonary fibrosis and both diabetes mellitus and gastro-oesophageal reflux.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is recognised increasingly as an important cause of morbidity[1] and premature mortality[2] in the UK and USA. Recent estimates suggest 4000 new cases of IPF occur each year in the UK[3] and 18,000 in the USA.[4] There is evidence that the incidence of IPF is increasing,[3] but its aetiology remains poorly understood.

Recently, two potential risk factors for IPF have been proposed. In a study of 52 Japanese cases, Enomoto et al[5] found a higher prevalence of diabetes mellitus compared to their controls, but a study by Miyake et al of 104 cases found no association with diabetes.[6] The case–control study of Raghu et al[7] found a higher prevalence of abnormal acid gastro-oesophageal reflux in their 17 cases. To investigate these new ideas further we have performed a case–control study using prospectively collected data from general practices in the UK to determine the role of diabetes mellitus and gastro-oesophageal reflux for IPF.

Methods

The Health Improvement Network (THIN) is a longitudinal primary care database which includes diagnostic and prescribing data recorded by UK general practitioners as part of routine clinical care. It has been shown to have a high level of completeness of clinical, diagnostic and prescribing data.[8,9]

Details of case identification of cases and controls have been published previously[3] but, briefly, we selected IPF cases from the period 1991–2003 who were over 40 years of age when they received their first diagnosis for IPF, and up to 4 contemporaneous controls per case matched by age, gender, and general practice. The Read Code (diagnostic terms) that we used to construct our look-up table to identify cases were ''cryptogenic fibrosing alveolitis'' and ''idiopathic fibrosing alveolitis'' which reflect the clinical terms commonly used in the UK over the last 20 years.

Our main exposures of interest were diabetes mellitus and gastro-oesophageal reflux. We also looked for associations with hypercholesterolaemia and gout, for which no associations between these conditions and IPF have been proposed. The rationale for this was that an association between IPF and chronic diseases in general could point towards ascertainment bias in the diagnosis of IPF for patients treated for chronic disease.

To examine these we extracted data on clinical diagnoses or relevant prescriptions (insulin, oral hypoglycaemics, antacids, ulcer drugs, allopurinol, lipid drugs) before the first diagnosis of IPF (for cases) or matching date (controls).

Our potential confounders were cigarette smoking, socio-economic status and use of prednisolone. We coded smoking habit as ex-, current-, or non-smoker. Our marker of socio-economic status was Townsend score, which is an index derived from 2001 census data comprising prevalence of household access to a car, owner occupation, overcrowding, and unemployment within the patient's postcode.

We used conditional logistic regression in Stata version 9 to estimate odds ratios for each exposure, matching by age, gender and practice. Initially we estimated odds ratios for each of our exposures and confounders in a series of univariate models. Variables were selected for multivariate analysis by identifying the variable within each group of related diagnoses and prescriptions which had the largest odds ratio with a p value of not more than 0.1.

We explored the influence of confounders in a series of bivariate models, in which we looked for a change in the odds ratio for exposure of 10% or more with the addition to the model of the putative confounder. We undertook further multivariate analysis to check for independent effects between each of the variables corresponding to diagnoses and prescriptions for diabetes and gastro-oesophageal reflux.

Prednisolone is known to cause diabetes mellitus and gastro-oesophageal reflux, and is often prescribed to people with respiratory symptoms. Therefore to provide further reassurance that there was no confounding by prednisolone, we carried out a restricted analysis excluding all cases and controls with any exposure to prednisolone.

The study protocol was reviewed and approved by the Nottingham Research Ethics Committee.

Results

We identified 920 people with IPF who were over the age of 40 years when they received their first diagnosis,[3] and 3593 matched controls. The mean age of people with IPF at presentation was 71 years (standard deviation 11 years) and 568 (62%) were male. The age distribution of cases is shown in Table 1. About a quarter of cases were current smokers, with a further fifth recorded as ex-smokers. In 14% of the

Table 1 Description of cases and controls.

	Cases	%	Controls	%
$n=$	920		3593	
Age				
Mean age	71.4		71.4	
Age group				
<55 years	79	9	311	9
55–64.9 years	166	18	646	18
65–74.9 years	290	32	1134	32
75–84.9 years	302	33	1176	33
>85 years	83	9	326	9
Gender				
Females	352	38	1365	38
Males	568	62	2228	62
Smoking habit				
Non-smoker	355	39	1420	40
Current smoker	240	26	877	24
Ex-smoker	192	21	714	20
Status not available	133	14	582	16
Socio-economic status (Townsend quintile)				
1 (least deprived)	174	19	718	20
2	169	18	665	19
3	189	21	667	19
4	158	17	670	19
5 (most deprived)	130	14	487	14
0 (unavailable)	100	11	386	11

cases, smoking status was not recorded. Overall there was no clear association between case status and Townsend score.

We recorded the results of our univariate analyses in Table 2. Odds ratios obtained for gout and allopurinol, and for hypercholesterolaemia, lipid drugs and statins were close to 1 and were not significant at the 5% level. Similarly, we found no significant associations for smoking or socio-economic status.

Odds ratios for gastro-oesophageal reflux and associated medication were all raised: diagnosis of gastro-oesophageal reflux 1.65 (95% confidence interval (CI) 1.29—2.10), antacids 1.71 (95% CI 1.44—2.02), ulcer drugs 2.22 (95% CI 1.89—2.60). We also found positive associations for diabetes mellitus 1.31 (95% CI 1.01—1.70), oral hypoglycaemic agents 1.40 (95% CI 1.04—1.88), insulin 2.56 (95% CI 1.60—4.11), and prescribing for prednisolone 5.61 (95% CI 4.64—6.77).

Table 2 Results of univariate analyses.

	Cases ($n = 920$)	Controls ($n = 3593$)	Odds ratio	(95% confidence interval)	
Diagnosis of diabetes mellitus	89 (10%)	275 (8%)	1.31	(1.01—1.70)	$p = 0.038$
Oral hypoglycaemic agents	64 (7%)	184 (5%)	1.40	(1.04—1.88)	$p = 0.027$
Insulin	29 (3%)	45 (1%)	2.56	(1.60—4.11)	$p < 0.001$
Diagnosis of gout	39 (4%)	154 (4%)	0.99	(0.68—1.44)	$p = 0.943$
Allopurinol	20 (2%)	92 (3%)	0.84	(0.52—1.38)	$p = 0.493$
Diagnosis of gastro-oesophageal reflux	108 (12%)	279 (8%)	1.65	(1.29—2.10)	$p < 0.001$
Antacids	272 (30%)	727 (20%)	1.71	(1.44—2.02)	$p < 0.001$
Ulcer drugs	375 (41%)	889 (25%)	2.22	(1.89—2.60)	$p < 0.001$
Diagnosis of hypercholesterolaemia	56 (6%)	220 (6%)	1.00	(0.73—1.37)	$p = 0.994$
All lipid drugs	90 (10%)	326 (9%)	1.11	(0.85—1.45)	$p = 0.432$
Statins only	78 (8%)	281 (8%)	1.12	(0.84—1.48)	$p = 0.441$
Prednisolone	334 (36%)	367 (10%)	5.61	(4.64—6.77)	$p < 0.001$
Smoking habit					
Non-smoker	355 (39%)	1420 (40%)	1.00		
Current smoker	240 (26%)	877 (24%)	1.12	(0.92—1.36)	
Ex-smoker	192 (21%)	714 (20%)	1.10	(0.89—1.35)	
Status not available	133 (14%)	582 (16%)	0.90	(0.71—1.14)	$p = 0.324$
Not ever smoked	355 (39%)	1420 (40%)	1.00		
Ever smoked	432 (47%)	1591 (44%)	1.11	(0.93—1.31)	
Status not available	133 (14%)	582 (16%)	0.90	(0.71—1.14)	$p = 0.178$
Smoking amount (cigarettes/day)					
Non-smoker, 0 cigs per day	488 (53%)	2002 (56%)	1.00		
1—9 cigs per day	44 (5%)	144 (4%)	1.29	(0.90—1.83)	
10—19 cigs per day	47 (5%)	171 (5%)	1.15	(0.81—1.62)	
20+ cigs per day	44 (5%)	180 (5%)	1.03	(0.72—1.47)	
Current smoker, 0 cigs per day	105 (11%)	382 (11%)	1.15	(0.89—1.48)	
Ex-smoker, 0 cigs per day	192 (21%)	714 (20%)	1.13	(0.93—1.38)	$p = 0.613$
Socio-economic status (Townsend quintile)					
1 (least deprived)	174 (19%)	718 (20%)	1.00		
2	169 (18%)	665 (19%)	1.05	(0.82—1.34)	
3	189 (21%)	667 (19%)	1.18	(0.92—1.51)	
4	158 (17%)	670 (19%)	0.99	(0.75—1.27)	
5 (most deprived)	130 (14%)	487 (14%)	1.11	(0.84—1.48)	
0 (unavailable)	100 (11%)	386 (11%)	1.11	(0.66—1.88)	$p = 0.686$

Insulin and ulcer drugs satisfied our criteria for inclusion in the multivariate analysis. Our multivariate model gave an odds ratios of 2.36 (95% CI 1.46—3.83, $p < 0.001$) for insulin and 2.20 (95% CI 1.88—2.58, $p < 0.001$) for ulcer drugs. We also undertook further multivariate analysis for diabetes and gastro-oesophageal reflux to check for independent effects between each of the variables corresponding to diagnoses and prescriptions; this did not produce any marked differences compared to the results shown in Table 3.

Table 3 also records the restricted multivariate analysis excluding cases and controls medicated with prednisolone. This gave an almost unchanged odds ratio of 2.40 for insulin (95% CI 1.26—4.58), and a slightly reduced odds ratio of 1.71 for ulcer drugs (95% CI 1.38—2.11).

Discussion

Findings

In this large case—control study of prospectively collected exposure data, we found that IPF is significantly associated with exposures relating to diabetes, the strongest association being with use of insulin. Our results were similar when we excluded people with prescriptions for prednisolone. We also found IPF to be significantly associated with exposures relating to gastro-oesophageal reflux, amongst which the strongest association was with prescribing for ulcer drugs. The odds ratio for this association was reduced from 2.20 to 1.71 by removing all people with any exposure to prednisolone, which suggests that the use of prednisolone partly explains this association. We found no significant associations between IPF and hypercholesterolaemia, gout, smoking or socio-economic status.

Strengths and weaknesses

The main strength of our study is the large number of cases, and that our data were collected prospectively which means that recall is not a source of bias. The main potential weaknesses of our study are the validity of the diagnoses of IPF and of exposures, and possible ascertainment bias.

THIN has been developed by the designer and former owner of the General Practice Research Database (GPRD). More than half of THIN practices previously contributed data to GPRD which has demonstrated high validity for diagnoses and coding of respiratory diseases.[10] The validity of the diagnoses is consistent with the expectation that general practitioners will record a diagnosis of IPF only when it is confirmed by a hospital referral, and will have coded it using ''cryptogenic fibrosing alveolitis'' and ''idiopathic fibrosing alveolitis'', which are the only relevant Read codes available to them in their computer system for recording such a diagnosis. Further reassurance about the validity of our disease diagnoses is given by the fact that the demographic profile and mortality of our cases appear similar to that reported for other cohorts.[1,11–13] The validity of the medication exposures derives from the fact that the records are integral to the generation of prescriptions in general practices.

The possibility of bias due to differential ascertainment arises because people with diagnosed diabetes or gastro-oesophageal reflux may have received a different level of medical attention than those without. We cannot exclude this as a source of bias, but the fact that associations between either reflux or diabetes and IPF are not widely recognised amongst general practitioners in the UK, together with the fact that we found no associations for gout and hypercholesterolaemia argues against this being an important bias in our dataset.

Table 3 Results of multivariate analyses.

	Cases	Controls	Odds ratio	(95% confidence interval)	
n	920	3593			
Insulin	29	45	2.36	(1.46—3.83)	$p < 0.001$
Ulcer drugs	375	889	2.20	(1.88—2.58)	$p < 0.001$
Excluding cases prescribed prednisolone					
n	586	3226			
Insulin	16	43	2.40	(1.26—4.58)	$p = 0.008$
Ulcer drugs	191	726	1.71	(1.38—2.11)	$p < 0.001$

Other studies

An association between gastro-oesophageal reflux and diffuse pulmonary fibrosis has been suspected for more than 30 years.[14] One study found that 16 out of 17 patients with IPF had evidence of reflux compared to 4 out of 8 patients with other interstitial lung diseases.[15] A more recent study found that gastro-oesophageal reflux is highly prevalent in IPF but often clinically occult.[7] To date, however, there has been no systematic epidemiological investigation of the link between gastro-oesophageal reflux and IPF.

The strength of the association which we found with gastro-oesophageal reflux was weaker than earlier studies. Amongst our 920 cases only 12% had a diagnosis of gastro-oesophageal reflux compared to 47% of the 55 cases in a smaller recent study,[7] and compared to 25% of the 17 cases in a pilot study.[15] Possible reasons for this (aside from variation arising from the relatively small sample sizes of earlier studies) include variations in criteria used for gastro-oesophageal reflux. Raghu et al counted all patients who on questioning reported the presence of ''classic symptoms'' whereas we counted pre-existing diagnoses.

There may also be differences in the denominator arising from differing case definitions, which would give rise to a dilution of the estimate of the odds ratio. For example, Raghu et al use criteria based on the international consensus statement[16] which may be more specific than our criteria. In the UK, only a small minority of patients have an open lung biopsy,[17] so our definition includes adults who have a diagnosis made on clinical grounds, and recorded using the terms ''cryptogenic fibrosing alveolitis'' and ''idiopathic fibrosing alveolitis'', which reflect the clinical terms commonly used in the UK over the last 20 years.

This variation in case definition may also be a contributory factor in explaining the much lower prevalence of

diabetes found in our study compared to the case—control study of Enomoto et al.[5] Their study of 52 patients and 184 controls in Japan found a prevalence of 33%, whereas our study found a recorded diagnosis of diabetes in 10% of our 920 cases (or, on a like for like basis with Enomoto et al, 9% amongst our 586 cases who had not received prednisolone prior to diagnosis). However, the adjusted odds ratio found in Enomoto's smaller study (odds ratio 4.06) falls within the 95% confidence intervals of our estimate (1.26—4.58) which is based on a larger sample. Miyake et al found a prevalence of 12.5% amongst their 104 cases.[6] Their adjusted odds ratio of 1.43 also falls within the confidence intervals of our estimate.

What does it mean clinically?

The association between IPF and a diagnosis of gastro-oesophageal reflux, or its management with medication, is consistent with the hypothesis that gastro-oesophageal reflux is an important risk factor for IPF. The temporality of pre-existing gastro-oesophageal reflux in this association is consistent with a causal link with gastro-oesophageal reflux or its management in some cases. Intervention trials are needed to determine whether treatments for reflux can slow disease progression in people with IPF.

Similarly, the associations with pre-existing diagnosis and management of diabetes mellitus are consistent with a relationship in which diabetes is a causal factor for IPF. Our finding of a stronger association with insulin than with oral hypoglycaemics is consistent with a relationship in which Type 1 and Type 2 diabetes represent exposures that are distinct in terms of their influence on the development of IPF, or one in which the early onset of the exposure is important. This suggests that clinicians should be alert to the possibility of diabetes mellitus in people diagnosed with IPF.

Conclusion

Our study provides further evidence that there is a temporal association between diabetes mellitus and IPF, and between gastro-oesophageal reflux and IPF. We did not find evidence to support a link with smoking or socio-economic status.

Conflict of interest

All of the authors state that they have no conflicts of interest to disclose.

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References

1. Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med* 1994;**150**(4):967—72.
2. Hubbard R, Johnston I, Coultas DB, Britton J. Mortality rates from cryptogenic fibrosing alveolitis in seven countries. *Thorax* 1996;**51**(7):711—6.
3. Gribbin J, Hubbard RB, Le Jeune I, Smith CJ, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. *Thorax* 2006;**61**(11):980—5.
4. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2006;**174**(7):810—6.
5. Enomoto T, Usuki J, Azuma A, Nakagawa T, Kudoh S. Diabetes mellitus may increase risk for idiopathic pulmonary fibrosis. *Chest* 2003;**123**(6):2007—11.
6. Miyake Y, Sasaki S, Yokoyama T, et al. Case—control study of medial history and idiopathic pulmonary fibrosis in Japan. *Respirology* 2005;(10):504—9.
7. Raghu G, Freudenberger TD, Yang S, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. *Eur Respir J* 2006;**27**(1):136—42.
8. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. *Inform Prim Care* 2004;**12**(3):171—7.
9. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf* 2007;**16**(4):393—401.
10. Hansell A, Hollowell J, Nichols T, McNiece R, Strachan D. Use of the General Practice Research Database (GPRD) for respiratory epidemiology: a comparison with the 4th Morbidity Survey in General Practice (MSGP4). *Thorax* 1999;**54**:413—9.
11. Schwartz DA, Helmers RA, Galvin JR, et al. Determinants of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1994;**149**(2 Pt 1):450—4.
12. Wells AU, Cullinan P, Hansell DM, et al. Fibrosing alveolitis associated with systemic sclerosis has a better prognosis than lone cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 1994;**149**(6):1583—90.
13. Mapel DW, Hunt WC, Utton R, Baumgartner KB, Samet JM, Coultas DB. Idiopathic pulmonary fibrosis: survival in population based and hospital based cohorts. *Thorax* 1998;**53**(6):469—76.
14. Mays EE, Dubois JJ, Hamilton GB. Pulmonary fibrosis associated with tracheobronchial aspiration. A study of the frequency of hiatal hernia and gastroesophageal reflux in interstitial pulmonary fibrosis of obscure etiology. *Chest* 1976;**69**(4):512—5.
15. Tobin RW, Pope CE, Pellegrini 2nd CA, Emond MJ, Sillery J, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;**158**(6):1804—8.
16. American Thoracic Society. European Respiratory Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med* 2000;**161**(2 Pt 1):646—64.
17. Hubbard R, Lewis S, Richards K, Johnston I, Britton J. Occupational exposure to metal or wood dust and aetiology of cryptogenic fibrosing alveolitis. (see comment). *Lancet* 1996;**347**(8997):284—9.