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**Risk factors for cardiovascular disease in people with idiopathic pulmonary fibrosis: a
population based study**

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Running head: Cardiovascular risk factors in IPF

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Abstract

Rationale & Objective

People with idiopathic pulmonary fibrosis (IPF) have been shown to be at an increased risk of cardiovascular disease but reasons for this are unknown. The aim of this study was to compare the prevalence of common cardiovascular risk factors in people with IPF and the general population and establish the incidence of ischaemic heart disease (IHD) and stroke after the diagnosis of IPF, controlling for these risk factors.

Methods

We used data from a large United Kingdom primary care database to identify incident cases of IPF and matched general population controls. We compared the prevalence of risk factors for cardiovascular disease and prescription of cardiovascular medications in people with IPF (before diagnosis) with general population controls, and assessed the incidence of IHD and stroke in people with IPF (after diagnosis) compared to controls.

Results

We identified 3,211 cases of IPF and 12,307 controls. Cases with IPF were more likely to have a record of hypertension (odds ratio [OR] 1.31, 95% confidence interval [CI] 1.19 - 1.44), and diabetes (OR 1.20, 95% CI 1.07 - 1.34) compared with controls; they were also more likely to have been prescribed several cardiovascular drugs. The rate of first time IHD events was more than twice as high in cases compared to controls (rate ratio [RR] 2.32, 95% CI 1.85-2.93; $p < 0.001$) but the incidence of stroke was only marginally higher ($p = 0.09$). Rate ratios for IHD and stroke were not altered substantially after adjusting for cardiovascular risk factors.

Conclusion

Several cardiovascular risk factors were more prevalent in people with IPF; however this did not account for the increased rate of IHD in this group of patients.

Abstract word count 257

Indexing terms

Hypertension; diabetes mellitus; prescriptions; myocardial ischemia; stroke.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrotic lung disease with few treatment options. The most common cause of morbidity and mortality in people with this condition is progression of fibrosis leading to respiratory failure, but several studies have identified an increased risk of acquiring comorbidities which contribute to the disease burden.^{1,2}

Cardiovascular diseases such as ischaemic heart disease and cerebrovascular disease constitute an important group of co-morbid conditions affecting those with IPF.¹⁻⁴ In a cohort of people referred for lung transplantation, Nathan and colleagues found significant coronary artery disease to be increased in people with IPF compared with people with chronic obstructive pulmonary disease (COPD), with worse outcomes for those with both IPF and coronary artery disease.⁵ Using United Kingdom (UK) longitudinal electronic health records, we have previously demonstrated that people with IPF have an increased risk of cardiovascular disease even before the IPF diagnosis is made.³

The reason behind this increase in cardiovascular disease seen in IPF is unknown. It has been suggested that certain risk factors for cardiovascular disease such as diabetes mellitus are more prevalent in those with IPF.⁶⁻⁸ A study by Reed and colleagues found a greater prevalence of hyperlipidaemia, hypertension and higher body mass index (BMI) amongst people with IPF compared to people with COPD.⁸ Studies looking at the rates of cigarette smoking amongst those with IPF are discordant; some showing a small increase in rates of smoking⁹ and others finding no difference from the general population.¹⁰ The prevalence of cardiovascular risk factors in people with IPF has yet to be explored in a large epidemiological study.

The aim of this study was to compare the prevalence of cardiovascular risk factors, and prescriptions for drugs commonly used to manage cardiovascular disease, in people with IPF to the general population. We also aimed to establish the incidence of ischaemic heart disease and stroke after the diagnosis of IPF controlling for the presence of cardiovascular risk factors and prescriptions for cardiovascular drugs.

Methods

Data source

We used The Health Improvement Network (THIN), a UK longitudinal database of electronic primary care records containing information recorded in routine clinical care, from face to face consultations, and following communication from secondary care.¹¹ Anonymised patient-level data include demographic information, medical diagnoses (coded using Read codes) and prescriptions. The version of THIN used for this study included information from 511 practices entered up to September 2011.

Study population

We identified individuals with a new diagnosis of IPF made after January 1st 2000 (see Appendix 1). Cases were included if their first diagnosis of IPF was recorded at least 12 months after registration with the practice, and if they were at least 40 years when first diagnosed. This definition was used to capture incident cases of IPF and improve diagnostic specificity.

We excluded people with co-existing diagnoses of connective tissue disease (Appendix 2), or a record of extrinsic allergic alveolitis, sarcoidosis, pneumoconiosis or asbestosis (Appendix 3) in addition to IPF because it was not clear which diagnosis was correct.

For each incident case of IPF, we randomly selected up to four general population controls, matched on age, gender and general practice. Each case was assigned an index date which corresponded to their first diagnosis of IPF; matched controls were assigned the same date as their case. All cases and controls had at least 12 months of computerised records prior to their index date.

Exposures and outcomes

We extracted data on diagnoses of ischaemic heart disease (IHD), ischaemic and haemorrhagic stroke, hypertension, diabetes, hypercholesterolaemia and prescriptions for cardiovascular and diabetic medications, as well as smoking habit (current smoker, ex-smoker, never smoker) using the data recorded closest to the index date, and BMI.

Statistical Analysis

We conducted a case-control study to compare the prevalence of risk factors for cardiovascular disease and prescription of cardiovascular medications in people with IPF, with general population controls. Conditional logistic regression was used to compare the odds of these exposures, prior to the index date, in cases and controls. We looked for evidence of effect modification by age and sex.

We performed a cohort study to investigate whether incidence of IHD or stroke was increased after diagnosis of IPF. For these analyses, we excluded people who had diagnoses of IHD or stroke prior to the index date. All individuals were assigned a start date which was their index date, and a stop date which was the first of: date of the outcome, date of death, or last date of data collection. Crude incidence rates of IHD and stroke were calculated. Cox regression, stratifying for the matching factors, was used to estimate rate ratios for first time IHD and stroke events in cases, compared to controls. We looked for evidence of

confounding by cardiovascular risk factors and prescriptions. Multiplicative interaction terms were applied to test for interactions between IPF and age, sex or diabetes. Proportional hazards assumption was confirmed using graphical methods and scaled Schoenfeld residuals.

Likelihood ratio tests were used for all hypothesis testing. Statistical analyses were conducted using Stata version 12 (Texas). With 3211 incident cases of IPF and 12,307 matched controls, we had in excess of 90% power to detect an odds ratios (OR) of 1.5 or greater for exposures affecting 5% of controls or to detect an OR of 1.3 or greater for exposures affecting 10% of controls.

Results

There were 3211 incident cases of idiopathic pulmonary fibrosis (IPF) and 12,307 matched general population controls. The cases consisted mainly of men (63.9%) and mean age at diagnosis was 75.7 years (standard deviation [SD]: 9.8). Both cases and controls had a median duration of 9.8 years (interquartile range [IQR]: 5.6-13.7) of computerised records prior to the index date.

Case-control study

Cases with IPF were 31% more likely to have a record of hypertension (odds ratio [OR] 1.31, 95% confidence interval [CI] 1.19 to 1.44; $p < 0.001$), and 20% more likely to have a record of diabetes mellitus prior to receiving a diagnosis of IPF compared to general population controls (OR 1.20, 95% CI 1.07 to 1.34; $p < 0.001$). We also found that cases were more than twice as likely to be ex-smokers before the diagnosis of IPF was made compared to controls (see Table 1). Cases with IPF were more likely to have been prescribed anti-anginals, ACE inhibitors or angiotensin II receptor antagonists, digoxin, anti-platelets and lipid lowering medication compared to general population controls (see Table 2). There was no evidence of effect modification by age or sex on any of these risk factors.

Cohort study

Median follow up time after the index date was 1.7 years (IQR 0.6 to 3.6) in cases with IPF and 3.3 years (1.5 to 5.8) for controls. During this time, 135 cases and 474 controls had a first time ischaemic heart disease event. The rate of first time ischaemic heart disease events was more than two times higher in cases with IPF compared to general population controls (rate ratio [RR] 2.32, 95% CI 1.85-2.93; $p < 0.001$) (See Table 3, Figure 1). The incidence rate of stroke during the follow up period was 11.3 per 1000 person years (95% CI

9.2 to 14.0) in cases with IPF and 10.3 per 1000 person years (95% CI 9.5 to 11.3) in the controls (see Table 3).

The rate ratios for ischaemic heart disease and stroke were not altered substantially after adjusting for the risk factors for cardiovascular disease listed in Table 1 or prescription of cardiovascular drugs listed in Table 2. There was no evidence of a statistical interaction between IPF and age or sex in any of our findings. Despite there being weak evidence that the effect of IPF on first time ischaemic heart disease events was modified by diabetes ($p=0.21$), the stratum specific ischaemic heart disease rate ratio for IPF with and without diabetes were 3.34 (95% CI 1.79 to 6.22) and 2.13 (95% CI: 1.64 to 2.77) respectively.

Thirteen per cent of the study population (2,053 individuals) was lost to follow up; this was similar in cases and controls (12.9% vs. 13.3%; $p=0.57$, chi squared test). A higher proportion of individuals who were lost to follow up did not have any cardiovascular risk factors and were not prescribed anti-anginals, anti-platelets or lipid lowering drugs. There was no evidence that the proportional hazards assumptions in our final models for ischaemic heart disease ($p= 0.31$) or stroke ($p=0.49$) were not met.

Table 1: Odds ratios for risk factors of cardiovascular disease comparing incident cases of idiopathic pulmonary fibrosis and matched general population controls

Risk factor		Cases (n=3211) (%)	Controls (n=12,307) (%)	Odds Ratio (95% CI)	p value*
Hypertension	No	2389 (74.4)	9670 (78.7)	1.00	
	Yes	822 (25.6)	2628 (21.3)	1.31 (1.19-1.44)	<0.001
Diabetes	No	2761 (86.0)	10,826 (88.0)	1.00	
	Yes	450 (14.0)	1481 (12.0)	1.20 (1.07-1.34)	0.003
Hyperlipidaemia	No	1361 (42.4)	5151 (41.9)	1.00	
	Yes	1850 (57.6)	7156 (58.2)	0.98 (0.90-1.06)	0.63
Smoking habit	Never smoked	972 (30.3)	5125 (41.7)	1.00	
	Ex-smoker	1243 (38.7)	3233 (26.3)	2.20 (1.99-2.43)	
	Current smoker	434 (13.54)	1661 (13.45)	1.44 (1.27-1.65)	<0.001
	Missing information	562 (17.5)	2255 (18.6)	-	
Body Mass Index (kg/m ²)	<18.5	88 (2.7)	197 (1.6)	1.77 (1.35-2.32)	
	18.5-24.9	946 (29.5)	3662 (29.8)	1.00	
	25-30	1309 (40.8)	4794 (39.0)	1.06 (0.96-1.17)	
	>31	485 (15.1)	1636 (13.3)	1.16 (1.02-1.32)	<0.001
	Missing data	383 (12.0)	2018 (16.4)	-	

*p value from Likelihood ratio test

Table 2: Odds ratios for prescribed cardiovascular medication comparing incident cases of idiopathic pulmonary fibrosis and matched general population controls

Cardiovascular drug		Cases (n=3211) (%)	Controls (n=12,307) (%)	Odds Ratio (95% CI)	p value*
Beta blockers	No	2021 (62.9)	8102 (65.8)	1.00	
	Yes	1190 (37.1)	4205 (34.2)	1.15 (1.05-1.24)	0.001
ACE inhibitors or angiotensin II receptor antagonists	No	1755 (54.7)	8043 (65.4)	1.00	
	Yes	1456 (45.3)	4264 (34.7)	1.64 (1.51-1.78)	<0.001
Calcium channel blockers	No	2083 (64.9)	8399 (68.3)	1.00	
	Yes	1128 (35.1)	3908 (31.7)	1.18 (1.08-1.28)	<0.001
Digoxin	No	2933 (91.3)	11,567 (94.0)	1.00	
	Yes	278 (8.7)	740 (6.0)	1.49 (1.28-1.72)	<0.001
Nitrates	No	2221 (69.2)	10,006 (81.3)	1.00	
	Yes	990 (30.8)	2301 (18.7)	2.00 (1.83-2.20)	<0.001
Anti-platelets	No	1591 (49.6)	7442 (60.5)	1.00	
	Yes	1620 (50.5)	4865 (39.5)	1.65 (1.52-1.80)	<0.001
Warfarin	No	2820 (87.8)	11,265 (91.5)	1.00	
	Yes	391 (12.2)	1042 (8.5)	1.52 (1.34-1.73)	<0.001
Lipid lowering drugs	No	1940 (60.4)	8147 (66.2)	1.00	
	Yes	1271 (39.6)	4160 (33.8)	1.36 (1.25-1.49)	<0.001

*p value from Likelihood Ratio Test

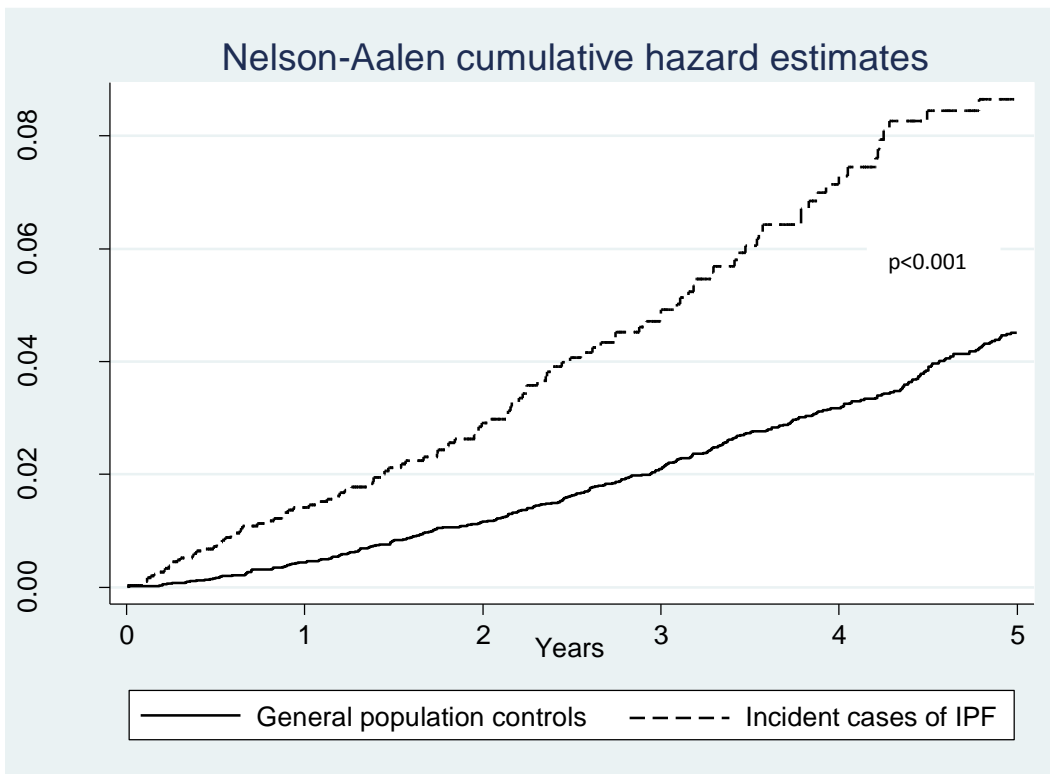
Table 3: Incidence rates and rate ratios for ischaemic heart disease and stroke, comparing incident cases of idiopathic pulmonary fibrosis and matched general population controls.

Outcome	Number of events in cases	Person-years	Crude rate in cases (per 1000 pyrs) (95% CI)	Number of events in controls	Person-years	Crude rate in controls (per 1000 pyrs) (95% CI)	Rate ratio* (95% CI)	p value#
Ischaemic heart disease	135	7618.7	17.6 (14.8-20.8)	474	47786.9	9.9 (9.2-10.9)	2.32 (1.85-2.93)	<0.001
Stroke	87	7671.6	11.3 (9.2-14.0)	523	50508	10.3 (9.5-11.3)	1.25 (0.97-1.61)	0.09

*Rate ratios stratified for matching variables

#p value from Likelihood Ratio Test

Figure 1: Cumulative incidence of ischaemic heart disease in incident cases of IPF and general population controls



Discussion

In this large population based study, we found that people with idiopathic pulmonary fibrosis (IPF) were more likely to have a recorded diagnosis of hypertension and diabetes mellitus before the diagnosis of IPF was made compared to the general population. People with IPF were also more likely to be prescribed anti-anginals, anti-platelets and lipid lowering medication compared to general population controls. Individuals with IPF had twice the rate of first time ischaemic heart disease events after their diagnosis compared to the general population, after adjusting for cardiovascular risk factors and prescription of cardiovascular drugs. In addition to the above, there was weak evidence that the incidence rate of strokes was higher in people with IPF.

The main strength of this study is the large number of individuals included in the study population and the long period of time over which the data were collected. This has enabled us to investigate in detail individual risk factors for cardiovascular disease and prescription of commonly used cardiovascular drugs, and to explore the possibility of confounding and effect modification. Studies of this nature and magnitude are difficult to conduct in a clinical setting. Our cohort study was restricted to individuals who had never had a previous ischaemic heart disease event or stroke, as the risk of subsequent cardiovascular events are likely to be different from the first. As our study is population based, the incident cases included are likely to capture individuals across the disease spectrum and avoid selection bias that can occur in studies conducted in tertiary referral centres. Furthermore, the use of electronic medical records limits the possibility of recall or observer bias.

The main limitation of our study is the validity of diagnoses of IPF within the dataset. We have previously demonstrated that diagnoses of pulmonary fibrosis in electronic primary

care are records are accurate.¹⁰ Furthermore, as IPF is usually diagnosed in secondary care, it seems unlikely that a record of this diagnosis will be found in primary care records without confirmation from secondary care. The age distribution of cases with IPF in this study is similar to other population based cohorts of IPF,¹²⁻¹⁶ providing reassurance of the validity of diagnosis of IPF in these data. In addition, a study by Fell and colleagues demonstrated that age is a strong predictor of IPF in patients with an atypical Usual Interstitial Pneumonia (UIP) radiographic pattern, whereby individuals over 65 years had 89% specificity for confirming IPF on lung biopsy.¹⁷ Eighty-one per cent of cases were over the age of 65 in our dataset, providing further evidence that most of our cases have UIP. In addition to this, the mortality rate for cases with IPF during the study period was 193.7 per 1000 person years (95% CI: 184.2 to 203.8) and the median survival was 3.5 years, both of which are similar to other population studies of IPF.^{12,16,18-20} There is also the possibility of misclassification of ischaemic heart disease, stroke and/or cardiovascular risk factors, however studies have also demonstrated the validity of recording of medical diagnoses^{21,22} and prescription records²³ in computerised longitudinal general practice databases.

The possibility of ascertainment bias in our cohort study needs to be acknowledged. Individuals with chronic diseases such as IPF are more likely than the general population to see their GP regularly, and this may explain why other illnesses are more likely to be investigated and diagnosed. This may have led to an overestimation in the association between IPF and the cardiovascular outcomes. However, our findings show a weak association between IPF and stroke, suggesting that any ascertainment bias, if present, is likely to be minimal. Another potential limitation of the study is that the general practices are self-selecting with regards to contributing to THIN. However, the population of

individuals from general practices that do contribute to THIN are thought to be broadly representative of the UK population. Thirteen per cent of the study population were lost to follow up, a higher proportion of which were people without cardiovascular risk factors or prescriptions for cardiovascular medication. This raises the possibility that people who were lost to follow up may have had a lower rate of ischaemic heart disease or stroke than those who remained in the study. Another limitation that needs consideration is that the median duration of follow-up after the index date for cases with IPF was shorter compared to the controls (1.7 vs. 3.3 years), which may have resulted in an underestimation in the incidence of IHD amongst cases.

The findings from our study are consistent with previous studies that have demonstrated an association between IPF and cardiovascular disease.^{1,3-5,24,25} A study by Panos et. al. showed that ischaemic heart disease and heart failure were common causes of death amongst patients with IPF.²⁶ In a cross sectional study of 630 patients referred for lung transplantation evaluation, Kizer et. al. found increased prevalence of angiographic coronary artery disease in patients with fibrotic lung disease compared to those with non-fibrotic lung diseases, after controlling for traditional risk factors (OR 2.18, 95%CI: 1.46-11.9).²⁴ This is similar to the findings of another study in lung transplantation candidates that found that angiographic evidence of coronary artery disease was significantly more common in people with lung fibrosis compared to those with chronic obstructive pulmonary disease (COPD) despite the smoking prevalence in being much higher in people with COPD.²⁵ A recent study of 73 IPF and 56 COPD patients found the prevalence of coronary artery disease was higher in those with IPF (65.8% vs. 46.1%), with more severe disease also being more common in

those with IPF.⁵ People with IPF who have severe coronary artery disease also appear to have worse outcomes.⁵

Using UK primary care data, we have previously found that people with IPF had an increased risk of acute coronary syndrome, angina and prescription of cardiovascular drugs compared to the general population, even before the diagnosis of IPF was made.³ We also found that the risk of acute coronary syndrome increased to three-fold in people with IPF compared to the general population after the diagnosis of IPF was established (RR 3.14, 95%CI: 2.02-4.87).³ Similar findings were reported from a hospital based case-control study which showed that the prevalence of coronary artery disease was five times higher in patients with IPF (OR 5.37, 95% CI 1.52-19.00; p<0.01).⁴

Despite the possibility of ascertainment bias, our findings suggest that IPF is an independent risk factor for ischaemic heart disease. This is consistent with the findings of other studies and suggests that simply targeting risk factors for cardiovascular disease in people with IPF may not be sufficient to reduce the incidence of ischaemic heart disease. It is possible, however, that IPF and ischaemic heart disease share other aetiological risk factors. Studies have suggested that people with IPF have an increased tendency to clot,^{14,27,28} and have higher Factor VIII levels than the general population.¹⁴ Previous studies have also demonstrated that elevated Factor VIII levels are associated with an increased risk of coronary artery disease.^{29,30}

In conclusion, we have found that people with IPF have increased prevalence of cardiovascular risk factors. People with IPF also have an increased risk of ischaemic heart disease that cannot be attributed to the increased prevalence of these risk factors alone.

While treatment of these risk factors must be considered during routine care of people with IPF, further research into the biological mechanism behind the increased risk is warranted.

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Contributions

Conception and design of the study were by RBH and VN, data analysis and interpretation were performed by WD with assistance from HAP, VN and RBH. The article was written by WD and VN, HAP and RBH had substantial involvement in its revision prior to submission. All authors approved the final manuscript before submission.

Guarantor statement

VN takes responsibility for (and is guarantor of) the content of this manuscript, including the data and analysis

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