



The association of pulmonary fibrosis with diabetes mellitus

To the Editor:

Idiopathic pulmonary fibrosis (IPF) is the most studied fibrotic lung disease and has overlapping pathogenesis with other fibrotic lung diseases. It is associated with a high prevalence of other comorbidities, such as COPD, lung cancer and coronary artery disease, due to common risk factors such as smoking and older age [1]. Several case-control studies have also suggested a link between IPF and diabetes mellitus. These studies have reported a higher prevalence of diabetes in IPF patients compared to matched controls [2–5]. In a small study, the presence of diabetes was also shown to increase the risk of mortality in IPF patients [6]. Given the limited data due to the small sizes of the prior studies, we sought to explore the prevalence of pulmonary fibrosis (PF) in diabetics compared to nondiabetics in a larger cohort stratified by sex, race and age. In addition, we evaluated differences in the underlying cause of death (UCD) in PF patients with and without diabetes.

This is a retrospective, population-based study using the Centers for Disease Control and Prevention (CDC) Multiple Cause of Death database, which contains information regarding the UCD and contributing conditions collected from death certificates of all US residents. Diabetics were identified using International Classification of Diseases, 10th revision (ICD-10) codes E10–E14. Decedents with PF were identified by first using ICD-10 code J84.1. Those with accompanying codes for secondary conditions associated with PF were excluded to identify those more likely to have IPF [7]. Since the use of ICD codes for PF and diabetes were rare below 45 years of age [8], we only included decedents aged ≥ 45 years. When comparing the risk of PF in diabetics compared to nondiabetics, logistic regression was performed to determine the adjusted risk for sex, age group and race. A similar methodology was used in prior studies to evaluate the relative risk of different conditions in the PF population compared to the non-PF population using the CDC Multiple Cause of Death database [9]. Chi-squared was used to compare differences in the UCD in patients with PF with and without diabetes. A p-value of < 0.05 was considered statistically significant. Poisson regression modelling was used to analyse temporal trends and negative binomial regression was used for overdispersed data [10]. All analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

From 2007 to 2017, there were 26 305 568 deaths in the USA. Of these patients, PF was present in 0.65% of diabetics and 0.80% of nondiabetics. The overall odds of having concurrent PF was significantly lower in diabetics (OR 0.81, 95% CI 0.79–0.82). In the year-by-year analysis, the risk of PF was lower in diabetics for every year (not shown).

Decedents were stratified by sex, age group and race. The risk of PF was lower in those with diabetes in all age strata and races, and both sexes (table 1).

When stratified by sex and age, the risk of PF was lower in diabetics compared to non-diabetics in both sexes in all age strata except females between ages 45–54 years (OR 0.93, 95% CI 0.80–1.08) (not shown). When stratified by sex and race, the risk of PF was lower in diabetics of both sexes in all races. Using logistic regression, the risk of PF remained significantly lower in diabetics after adjusting for sex and age (adjusted OR 0.82, 95% CI 0.80–0.83) and for sex and race (adjusted OR 0.80, 95% CI 0.79–0.81).



@ERSpublications

The association between diabetes and pulmonary fibrosis is not well understood. This large study demonstrates that the prevalence of pulmonary fibrosis is lower in diabetic decedents compared to nondiabetic decedents. <https://bit.ly/3gNgjeU>

Cite this article as: Jeganathan N, Miot C, Sathanathan A, *et al.* The association of pulmonary fibrosis with diabetes mellitus. *ERJ Open Res* 2020; 6: 00237–2020 [<https://doi.org/10.1183/23120541.00237-2020>].

Copyright ©ERS 2020. This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0.



TABLE 1 Prevalence of pulmonary fibrosis (PF) in decedents with and without diabetes mellitus (DM)

| Variable | Decedents without DM [#] | | | | | Decedents with DM [¶] | | | | | OR* (95% CI) |
|-------------------------|-----------------------------------|------------|------------------------|--------------------------------------|-------------------|--------------------------------|------------|------------------------|--------------------------------------|-------------------|------------------|
| | Total deaths | PF present | Total deaths with PF % | PF mortality rate % change 2007–2017 | p-value for trend | Total deaths | PF present | Total deaths with PF % | PF mortality rate % change 2007–2017 | p-value for trend | |
| Sex | | | | | | | | | | | |
| Female | 12 136 433 | 86 119 | 0.71 | −4.5 | 0.07 | 12 435 09 | 7022 | 0.56 | −14.0 | −0.01 | 0.79 (0.78–0.81) |
| Male | 11 551 233 | 104 316 | 0.90 | +6.0 | 0.03 | 13 743 93 | 9964 | 0.72 | | | 0.80 (0.78–0.82) |
| Age years | | | | | | | | | | | |
| 45–54 | 1 803 885 | 4 879 | 0.27 | −17.3 | 0.001 | 1 726 21 | 374 | 0.22 | | | 0.80 (0.72–0.89) |
| 55–64 | 3 221 877 | 16 158 | 0.50 | −16.7 | <0.001 | 4 116 16 | 1 645 | 0.40 | −17.8 | 0.03 | 0.80 (0.76–0.84) |
| 65–74 | 4 296 696 | 40 423 | 0.95 | −13.7 | <0.001 | 6 143 78 | 4 352 | 0.71 | −24.6 | <0.001 | 0.75 (0.73–0.78) |
| 75–84 | 6 221 180 | 69 375 | 1.12 | −2.17 | 0.002 | 7 668 51 | 6 443 | 0.84 | −6.3 | 0.001 | 0.75 (0.73–0.77) |
| ≥85 | 8 144 028 | 59 600 | 0.73 | +3.4 | 0.03 | 6 524 36 | 4 172 | 0.64 | | | 0.87 (0.85–0.90) |
| Race | | | | | | | | | | | |
| Native-American | 1 180 36 | 1 433 | 1.21 | +24.1 | <0.001 | 24 513 | 207 | 0.84 | | | 0.69 (0.60–0.80) |
| Asian | 4 904 43 | 4 407 | 0.90 | | | 75 862 | 518 | 0.68 | | | 0.76 (0.69–0.83) |
| Black | 2 466 550 | 8 795 | 0.36 | −8.0 | 0.01 | 3 827 89 | 1 213 | 0.32 | −17.8 | 0.003 | 0.89 (0.84–0.94) |
| White | 19 327 231 | 161 217 | 0.83 | +5.1 | 0.06 | 18 954 44 | 13 132 | 0.69 | | | 0.83 (0.81–0.84) |
| Hispanic | 1 223 991 | 14 279 | 1.17 | | | 2 319 54 | 1 883 | 0.81 | | | 0.69 (0.66–0.73) |
| UCD | | | | | | | | | | | |
| PF | | 132 322 | | | | | 9 807 | | | | 0.60 (0.58–0.62) |
| Ischaemic heart disease | | 9 153 | | −27.7 | 0.002 | | 1 486 | | | | 1.90 (1.79–2.01) |
| Lung cancer | | 4 930 | | | | | 391 | | | | 0.89 (0.80–0.98) |
| Pneumonia | | 1 737 | | | | | 97 | | | | 0.62 (0.51–0.77) |
| Heart failure | | 1 380 | | | | | 118 | | | | 0.96 (0.79–1.16) |
| Cerebrovascular disease | | 1 241 | | | | | 152 | | | | 1.38 (1.16–1.63) |
| Pulmonary heart disease | | 875 | | | | | 77 | | | | 0.99 (0.78–1.25) |
| Other | | 38 797 | | | | | 4 858 | | | | 1.57 (1.51–1.62) |

International Classification of Diseases, 10th revision, codes used for underlying cause of death (UCD) are as follows. Pulmonary fibrosis: J84.1; ischaemic heart disease: I20–I25; lung cancer: C34–C34.9; pneumonia: J09–J18.9; heart failure: I50–I50.9; cerebrovascular disease: I60–I69.8; pulmonary heart disease: I26–I27.9. If no data are shown for % change in rate, the regression analysis of the data did not indicate a significant change in trend during the time period. [#]: n=23 687 666; [¶]: n=2 617 902; *: the overall risk of PF in diabetics compared to nondiabetics.

The overall crude mortality rate from PF was 15 per 100000 population (17.6 in males and 12.7 in females). The mortality rate from PF was unchanged from 2007 to 2017 in both diabetics and nondiabetics. In both groups, when stratified by demographics, a negative trend was noted in females, black people and those between ages 55–84. In nondiabetics, an increasing trend was noted in males, those aged ≥ 85 years, white people and Native Americans.

PF decedents with diabetes, compared to PF alone, were less likely to have PF, lung cancer and pneumonia as the UCD, and were more likely to have ischaemic heart disease, cerebrovascular disease or other causes listed as the UCD (table 1).

To date, our study represents the largest analysis examining the association between PF and diabetes. We report that the presence of PF is lower in decedents with diabetes compared to those without. This finding was consistent irrespective of sex, age group, race or year of death. We also performed a reverse analysis evaluating the percent of PF decedents with diabetes (8.2%) compared to non-PF decedents with diabetes (9.9%), which showed lower odds of having diabetes in PF decedents compared to non-PF decedents (OR 0.81, 95% CI 0.80–0.83). A possible explanation for this finding is a lower incidence of PF in diabetics or improved survival of PF patients with diabetes.

Several case–control studies have reported a higher prevalence of diabetes in IPF patients (10% to 33%) compared to matched controls [2–5]. However, these studies were small and mostly single-centred, and therefore could have been influenced by selection bias. Ascertainment bias may also have been present as patients with IPF are more likely to see their physician regularly and therefore have other illnesses diagnosed.

Contrary to the prior studies, our large study suggests that the prevalence of PF may be lower in diabetics compared to nondiabetics. This may be partly due to diabetic decedents dying at a younger age from cardiac conditions before IPF can develop or be clinically recognised. This is supported by our findings that the percentage of decedents over the age of 85 years was lower in diabetics and that PF decedents with diabetes had higher odds of dying from ischaemic heart disease. Large longitudinal epidemiological studies are needed to understand the impact of diabetes on the risk of developing IPF and outcomes.

The lower prevalence of PF in diabetic decedents could also be due to improved survival time. Acute exacerbation of IPF shares several pathophysiological features with acute respiratory distress syndrome, and is a major cause of the decline in lung function and mortality [11]. Several studies have shown that pre-existing diabetes is associated with a decreased risk of acute respiratory distress syndrome and, therefore, may similarly decrease the risk of acute exacerbations of IPF.

Consistent with other recently published studies, we noted declining PF-related mortality rates in females, black people and those aged 55–84 years [12]. These trends were more pronounced in diabetics due to concomitant decline in overall diabetes-related deaths in these demographics (not shown). The relative risk of PF in diabetics compared to nondiabetics did not change significantly during this period.

The strengths of this study are the large numbers and inclusion of the entire US population without sampling. The major limitation of this database, like other large epidemiological studies, is the inability to confirm the accuracy of the diagnosis or the ICD coding on the death certificate. Studies with IPF have previously noted under-reporting on death certificates. However, we would expect any such misclassification to be independent of whether a person has diabetes or not. The reporting of IPF seems to have improved and in a validation study in 2010, 82% of decedents with IPF had the diagnosis included in the death certificate [13]. In a population-based study of residents aged ≥ 50 years in Olmstead County, Minnesota, the overall incidence of IPF between 1997 and 2005 was 17.4 per 100000 population using broad criteria (24 in males and 13.4 in females) [14]. Since IPF has a short survival duration, the mortality rates likely mirror the incidence. In our study, the overall crude mortality rate for PF was comparable to the reported incidence. More current validation studies are needed to estimate the accuracy of reporting.

Diabetes is also likely under-reported in this database. Given the large numbers in this study, the finding of lower odds of PF with diabetes is unlikely to be due to chance alone. It would also be expected that any misclassification in diabetes would bias the association toward the null, suggesting the association between diabetes and PF maybe even stronger than we report without the misclassification. To support this claim, we analysed another chronic pulmonary condition, COPD, that has been known to have a higher prevalence in diabetics compared to nondiabetics [15]. In this analysis, the overall odds of having concurrent COPD was higher in diabetics (OR 1.24, 95% CI 1.23–1.24) compared to nondiabetics.

Niranjan Jeganathan ¹, **Christelle Miot**², **Airani Sathananthan**³ and **Matheni Sathananthan**²

¹Dept of Medicine, Division of Pulmonary, Critical Care, Hyperbaric, Allergy and Sleep Medicine, Loma Linda University Health, Loma Linda, CA, USA. ²Dept of Medicine, Loma Linda University Health, Loma

Linda, CA, USA. ³College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, CA, USA.

Correspondence: Niranjn Jeganathan, Dept of Medicine, Division of Pulmonary, Critical Care, Hyperbaric, Allergy and Sleep Medicine, Loma Linda University Health, 11234 Anderson Street, Room 6424, Loma Linda, CA 92354, USA. E-mail: njeganathan@llu.edu

Received: 2 May 2020 | Accepted after revision: 7 Aug 2020

Author contributions: N. Jeganathan conceived the idea, designed the study, analysed the data and drafted the manuscript. C. Miot assisted with data collection and drafted the manuscript. A. Sathananthan and M. Sathananthan assisted with data analysis and editing.

Conflict of interest: None declared.

References

- 1 Oldham JM, Collard HR. Comorbid conditions in idiopathic pulmonary fibrosis: recognition and management. *Front Med* 2017; 4: 123.
- 2 Dalleywater W, Powell HA, Hubbard RB, *et al.* Risk factors for cardiovascular disease in people with idiopathic pulmonary fibrosis: a population-based study. *Chest* 2015; 147: 150–156.
- 3 Garcia-Sancho Figueroa MC, Carrillo G, Perez-Padilla R, *et al.* Risk factors for idiopathic pulmonary fibrosis in a Mexican population. A case-control study. *Respir Med* 2010; 104: 305–309.
- 4 Gribbin J, Hubbard R, Smith C. Role of diabetes mellitus and gastro-oesophageal reflux in the aetiology of idiopathic pulmonary fibrosis. *Respir Med* 2009; 103: 927–931.
- 5 Enomoto T, Usuki J, Azuma A, *et al.* Diabetes mellitus may increase risk for idiopathic pulmonary fibrosis. *Chest* 2003; 123: 2007–2011.
- 6 Hyldgaard C, Hilberg O, Bendstrup E. How does comorbidity influence survival in idiopathic pulmonary fibrosis? *Respir Med* 2014; 108: 647–653.
- 7 CDC WONDER Multiple cause of death, 2004–2017. Available from: <https://wonder.cdc.gov/mcd.html>. Date last updated: December 6, 2018. Date last accessed: May 19, 2019.
- 8 CDC. National Diabetes Statistics Report, 2017. Atlanta, US Department of Health and Human Services, 2017.
- 9 Sprunger DB, Olson AL, Huie TJ, *et al.* Pulmonary fibrosis is associated with an elevated risk of thromboembolic disease. *Eur Respir J* 2012; 39: 125–132.
- 10 Grinshteyn E, Hemenway D. Violent death rates: the US compared with other high-income OECD countries, 2010. *Am J Med* 2016; 129: 266–273.
- 11 Marchioni A, Tonelli R, Ball L, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis: lessons learned from acute respiratory distress syndrome? *Crit Care* 2018; 22: 80.
- 12 Fernandez Perez ER. Changing trends in age-adjusted pulmonary fibrosis mortality in the USA: a joinpoint regression analysis. *Eur Respir J* 2019; 54: 1900364.
- 13 Hutchinson JP, McKeever TM, Fogarty AW, *et al.* Increasing global mortality from idiopathic pulmonary fibrosis in the twenty-first century. *Ann Am Thorac Soc* 2014; 11: 1176–1185.
- 14 Fernandez Perez ER, Daniels CE, Schroeder DR, *et al.* Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study. *Chest* 2010; 137: 129–137.
- 15 Ehrlich SF, Quesenberry CP, Jr., Van Den Eeden SK, *et al.* Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. *Diabetes Care* 2010; 33: 55–60.