The role of cigarette smoking-derived pollutants in the risk of mortality in idiopathic pulmonary fibrosis

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Reply to T. Yasuma and co-workers:

We thank T. Yasuma and co-workers for their valuable comments on our paper describing the association between individual-level long-term concentrations of air pollutants at the residential addresses of patients with idiopathic pulmonary fibrosis (IPF) and mortality among them [1]. We agree that the release of nitrogen dioxide (NO_2) or particulate matter in cigarette smoke is one of the considerations in interpreting our results. Thus, we stratified all patients into ever- and non-smokers according to their smoking status and analysed the effect of air pollutants on mortality risk in these patients using our health analysis models that included different sets of confounders (figure 1).

Among the 1114 patients with IPF, 846 (75.9%) were ever-smokers and 268 (24.1%) were non-smokers. Ever-smokers had a higher proportion of males (97.2% *versus* 25.0%; p<0.001) and higher baseline forced vital capacity (71.6% *versus* 67.0% predicted; p<0.001) than non-smokers. Furthermore, the former were less frequently treated with anti-inflammatory agents compared to the latter (38.4% *versus* 48.1%; p=0.004); however, there were no significant between-group differences in age (65.6 *versus* 65.9 years; p=0.659), body mass index (24.1 *versus* 24.2 $kg \cdot m^{-2}$; p=0.460), and diffusing capacity for carbon monoxide (57.1% *versus* 58.2% predicted; p=0.427). Furthermore, no significant between-group differences were found in the annual average concentrations of NO_2 (22.4 *versus* 22.9 parts per billion; p=0.439) and particulate matter with a 50% cut-off aerodynamic diameter of 10 µm (PM_{10}) (55.9 *versus* 58.2 $\mu g \cdot m^{-3}$; p=0.901). Moreover, there was no significant between-group difference in the median survival period (4.3 years *versus* 3.9 years; p=0.815).

Hazard ratios of mortality for NO_2 were relatively similar between the ever- and non-smokers; furthermore, the confidence intervals of the two groups overlapped, indicating no significant difference between these two smoking statuses in models 1–4, adjusted for different sets of individual- or area-level variables (figure 1a). Hazard ratios of mortality for PM_{10} did not show significant between-group differences in all models (figure 1b).

Our subgroup analysis based on the smoking status of the patients with IPF did not show any differences between ever-smokers and non-smokers in the association between air pollutants and mortality risk. IPF mostly occurs in old males and ever-smokers [2]; furthermore, cigarette smoking is associated with IPF development [3, 4]. Meanwhile, the effect of smoking on the prognosis of IPF remains controversial [5, 6]. Smokers exhibit higher survival rates [5–7] and lower frequency of experiencing acute exacerbations [7, 8] than non-smokers. Kishaba *et al.* [7], in their study including 98 patients with IPF, reported that ever-smokers (n=66) exhibited a lower frequency of experiencing acute exacerbations (18.2% *versus* 50.0%; p<0.001) and a longer median survival period (26.3 *versus* 18.5 months; p<0.001) than never-smokers (n=32). Furthermore, Song *et al.* [8], in their study on 461 patients with IPF, found that smoking was a protective factor for acute exacerbations (HR 0.585, 95% CI 0.342–1.001; p=0.050). These findings may be attributable to the "healthy smoker" effect [9]: *i.e.* diseases are diagnosed early in smokers owing to their frequent hospital visits due to smoking-related respiratory symptoms, or people whose lungs are relatively resistant to the effects of smoking become smokers. Cigarette smoking releases particulate matter and free radicals, particularly reactive oxygen and nitrogen species [10]; therefore, exposure to cigarette smoke-derived pollutants may exacerbate air pollutant-related mortality in patients with IPF having a smoking history. However, our analysis did not show any differences in the association between

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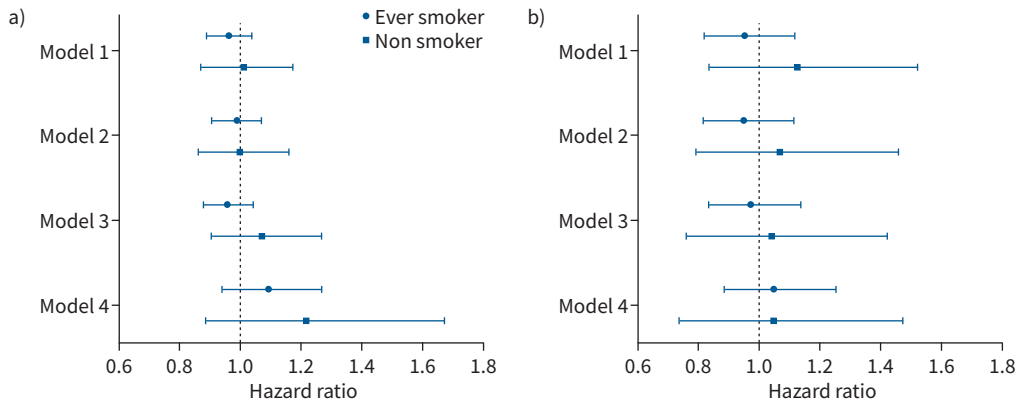

FIGURE 1 Comparison of the effect of air pollutant concentrations on mortality risk in patients with idiopathic pulmonary fibrosis (IPF) stratified by smoking status. Effect of a) nitrogen dioxide and b) particulate matter with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10}) on IPF mortality. Symbols and error bars represent hazard ratios and 95% confidence intervals presented as per 10 $\mu g \cdot m^{-3}$ increase in PM_{10} or 10 parts per billion increase in nitrogen dioxide. Model 1: unadjusted; model 2: adjusted for age, sex and diagnosis year; model 3: adjusted for variables in model 2 with body mass index, lung function (forced vital capacity and diffusing capacity for carbon monoxide) and treatment (antifibrotic agents, steroids with or without immunosuppressants, and no treatment); and model 4: adjusted for variables in model 3 with proportion of educational attainment equal to or higher than high school and gross regional domestic product in each residential district.

air pollutants and IPF mortality after stratification by smoking status. Nevertheless, some points related to these findings require consideration. We could not explore the effects of current or passive smoking because limited data are available on the smoking history of the patients' family members or neighbours. Moreover, the risk might be similar in former smokers and non-smokers owing to the ceased influx of air pollutants from cigarette smoke.

In conclusion, our results suggest that the effect of air pollutants on mortality risk in patients with IPF is independent of their smoking status. Well-designed prospective studies evaluating the interaction between smoking and air pollution are warranted to explore the effect of cigarette smoke-derived pollutants on mortality risk in patients with IPF.

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References

1 Yoon H-Y, Kim S-Y, Kim O-J, *et al.* Nitrogen dioxide increases the risk of mortality in idiopathic pulmonary fibrosis. *Eur Respir J* 2021; 57: 2001877.

2 Raghu G, Collard HR, Egan JJ, *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011: 183: 788–824.

3 Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? *Proc Am Thorac Soc* 2006; 3: 293–298.
4 Ekström M, Gustafson T, Boman K, *et al.* Effects of smoking, gender and occupational exposure on the risk of severe pulmonary fibrosis: a population-based case-control study. *BMJ Open* 2014; 4: e004018.
5 Antoniou KM, Hansell DM, Rubens MB, *et al.* Idiopathic pulmonary fibrosis: outcome in relation to smoking status. *Am J Respir Crit Care Med* 2008; 177: 190–194.
6 Kärkkäinen M, Kettunen HP, Nurmi H, *et al.* Effect of smoking and comorbidities on survival in idiopathic pulmonary fibrosis. *Respir Res* 2017; 18: 160.
7 Kishaba T, Nagano H, Nei Y, *et al.* Clinical characteristics of idiopathic pulmonary fibrosis patients according to their smoking status. *J Thorac Dis* 2016; 8: 1112–1120.
8 Song JW, Hong SB, Lim CM, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *Eur Respir J* 2011; 37: 356–363.
9 Becklake MR, Lalloo U. The 'healthy smoker': a phenomenon of health selection? *Respiration* 1990; 57: 137–144.
10 Pryor WA, Stone K. Oxidants in cigarette smoke. Radicals, hydrogen peroxide, peroxynitrate, and peroxynitrite. *Ann N Y Acad Sci* 1993: 686: 12–27.