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Long-term air pollution exposure is associated with increased severity of idiopathic pulmonary fibrosis in the IPF-PRO Registry

Coralynn Sack,[1] Daniel Wojdyla,[2] Maeve G MacMurdo,[3] Amanda Gassett,[1] Joel D Kaufman,[1] Ganesh Raghu,[1] Carrie A Redlich,[4] Peide Li,[5] Amy L Olson,[5] Thomas B Leonard,[5] Jamie L Todd,[2,6] Megan L Neely,[2,6] Laurie D Snyder,[2,6] Mridu Gulati,[4] on behalf of the IPF-PRO Registry investigators

[1]University of Washington, Seattle, WA, USA; [2]Duke Clinical Research Institute, Durham, NC, USA; [3]Cleveland Clinic, Cleveland, OH, USA; [4]Yale School of Medicine, New Haven, CT, USA; [5]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; [6]Duke University Medical Center, Durham, NC, USA.

Rationale: While exposure to ambient air pollution is a known risk factor for adverse pulmonary outcomes, its impact in individuals with idiopathic pulmonary fibrosis (IPF) is less established. We hypothesized that long-term exposure to air pollution would be associated with increased IPF morbidity and mortality.

Methods: We performed cross-sectional and longitudinal analyses of participants in the IPF-PRO Registry, a multicenter, observational registry that enrolled individuals with newly diagnosed or confirmed IPF (within the past 6 months) from 46 sites across the US from June 2014 to October 2018. Five-year average pollution exposures ($PM_{2.5}$, NO_2, O_3) were estimated at home address with validated national spatio-temporal models. Multivariable regression models estimated the association between pollution exposure and physiologic measurements (FVC, DLCO, supplemental oxygen use at rest and quality of life measurements (St. George's Respiratory Questionnaire [SGRQ], EuroQoL, Cough and Sputum Assessment Questionnaire [CASA-Q]) at baseline. Cox proportional hazard regression models estimated the association between pollution exposure and a composite outcome of mortality, lung transplant, or ≥10% absolute decline in % predicted FVC in the 1 year after enrollment. Models were adjusted for potential individual-level and spatial confounders, including proxies for disease onset. Gene-environmental interactions with MUC5B and telomere length were assessed.

Results: Of 835 participants, 94% were non-Hispanic Whites, 76% were male, mean (SD) age was 70 (7.7) years. Mean (SD) 5-year $PM_{2.5}$ exposure was 8.1 (8) $\mu g/m^3$, positively correlated

with NO_2 (Pearson correlation coefficient [r] = 0.37) and negatively correlated with O_3 (r = -0.38) In fully adjusted analyses, each 2µg/m^3 increase in $PM_{2.5}$ exposure was associated with -2.86% [95% confidence interval (CI) -4.97, -0.76] lower % predicted FVC, -2.05% [95% CI -3.79, -0.30] lower % predicted DLCO, and worse reported quality of life per SGRQ and EuroQoL questionnaires (Table). Each 3 parts per billion (ppb) increase in O_3 exposure was associated with a 1.57% [95% CI 0.15, 2.98] higher % predicted FVC, although this effect was attenuated in multi-pollutant models. Within 1 year of enrollment, 22% had experienced the composite outcome. There was no association between NO_2 and baseline measures, between pollution exposure and longitudinal outcomes, or evidence for gene-environmental interactions.

Conclusion: Long-term exposure to $PM_{2.5}$ was associated with increased IPF severity, but not with short-term disease progression or mortality. The unexpected relationship between O_3 exposure and increased FVC may be partially explained by the negative spatial correlation with other important co-pollutants and geographic cofactors that contribute to disease presentation.

Table. Associations between ambient air pollution (5-year estimates) and selected parameters of disease severity at enrollment into IPF-PRO Registry

Outcomes	Base adjusted model[1]		Fully adjusted model[2]	
	Change in means[3] (95% CI)	p-value	Change in means[3] (95% CI)	p-value
% predicted FVC				
$PM_{2.5}$	-3.37 (-5.31, -1.44)	<.001	-2.86 (-4.97, -0.76)	0.008
NO_2	-0.19 (-1.48, 1.10)	0.769	-0.71 (-2.16, 0.75)	0.340
O_3	1.71 (0.41, 3.00)	0.010	1.57 (0.15, 2.98)	0.030
% predicted DL_{CO}				
$PM_{2.5}$	-2.90 (-4.52, -1.28)	<.001	-2.05 (-3.79, -0.30)	0.022
NO_2	0.63 (-0.42, 1.68)	0.241	0.11 (-1.09, 1.31)	0.857
O_3	1.51 (0.43, 2.58)	0.006	1.09 (-0.09, 2.26)	0.070
SGRQ total score				
$PM_{2.5}$	3.03 (0.94, 5.12)	0.005	2.25 (-0.05, 4.56)	0.055
NO_2	-1.14 (-2.54, 0.26)	0.110	-0.59 (-2.18, 0.99)	0.463
O_3	-0.50 (-1.92, 0.93)	0.494	0.38 (-1.17, 1.93)	0.632
EuroQoL score				
$PM_{2.5}$	-0.04 (-0.06, -0.02)	0.001	-0.04 (-0.06, -0.01)	0.007
NO_2	-0.00 (-0.02, 0.01)	0.763	-0.01 (-0.03, 0.01)	0.347
O_3	0.02 (-0.00, 0.03)	0.066	0.01 (-0.01, 0.02)	0.410

[1] Adjusted for age, sex, smoking (ever/ never), anti-fibrotic treatment (yes/no) and time since diagnosis at enrollment.
[2] Adjusted for age, sex, smoking, anti-fibrotic treatment (yes/no), time since diagnosis, region, social vulnerability index at enrollment and site (random).
[3] Estimated change in means for 2µg/m^3 increase in $PM_{2.5}$, 4ppb increase in NO_2, 3ppb increase in O_3.

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