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Air Pollution as a Risk Factor for Lung Cancer: Potential Mechanisms

To the Editor:

Given our active research in the areas of epidemiology and mechanisms of obstructive lung disease and how/why chronic obstructive pulmonary disease (COPD) and lung cancer fit as closely together as they do, we were particularly interested in the recent stimulating article by Huang and colleagues (1) and the accompanying editorial by Chistiani (2), published online on August 9, 2021. The tight focus of each article was a timely analysis of the powerful UK Biobank Cohort database indicating genetic- and air pollution–related risks for lung cancer, with some other relevant factors taken into account in the analyses.

We were interested that neither article mentions COPD because there is evidence for this being a major causative link to lung cancer in smokers, which remains after accounting for the risk associated with smoking *per se*. This may well be related to the well-described underlying small airway remodeling pathology in smokers, with fibrotic narrowing/obliteration of small airways that leads to airway obstruction (3). Furthermore, there is increasing evidence for the specific linkage process between smoking, COPD, and lung cancer being a pathway though a cascade of reactive oxygen species activating the airway epithelium, leading to basal (stem) cell genetic reprogramming. This then leads to growth-factor production, strategic kinase, and transcription factor mobilization and ultimately to a final common mechanism of epithelial–mesenchymal transition (EMT). EMT is associated with myofibroblast proliferation and secondary excessive and abnormal matrix protein production with airway wall thickening (4). EMT is recognized as a vital, common part of malignancy pathogenesis across a swathe of epithelial cancers and thus is a mechanistically plausible etiological link between COPD and lung cancer development (3).

It is known that occupational and general air pollution gives rise to chronic fixed airflow obstruction with modulation of these effects by antioxidant gene polymorphisms (5). In view of this background, we would be very interested to know if Huang and colleagues (1) in their studies of this large United Kingdom population database have been able to explicitly integrate obstructive lung function spirometric abnormalities into their analysis, looking specifically for mediation or interactions by airway obstruction in the apparent air pollution effect on lung cancer. We believe that if it is possible within the UK Biobank data set, such an analysis could help inform and/or confirm potentially core relationships between environmental air pollution exposures, airway pathology, and the etiology of lung cancer in this globally relevant context of air pollution. ■

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Reply to Ward *et al.*

From the Authors:

We read the response letter by Ward and colleagues to our manuscript (1), and the accompanying editorial by Christiani (2),

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Table 1. Mediation Analysis of COPD on the Associations between Air Pollution and Lung Cancer Risk

Pollution	Total Effect [β (95% CI)]	Natural Direct Effect [β (95% CI)]	Natural Indirect Effect [β (95% CI)]	Mediation Proportion [% (95% CI)]
$PM_{2.5}$	0.454 (0.198–0.691)	0.374 (0.117–0.615)	0.080 (0.066–0.095)	17.56 (11.13–41.43)
PM_{10}	0.336 (0.048–0.618)	0.309 (0.024–0.592)	0.027 (0.015–0.039)	7.91 (2.97–34.27)
NO_2	0.076 (0.011–0.134)	0.061 (–0.004–0.119)	0.015 (0.012–0.018)	19.99 (10.15–95.45)
NO_x	0.098 (0.034–0.151)	0.079 (0.017–0.133)	0.019 (0.016–0.023)	19.43 (11.85–50.97)

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; NO_2 = nitrogen dioxide; NO_x = nitrogen oxides; $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; PM_{10} = particulate matter ≤10 μm in aerodynamic diameter.
Adjusted for age, sex, body mass index, household income, education level, smoking status, and pack-years of smoking.

with great interest and value the insightful suggestions they raise. We agreed with that there is a mechanistically plausible etiological link between chronic obstructive pulmonary disease (COPD) and lung cancer development. Previous studies have also shown that personal medical history of COPD was an independent risk factor of lung cancer (3).

As suggested, we further integrated COPD at baseline into our analysis to dissect the complex relations of air pollution, COPD, and incident lung cancer events in the UK Biobank. We defined participants with hospital admission records of COPD before the date of baseline assessment, self-reported COPD, or those with mild to moderate airflow obstruction (defined as post-bronchodilator FEV_1/FVC <0.70) at the baseline assessment as prevalent COPD (4). We also defined particulate matter ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$), particulate matter ≤10 μm in aerodynamic diameter (PM_{10}), and nitrogen dioxide (NO_2) as high- and low-exposure category according to World Health Organization guidelines, except for nitrogen oxides (NO_x), of which the median level was used. Cross-sectional analyses showed that higher exposures to $PM_{2.5}$, PM_{10}, NO_2, and NO_x were significantly associated with higher risk of prevalent COPD at baseline after adjusting for age, sex, body mass index, household income, education level, smoking status, and pack-years of smoking ($PM_{2.5}$ [odds ratio (OR), 1.47; 95% confidence interval (CI), 1.40–1.54, per 5 μg/m^3]; PM_{10} [OR, 1.13; 95% CI, 1.07–1.20, per 10 μg/m^3]; NO_2 [OR, 1.08; 95% CI, 1.06–1.09, per 10 μg/m^3]; and NO_x [OR, 1.10; 95% CI, 1.08–1.11, per 20 μg/m^3]). In addition, we observed that participants with prevalent COPD at baseline had significantly higher risk of incident lung cancer during the

Table 2. Joint Effect and Additive Interaction between Air Pollution and COPD

Air Pollutant	Pollution Category	COPD	HR (95% CI)	*P* Value	RERI* (95% CI)	AP* (95% CI)
$PM_{2.5}$†	Low	Without	Ref.			
	High	Without	1.09 (0.93 to 1.29)	0.290		
	Low	With	2.56 (2.15 to 3.04)	$<2\times10^{-16}$		
	High	With	3.01 (2.55 to 3.55)	$<2\times10^{-16}$	0.36 (0.14 to 0.58)	0.12 (0.05 to 0.19)
PM_{10}‡	Low	Without	Ref.			
	High	Without	0.99 (0.83 to 1.18)	0.898		
	Low	With	2.51 (2.16 to 2.90)	$<2\times10^{-16}$		
	High	With	3.02 (2.53 to 3.60)	$<2\times10^{-16}$	0.53 (0.29 to 0.76)	0.17 (0.10 to 0.24)
NO_2§	Low	Without	Ref.			
	High	Without	1.03 (0.78 to 1.37)	0.815		
	Low	With	2.69 (2.38 to 3.04)	$<2\times10^{-16}$		
	High	With	2.64 (2.01 to 3.45)	$<2\times10^{-16}$	−0.09 (−0.43 to 0.27)	−0.03 (−0.19 to 0.09)
NO_x‖	Low	Without	Ref.			
	High	Without	1.06 (0.91 to 1.24)	0.443		
	Low	With	2.38 (2.00 to 2.83)	$<2\times10^{-16}$		
	High	With	3.07 (2.62 to 3.58)	$<2\times10^{-16}$	0.63 (0.42 to 0.84)	0.20 (0.14 to 0.27)

Definition of abbreviations: AP = attributable proportion due to the interaction; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; NO_2 = nitrogen dioxide; NO_x = nitrogen oxides; $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; PM_{10} = particulate matter ≤10 μm in aerodynamic diameter; Ref. = reference; RERI = relative excess risk due to the interaction; WHO = World Health Organization.
Adjusted for age, sex, body mass index, household income, education level, smoking status, and pack-years of smoking.
*To estimate RERI and AP, the low-pollution category and the without COPD groups were the reference categories.
†Defined by WHO guideline value of $PM_{2.5}$: low (<10 μg/m^3) and high (≥10 μg/m^3).
‡Defined by WHO guideline value of PM_{10}: low (<20 μg/m^3) and high (≥20 μg/m^3).
§Defined by WHO guideline value of NO_2: low (<40 μg/m^3) and high (≥40 μg/m^3).
‖Defined by median of NO_x: low (<41.75 μg/m^3) and high (≥41.75 μg/m^3).

follow-up, with a hazard ratio (HR) of 2.68 (95% CI, 2.37–3.02) after adjusting the above covariates. These results indicated that COPD might be a mediator between air pollution and incident lung cancer.

We then performed a mediation analysis using natural effect models within the R package "medflex" (5). As expected, we observed significant mediation effects by prevalent COPD in the apparent air pollution effect on lung cancer, with a mediation proportion of 17.56% for $PM_{2.5}$, 7.91% for PM_{10}, 19.99% for NO_2, and 19.43% for NO_x (Table 1). Compared with participants without COPD at baseline and with low exposure to air pollution, those participants with COPD and with high exposure to air pollution had significantly increased risk of incident lung cancer ($PM_{2.5}$ [HR, 3.01; 95% CI, 2.55–3.55]; PM_{10} [HR, 3.02; 95% CI, 2.53–3.60]; NO_2 [HR, 2.64; 95% CI, 2.01–3.45]; and NO_x [HR, 3.07; 95% CI, 2.62–3.58]). Furthermore, we also observed positive additive interactions for air pollutants and prevalent COPD in the development of lung cancer (Table 2). The relative excess risk because of the interactions were estimated to be 0.36 (95% CI, 0.14–0.58) for $PM_{2.5}$, 0.53 (95% CI, 0.29–0.76) for PM_{10}, and 0.63 (95% CI, 0.42–0.84) for NO_x, which indicated that there were 12%, 17%, and 20% of the increased risk attributable to the additive interactions. However, we did not observe significant additive interactions for NO_2 exposure and prevalent COPD.

Taken together, our analyses supported the core relationships between environmental air pollution exposures, airway pathology, and the etiology of lung cancer in the globally relevant context of air pollution. Chronic inflammation associated with COPD may result in repeated airway epithelial injury and accompanying high cell turnover rates and propagation of DNA errors resulting in amplification of the carcinogenic effects of air pollution exposures (6). However, the hypothesized pathway was only one of the potential carcinogenic mechanisms of air pollution, as less than one-fifth of the total effects were mediated by COPD (7). In addition, it should be noted that it is difficult to disentangle the effects of single components from the complex mixture of air pollution; thus, further exposure pattern analysis may provide deeper insights. ■

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Pleuroparenchymal Fibroelastosis Induced by Liver Transplantation?

To the Editor:

We read with great interest the report by Goondi and colleagues involving pleuroparenchymal fibroelastosis (PPFE) associated with a liver transplant (1). A diagnosis of PPFE was established based on a multidisciplinary evaluation of clinical, radiologic, and pathologic (autopsy) findings. Because the patient had a history of liver transplantation 3 years earlier and had no evidence of connective tissue disease, occupational exposure, infections, or malignancies, Goondi and colleagues suggested that the liver transplant led to the development of PPFE. This case provides new insight into the pathogenesis of PPFE; however, we have some concerns regarding the links between PPFE and liver transplantation.

PPFE is a rare interstitial pneumonia that is characterized by pleural and subpleural fibroelastosis, predominantly in the upper lobes of the lung (2). It is known that PPFE occurs as a late-onset pulmonary complication after lung transplant and hematopoietic stem cell transplant. PPFE associated with lung transplantation represents an important histopathologic correlate of restrictive allograft syndrome, as a form of chronic lung allograft dysfunction (3). Concurrent bronchiolitis obliterans has also been identified in a majority of cases. Similarly, PPFE after hematopoietic stem cell transplant frequently occurs together with bronchiolitis obliterans as a form of chronic graft-versus-host disease (cGVHD) (4). Thus, transplant-related PPFE is believed to be a manifestation of late graft failure or cGVHD.

If transplant-related PPFE is a manifestation of late graft failure or cGVHD, how does liver transplant cause the development of

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