in many countries. Using data from the UK Biobank study, Huang and colleagues (1) reported associations between concentrations of ambient air pollutants (particulate matter ⩽2.5 μm in aerodynamic diameter, particulate matter ⩽10 μm in aerodynamic diameter, $NO_2$, and NOx) at baseline, estimated using land-use regression models, and incident lung cancer. Findings of this study provided compelling evidence for the link between air pollution and lung cancer, but it is of importance to understand underlying mechanisms of these associations. Commenting on this article, Ward and colleagues (3) discussed a mechanistically plausible etiological link between COPD and lung cancer and made the sensible suggestion of exploring the role of COPD as a mediator of the observed air pollution–lung cancer associations. In response to this suggestion, Huang and colleagues conducted a formal mediation analysis and found COPD only mediated 7.9–19.9% of the associations between air pollutants and incident lung cancer. Together, these findings provide more insights into the long-term impact of air pollution on lung cancer and potential biological pathways via inflammatory lung diseases such as COPD.

The authors' finding of less than 20% of the total effect of air pollution on lung cancer being mediated through COPD is surprising given previous data suggesting that COPD is a common and independent risk factor for newly diagnosed lung cancer (5). In the present study, COPD was defined as any of airflow limitation ($FEV_1/FVC < 0.7$), self-reported COPD, and/or a history of hospital admission due to COPD. Although these definitions of COPD are widely accepted, it does not comprehensively capture the totality of underlying smoking or pollution-related airway disease processes on the causal pathway between air pollution and lung cancer, which could underestimate the amount mediated.

There is a long lag period before airflow obstruction (mostly in large airways or aggregate substantial small airways) reaches the arbitrary cutoff of 0.7 and COPD can be diagnosed by conventional criteria. For example, some people with clear evidence of abnormalities in lung structure on computed tomography scans do not exhibit airflow limitation. Indeed, previous studies have suggested that up to 40% of small airways are destroyed before $FEV_1$ falls (6), and moreover, some people experience accelerated lung function decline but their $FEV_1/FVC$ remains over the traditional cutoff for many years. Thus, there is now increasing recognition of the "pre-COPD" paradigm, which refers to individuals on course to develop COPD (7). This concept encompasses symptoms, functional decline, and structural abnormalities as part of the pre-COPD syndrome.

Given that core underlying pathophysiological features and processes in pre-COPD are likely to mediate the association between air pollution and lung cancer, investigating both pre-COPD and diagnosed COPD as mediators together will help the field understand the full contribution of COPD to the pollution-lung cancer relationship. We acknowledge that the limited data from the UK Biobank study may not allow such comprehensive analyses, but there is still room for further exploration of the existing data. These include further mediation analysis investigating the lowest quartile of $FEV_1$, FVC, and $FEV_1/FVC$ at baseline and decline in these lung function indices, even if only available for a subsample.

Therefore, we suggest these extra analyses should ideally be conducted on the available data in this database to provide further insights into this critical area of research. ■

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## Reply to Bui *et al.*

*From the Authors*:

We read with great interest Dr. Bui's response letter to our manuscript (1). Using data from the UK Biobank, we have reported significant associations between ambient air pollutants and incident lung cancer, and found chronic obstructive pulmonary disease (COPD) mediated 7.9–19.9% of the associations between air pollutants and incident lung cancer (2).



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**Table 1.** Mediation Analysis of Pre–Chronic Obstructive Pulmonary Disease and Prevalent Chronic Obstructive Pulmonary Disease 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) |
|---|---|---|---|---|---|
| $FEV_1$ | $PM_{2.5}$ | 0.460 (0.215–0.682) | 0.376 (0.132–0.601) | 0.084 (0.069–0.100) | 18.26 (11.58–38.68) |
| | $PM_{10}$ | 0.340 (0.029–0.622) | 0.294 (0.020–0.566) | 0.045 (0.033–0.059) | 13.36 (5.98–69.81) |
| | $NO_2$ | 0.077 (0.018–0.138) | 0.060 (0.002–0.120) | 0.017 (0.014–0.020) | 21.95 (11.82–82.71) |
| | NOx | 0.099 (0.044–0.159) | 0.078 (0.022–0.138) | 0.021 (0.018–0.025) | 21.53 (13.16–50.42) |
| FVC | $PM_{2.5}$ | 0.462 (0.217–0.684) | 0.381 (0.137–0.607) | 0.081 (0.066–0.097) | 17.51 (11.17–37.12) |
| | $PM_{10}$ | 0.338 (0.028–0.620) | 0.290 (0.024–0.560) | 0.048 (0.037–0.061) | 14.23 (6.24–75.93) |
| | $NO_2$ | 0.077 (0.018–0.138) | 0.060 (0.001–0.121) | 0.016 (0.013–0.020) | 21.39 (11.71–81.74) |
| | NOx | 0.100 (0.044–0.160) | 0.079 (0.023–0.139) | 0.020 (0.017–0.024) | 20.49 (12.30–47.75) |
| $FEV_1$/FVC | $PM_{2.5}$ | 0.453 (0.207–0.676) | 0.368 (0.125–0.595) | 0.085 (0.071–0.100) | 18.73 (12.11–39.02) |
| | $PM_{10}$ | 0.334 (0.023–0.618) | 0.318 (0.005–0.597) | 0.016 (0.006–0.028) | 4.80 (0.41–27.79) |
| | $NO_2$ | 0.077 (0.019–0.138) | 0.062 (0.003–0.121) | 0.015 (0.012–0.018) | 19.61 (10.68–76.46) |
| | NOx | 0.098 (0.043–0.158) | 0.077 (0.023–0.136) | 0.020 (0.016–0.024) | 20.84 (12.90–49.26) |

*Definition of abbreviations*: CI = confidence interval; $NO_2$ = nitrogen dioxide; NOx = 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.

On that basis, Dr. Bui and colleagues proposed that the definition of COPD did not capture the totality of pollution-related airway disease processes, which might underestimate the amount mediated. Instead, they suggested we investigate the role of the "pre-COPD" paradigm, which refers to individuals on course to develop COPD. As suggested, we further defined participants into three categories, including prevalent COPD, pre-COPD, and non-COPD. The prevalent COPD was defined as those with hospital admission records of COPD before the date of baseline assessment, self-reported COPD, or with $FEV_1/FVC < 0.70$ at the baseline assessment; the pre-COPD referred to those at the lowest quartile of $FEV_1$, FVC, or $FEV_1$/FVC but did not meet the definition of prevalent COPD, respectively; and the non-COPD meant the rest of the others. We then performed a mediation analysis using natural effect models within the R package medflex (3), and the 95% confidence interval (95% CI) was estimated with 500 bootstrap replications. As only 38,382 participants (including 40 with incident lung cancer) repeated measures of lung function, we did not evaluate the mediation proportion of decline in these lung function indices. In addition, we also performed a sensitivity analysis to estimate the mediation proportion by taking lung function indices as continuous variables.

Cross-sectional analyses showed that exposures to higher air pollutants were significantly associated with both pre-COPD and prevalent COPD simultaneously. For example, if we defined pre-COPD according to the lowest quartile of $FEV_1$/FVC, per 5 $ug/m^3$ increase of particulate matter ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$) was associated with a odds ratio of 1.17 (95% CI, 1.10–1.25) for pre-COPD and 1.50 (95% CI, 1.42–1.57) for prevalent COPD. In addition, compared with participants without COPD, we observed that participants with pre-COPD and prevalent COPD at baseline had significantly increased risk of incident lung cancer, with hazard ratios of 1.79 (1.48–2.16) and 3.03 (2.65–3.45), respectively, after adjusting for age, sex, body mass index, household income, education

**Table 2.** Mediation Analysis of Lung Function Indices 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) |
|---|---|---|---|---|---|
| $FEV_1$ | $PM_{2.5}$ | 0.469 (0.223–0.692) | 0.393 (0.143–0.617) | 0.076 (0.062–0.088) | 16.19 (10.31–34.81) |
| | $PM_{10}$ | 0.342 (0.052–0.627) | 0.253 (0.039–0.539) | 0.088 (0.073–0.102) | 25.83 (14.81–80.71) |
| | $NO_2$ | 0.078 (0.020–0.140) | 0.060 (0.001–0.121) | 0.018 (0.015–0.021) | 23.37 (12.38–92.65) |
| | NOx | 0.102 (0.043–0.160) | 0.081 (0.022–0.138) | 0.021 (0.018–0.024) | 20.48 (12.95–49.13) |
| FVC | $PM_{2.5}$ | 0.462 (0.221–0.685) | 0.432 (0.187–0.657) | 0.030 (0.022–0.039) | 6.50 (3.81–15.71) |
| | $PM_{10}$ | 0.335 (0.044–0.622) | 0.277 (0.012–0.562) | 0.057 (0.045–0.071) | 17.10 (8.20–91.86) |
| | $NO_2$ | 0.076 (0.018–0.137) | 0.068 (0.009–0.128) | 0.009 (0.007–0.011) | 11.33 (5.92–49.33) |
| | NOx | 0.101 (0.043–0.159) | 0.092 (0.034–0.149) | 0.009 (0.007–0.011) | 8.80 (5.25–21.67) |
| $FEV_1$/FVC | $PM_{2.5}$ | 0.455 (0.205–0.676) | 0.363 (0.120–0.582) | 0.092 (0.076–0.109) | 20.29 (13.52–42.72) |
| | $PM_{10}$ | 0.331 (0.040–0.619) | 0.328 (0.038–0.616) | 0.003 (0.001–0.015) | 0.87 (0.01–6.01) |
| | $NO_2$ | 0.078 (0.019–0.139) | 0.062 (0.003–0.122) | 0.015 (0.012–0.019) | 19.91 (10.60–79.26) |
| | NOx | 0.099 (0.042–0.157) | 0.077 (0.019–0.134) | 0.022 (0.018–0.026) | 22.43 (14.17–55.35) |

For definition of abbreviations, *see* Table 1.
Adjusted for age, sex, body mass index, household income, education level, smoking status, and pack-years of smoking.

level, smoking status, and pack-years of smoking. The result of cross-sectional analyses and the association between pre-COPD and lung cancer supported the pre-COPD might be also acted as a mediator between air pollution and incident lung cancer.

We defined non-COPD as 0, pre-COPD as 1, and prevalent COPD as 2 and then performed a mediation analysis by taking pre-COPD and prevalent COPD as mediators. As shown in Table 1, the mediation proportions ranged between 17.51% and 18.73% for $PM_{2.5}$, between 4.80% and 14.23% for particulate matter ⩽10 μm in aerodynamic diameter ($PM_{10}$), between 19.61% and 21.95% for $NO_2$, and between 20.49% and 21.53% for NOx, in different definitions of pre-COPD based on $FEV_1$, FVC, or $FEV_1$/FVC. In addition, we also repeated the analysis by taking lung function incidences ($FEV_1$, FVC, and $FEV_1$/FVC) as mediators directly (Table 2) and found the mediation proportions were 6.5–20.29% for $PM_{2.5}$, 0.87–25.83% for $PM_{10}$, 11.33–23.37% for $NO_2$, and 8.80–22.43% for NOx.

Overall, our results supported the hypothesis that pre-COPD is also likely to mediate the associations between air pollution and lung cancer. However, the mediation proportions were still low if we further took pre-COPD into account. Although COPD is a common and independent risk factor for newly diagnosed lung cancer, this did not mean COPD or pre-COPD was a necessary intermediate process in the development of lung cancer. In our analysis, we found that around 20% of the associations between air pollution and incident lung cancer were mediated by prevalent COPD and pre-COPD. The possible explanations included *1*) air pollutants may have multiple direct carcinogenic biological effects, such as activation of tumor suppressor genes and inactivation of oncogenes (4, 5), transcription changes in genes (6), inhibition of apoptosis (7), and epigenetic changes (8), which directly lead to lung cancer rather than through damage to lung function; or *2*) the path-specific assumptions of natural effect model in R package medflex might not be in line with the damage effects of air pollutants on lung function and lung cancer, which leads to an underestimation of the proportion of mediation (3). ■

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