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Reply to Lee *et al.*

From the Authors:

We thank Lee and colleagues for their interest in our publication, which developed and validated risk models of lung cancer for never- and ever-smokers in China (1), and we wish to respond to the main topics addressed in their letter to the editor.

As the authors noted, the impact of air pollution and dietary factors on lung cancer incidence is of considerable public health importance. A previous comparative assessment showed that particulate matter 2.5 was one of the modifiable risk factors of lung cancer and accounted for 14.4% of the total attributable cancer deaths in mainland China (2). There is also an existing meta-analysis that showed that several fruits and vegetables containing carotenoids and other phytochemicals may provide protection from lung cancer (3). However, these two variables were generally excluded from the prediction of individualized lung cancer risks. We searched the PubMed database without date restrictions for the development and validation of prediction models for lung cancer that could be used in lung cancer screening programs before November 24, 2021. A total of 53 studies were identified as reporting risk predictions of lung cancer. Among these studies, none included air pollution, and only one study considered dietary factors on the basis of a case-control study design (4). The difficulties in accurately measuring these variables at the individual level and the limited improvement in model performance by these variables may be the possible explanations.

In our study, the reason for not including the two variables in the prediction models was due to the difficulties in accurately measuring the actual exposure of the two variables at the individual level. For the variable of air pollution, using overall environment across each province to represent the individual-level exposure is a potential option. However, individuals within the same community but who vary in age, sex, occupation, living condition, and other unmeasured characteristics may have different exposures to the air pollution. Individual reporting of exposure to severe air pollution (binary) was available in our study, but individual perception of pollution is subjective and hard to evaluate using a uniform standard. The addition of this variable did not substantially increase the area under the receiver operating characteristic curve of the prediction model for both never-smokers (0.697 [95% confidence interval, 0.681–0.713] vs. 0.701 [0.685–0.716]) and ever-smokers (0.723 [0.704–0.743] vs. 0.724 [0.704–0.743]).

For the variable of dietary factors, the data on vegetable consumption, including the intake frequency and amount (never, $<$2.5 kg/wk, or $\geqslant$2.5 kg/wk), were collected at the cohort entry by self-report. Studies have shown that relying on one measure of the dietary factors from the questionnaire-based survey may not be accurate enough to infer an association (5, 6). Moreover, our questionnaire collected the intake from 2 years before the survey to the time of survey, which may not be the etiologically relevant exposure period. *Post hoc* analyses found that the area under the receiver operating characteristic curve did not significantly increase after considering the variable of dietary factors for both never-smokers (0.697 [0.681–0.713] vs. 0.700 [0.684–0.715]) and ever-smokers (0.723 [0.704–0.743] vs. 0.725 [0.706–0.744]).

Finally, we appreciate the suggestions that the authors provided, as they are of great help to us. It is undoubtedly important to continue improving the measurement of environmental and dietary variables, such as obtaining sequential information on environmental and nutritional exposures during the life period before lung cancer occurs, and possibly using instruments such as a portable detector for particulate matter 2.5 or food diaries to ascertain individual-level exposure information (7). We will consider updating our prediction models with the addition of these two variables when accurate measurements at the individual level are available. ■

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Definition of Chronic Obstructive Pulmonary Disease: Occupational Environmental Contribution

To the Editor:

The recent proposal to reclassify chronic obstructive pulmonary disease appropriately identifies environmentally related disease (1). However, in addition to biomass and pollution exposure, the critical role of occupation in the development (2) and worsening (3) of chronic obstructive pulmonary disease should be acknowledged. ■

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Chronic Obstructive Pulmonary Disease Definition: Is It Time to Incorporate the Concept of Failure of Lung Regeneration?

To the Editor:

We applaud the proposal of Celli and colleagues (1) to provide an updated definition of chronic obstructive pulmonary disease (COPD), driven by the slow progress of therapeutic interventions to decrease morbidity and mortality. This authoritative group of experts focused on two main limitations of the previous COPD definition: *1*) the lack of identification of the disorder at its early stages in the absence of flow limitation; and *2*) the consideration of COPD as a single disease despite diverse causes other than cigarette smoking. The proposed solutions are aimed to encourage novel treatments and translational studies: *1*) incorporating into the definition objectivable early computed tomography (CT) scan changes; and *2*) describing the heterogeneity of COPD according to its recognizable causes. We noted that the revised definition of COPD addressed a clinician's typical point of view, probably with the same basic intentions of the Global Initiative for Chronic Obstructive Lung Disease guidelines. Will this be enough to describe the essential nature of COPD and particularly to stimulate more efficacious therapeutic interventions? We wish all the best for this attempt, but we argue that a change of paradigm (e.g., regenerative pathways) is desirable to drive novel therapeutic approaches. It was only in 2012 that the first demonstration of adult lung growth in humans by a multidisciplinary team of investigators focused on translational bench-to-bedside medicine (2). Now, we have abundant evidence that the lung, the organ of our body most widely exposed to the external environment, has extensive regenerative ability to respond to most injuries, rapidly regenerating damaged tissue (3, 4). COPD is characterized by both distal airways and parenchymal remodeling, which may be practically considered as due to failed regenerative processes. Recently, the highly talented interdisciplinary biomolecular investigators led by Ed Morrisey found that endothelial and mesenchymal cells in patients with COPD have different gene expression patterns from healthy individuals. In particular, they showed that the distal airway multipotent respiratory airway secretory (RAS) cells, usually able to regenerate alveoli in humans by differentiating into alveolar type II epithelial (ATII) pneumocytes cells, follow an aberrant differentiation trajectory leading to the accumulation of RAS-to-ATII transitioning

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