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Reply to Noboa-Sevilla *et al.*

From the Authors:

We thank Noboa-Sevilla and colleagues for their letter in response to our manuscript (1). We agree the methodology used to ascertain progression status in patients with fibrotic interstitial lung disease (ILD) is of critical importance. In our study, we sought to validate the proposed criteria for progressive pulmonary fibrosis (PPF), including those comprising the recent international PPF guideline (2), by ascertaining whether each criterion was associated with transplant-free survival. Given the strong link between 10% or higher relative FVC decline and subsequent mortality (3–10), we focused on proposed PPF criteria satisfied in the absence of such decline. Our rationale is that only criteria providing prognostic information independent of this well-established marker of ILD progression are likely to be of clinical value. We elected to model a 10% or higher relative FVC decline as this approach has been shown to capture more patients than an absolute decline threshold in patients with IPF without sacrificing prognostic value (5).

As Noboa-Sevilla and colleagues correctly highlight, our approach resulted in differences in the criteria modeled in our investigation and those proposed by the PPF guideline. We fully acknowledge that different sets of patients are captured using 5–9% FVC decline (relative and absolute) and 5% or higher absolute FVC decline thresholds, as the former excludes those with concurrent 10% or higher relative FVC decline, whereas the latter does not. We maintain that separating those with 5–9% FVC decline (relative and absolute) from those with 10% or higher relative FVC is preferred to modeling 5% or higher FVC (relative and absolute), as our data suggest these groups are inherently different with regard to outcome risk. We share the concern outlined by others that the PPF guideline may have been premature given the paucity of data to inform these criteria in the target population (11), with our data suggesting that substantial heterogeneity exists within the PPF phenotype (1).

Noboa-Sevilla and colleagues also call important attention to the timeframe over which PPF criteria may be satisfied, nicely contrasting our approach to the one proposed in the PPF guideline. In a prior study assessing lung function trajectory after satisfying PPF criteria, we found that progression can occur up to 10 years after diagnosis (12). Accordingly, we support others who have called for the dissociation of progression criteria from rigid timelines (13). The use of established timelines is understandable when applying composite criteria, but our data suggest that standalone PPF criteria, namely 5–9% relative FVC decline, computed tomography progression of fibrosis, and 15% or higher relative D_{LCO} decline, perform as well, and sometimes better, than composite criteria that include these features (1). In conclusion, we agree with Noboa-Sevilla and colleagues that the international community must come together to collaboratively study, define, and evolve the phenotype we have labeled PPF. The era of single-center ILD studies is over. It took decades to establish consensus surrounding IPF, and our patients with progressive disease must not wait that long. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Early Life Exposure to Tobacco Smoke and Lung Cancer in Adulthood

To the Editor:

A significant and well-constructed United Kingdom Biobank prospective cohort study named "In Utero and Childhood/Adolescence Exposure to Tobacco Smoke, Genetic Risk, and Lung Cancer Incidence and Mortality in Adulthood" was recently published in the *Journal* (1). He and colleagues have clearly identified that exposure to tobacco smoke in early life, with careful and quantifiable consideration of lung polygenic cancer risk via genome-wide association studies, was significantly associated with risks of lung cancer incidence and mortality in adulthood (1). This manuscript undoubtedly provides important information on lung cancer prevention in people's early life while urging a more rapid and powerful need for tobacco control among pregnant couples, children, and adolescents. And we want to take this opportunity to share some additional thoughts about this elaborate work.

First, as the authors declared in Methods and study limitations, the definition of early life tobacco exposure was self-reported and retrospectively collected after a long period of time in which recall bias seemed to be huge and inevitable. To reduce this kind of bias, we suggested the authors could perhaps consider using measurable biomarkers, like serum cotinine, to define tobacco smoke exposure, that was more precise and stable (2). And defining smoking exposure via serum cotinine made it possible to not only distinguish secondhand smoke and active smoke but also quantify the amount of tobacco smoke exposure to assess its dose–dependent relationship with lung cancer incidence and mortality (3). If serum cotinine was not available in this cohort, the authors could also take the smoking status of the father during the children's early life into consideration because the impact of active smoke and secondhand smoke on cancer might not be the same.

Furthermore, we thought the mechanism behind the impact of early life tobacco smoke exposure on lung cancer development merited further discussion. Though not fully understood, untimely telomere length reduction could play an unfavorable role in cancer development. Whiteman and colleagues reported that maternal smoking during pregnancy was associated with shortened fetal telomere length, leading to early intrauterine programming for accelerated aging (4). Another HELIX (Human Early Life Exposome) cohort study revealed that both active smoke and secondhand smoke during pregnancy could accelerate telomere shortening in children (5), which might be strong risk factors for lung cancer risk and mortality. And many researchers showed that tobacco smoke induced abnormal oxidative stress followed by DNA breakage, resulting in the reduction of telomere length (6). Oxidative stress, characterized as excessive exogenous and endogenous reactive oxygen species aggregation, could lead to rapid and even specific telomeric DNA damage while inhibiting protective DNA damage response and hampering DNA repair (6). Impaired telomeres could also lead to mitochondrial dysfunction via activating tumor repressor gene p53 to promote oxidative stress (6). At the same time, oxidative stress-induced inflammation with elevated inflammatory cytokines such as IL-6 and TNFα (tumor necrosis factor α) could further aggravate the telomere-shortening process and cell injury (6).

In conclusion, this work obtaining data from a prospective United Kingdom Biobank cohort illustrated a strong negative effect of early year tobacco smoke exposure on lung cancer incidence and mortality in adulthood very well, raising public attention on tobacco control from an early life stage. We thank and congratulate the authors again for their elaborate and illuminating paper. ■

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