THE THEORETICAL PROBLEMS DO NOT MATERIALLY AFFECT THE RESULTS OF OUR META-ANALYSIS OF SMOKING AND COVID-19 DISEASE PROGRESSION

Roengrudee Patanavanich[1] MD LLM PhD
Stanton A. Glantz[2] PhD

[1]Department of Community Medicine
Faculty of Medicine Ramathibodi Hospital
Mahidol University, Thailand

[2]Professor of Medicine (retired)
Center for Tobacco Control Research and Education
Department of Medicine
University of California San Francisco
San Francisco, CA, U.S.A. 94143-1390

Corresponding author:
Stanton A. Glantz, PhD
Stanton.Glantz@sonic.net
415-564-4801

In an ideal meta-analysis, all studies being pooled would use the same endpoints and methodologies. Unfortunately, this situation rarely, if ever, exists, so analysts are required to apply judgement when deciding when studies are comparable enough to combine to obtain pooled estimates of the effect of the intervention of interest. Yue et al.[1] raise three questions about how we made these decisions in our meta-analysis of the relationship between smoking and COVID-19 disease progression.[2]

They note that the paper by Kim et al.[3] only reported smoking status for 27 of the 28 hospitalized COVID-19 patients they studied, but did not report which patient did not have data on smoking status. We based our analysis on the data in Table 2 of Kim et al[3], which, as Yue et al correctly note, implicitly assumes that the one patient without data on smoking was a nonsmoker. Doing so biases the estimate of the effect of smoking toward the null, making our analysis conservative.

We emailed Dr. Kim and asked which patient did not have smoking status. They informed us that a patient that they did not include in their Table 1 was a former smoker (patient #6 in Table 2). This new information had little effect on the pooled association between current or former smoking and COVID-19 progression (OR 1.90, 95% CI 1.41-2.57, p = 0.001 with the new information vs. OR 1.91, 95% CI 1.42–2.59, p = 0.001 reported in our paper).

To base our analysis on as much as the available evidence as possible, we included one case series[4] with the 18 retrospective studies. The OR from the case series is not significantly different from the pooled OR for the other studies (p=0.802 by metaregression) and dropping this study from the analysis has little effect on heterogeneity of the remaining studies (I^2= 41.2% [p=0.035] without the study vs. 38.0% [p=0.048] with all 19 studies) or the pooled estimate of the risk of COVID-19 disease progression (OR 1.92, 95% CI 1.41 -2.61, p<0.001 without the case series). In addition, Aggarwal et al.[5] combined both retrospective and case series reports to find an association between COVID-19 and cardiovascular disease. In addition, meta-analyses published after ours (Alqahtani et al.[6] and Reddy et al.[7]) also included case series reports with retrospective studies in their meta-

analysis of the association between smoking and COVID-19, both of which found significant associations, consistent with our findings.[2]

Yue et al noted that in the Limitation section, we[2] stated that only three studies (references 8, 13, and 24 in our meta-analysis) separated current and former smokers in different categories, which left out another two (references 9 and 16). They are correct that this statement was wrong. As noted in the Methods section, however, we stated that "five studies (references 8, 9, 13, 16, and 24 in the paper) assessed whether the patient was a current or former smoker (as separate categories)." Also, in the Supplemental Table, and, most important, in our meta-analysis, we identified that smoking status of these five studies as "current, former, and never." We have submitted an erratum correcting the statement in Limitations to read "only five studies (references 8, 9, 13, 15, and 24 in the paper) separated current and former smokers in different categories." The erroneous statement in Limitations does not affect the results reported in the paper.

Yue et al. commented that there were seven studies (references 12, 14, 18, 20, 23, 25, and 26 in this meta-analysis) that only reported current smokers. Actually, there are nine studies (references 10, 12, 14, 18, 20, 21, 23, 25, and 26 in the paper) that only reported current smokers and there are five studies (references 11, 16, 17,19, and 22 in the paper) assessed whether the patient had a "history of smoking."

We clearly described the ambiguity of smoking status of the studies in the Methods and discussed it in the Limitations. One further consideration of this issue, we realized that the control group in the studies of current smokers may or may not include former smokers, (i.e., it is not clear if these studies are comparing current to never smokers or current to noncurrent smokers, which would include former smokers in the control group). As a result, we determined that the sensitivity analysis in the paper could be unreliable and submitted an erratum to clearly address this issue in Limitations and drop the sensitivity analysis.

We agree that the lung function of smokers may not completely recover after ceasing smoking. Thus, including former smokers to the non-exposed group would also bias the effect estimate to the null.

We agree with Yue et al that more precise collection of data on smoking status should be collected to provide more precise estimates of the effect of smoking on COVID-19 risk and disease progression. (The same holds for e-cigarettes.) However, subject to the limitations on the assessment of smoking status presented in our paper and this response, the fundamental conclusion in our paper that a history of smoking is associated with increased risk of disease progression stands. Our conclusion is also consistent with meta-analysies[6,7] published after ours that also concluded that smoking is associated with COVID-19 progression.

Conflict of Interest

The authors declared no conflict of interest.

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