odds ratio [aOR] = 1.20 and 1.32 for former and current EC use, respectively) and wheezing (aOR = 1.41 and 1.51 for former and current EC use, respectively). However, the significance of the findings needs careful review.

As in previous surveys investigating the association between EC use and respiratory symptoms, cigarette smoking history was either not considered or insufficiently adjusted for in the analysis. Using a binary version of the cigarette smoking status (i.e., yes/no) as a proxy for a measure of cumulative physiological damage is woefully incomplete and may also lead to false-positive results. The study by Xie and colleagues is no exception. Better self-reported measures exist, such as those taking into account the duration and/or intensity of cigarette smoking, which have a much stronger association with health risks. For example, the use of pack-years of smoking shows a clear dose–response association between exposure to tobacco cigarettes and the risk of new-onset asthma (2). A binary measure of current smoking status is simply not able to capture all the dimensions of tobacco use that are relevant to health outcomes, including respiratory symptoms, and a more analytical approach (i.e., pack-years) is required. A clear and compelling demonstration of the importance of controlling for more detailed measures of cigarette smoking has recently been published by Sargent and colleagues (3). These authors also examined the association between EC use and respiratory symptoms using PATH and found that adjusting for pack-years of smoking attenuated the association to nonsignificance in their analyses (e.g., from OR, 1.53 [95% confidence interval, 0.98–2.40] to 1.05 [0.67–1.63]). Thus, adjusting for binary measures of cigarette smoking is insufficient to control for the cumulative lifetime exposure necessary to explain health risks, and Sargent and colleagues demonstrate this using the same dataset that Xie and colleagues use.

As noted by Xie and colleagues, a limitation of the study is that "exposure and outcome measures were self-reported and may be subject to misclassification". Thus, the accuracy of the data collected is another problem of PATH datasets.

In Xie and colleagues, it was also shown that the lower odds of developing wheeze in exclusive EC users compared with combustible cigarette smokers became not significant in the fully adjusted model. Thus, what made sense in the unadjusted model could not be confirmed in the adjusted model. When findings are so unstable, it is a long shot drawing clinical conclusions.

Some researchers do not recognize the limitations of Xie and colleagues and similar work using PATH datasets. The recent commentary by Klein (4), for example, takes for granted that respiratory symptoms are causally linked to vaping when they are not. Despite substantial evidence from analytical chemistry and exposure studies demonstrating that chemical production in EC emission aerosols does not pose a major health concern according to quantitative risk assessment (5, 6), the health impact of ECs is still a matter of debate (7, 8). ■

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

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## References

1. Xie W, Tackett AP, Berlowitz JB, Harlow AF, Kathuria H, Galiatsatos P, *et al.* Association of electronic cigarette use with respiratory symptom development among U.S. young adults. *Am J Respir Crit Care Med* 2022;205:1320–1329.
2. Polosa R, Knoke JD, Russo C, Piccillo G, Caponnetto P, Sarvà M, *et al.* Cigarette smoking is associated with a greater risk of incident asthma in allergic rhinitis. *J Allergy Clin Immunol* 2008;121:1428–1434.
3. Sargent JD, Halenar MJ, Edwards KC, Woloshin S, Schwartz L, Emond J, *et al.* Tobacco use and respiratory symptoms among adults: findings from the longitudinal population assessment of tobacco and health (PATH) study 2014-16. *Nicotine Tob Res* [online ahead of print] 2 April 2022; DOI: 10.1093/ntr/ntac080.
4. Klein JD. Another study shows electronic cigarettes harm lungs: it is time for researchers to move from the tobacco playbook to a tobacco endgame. *Am J Respir Crit Care Med* 2022;205:1265–1266.
5. Chen J, Bullen C, Dirks K. A comparative health risk assessment of electronic cigarettes and conventional cigarettes. *Int J Environ Res Public Health* 2017;14:382.
6. Rodrigo G, Jaccard G, Tafin Djoko D, Korneliou A, Esposito M, Belushkin M. Cancer potencies and margin of exposure used for comparative risk assessment of heated tobacco products and electronic cigarettes aerosols with cigarette smoke. *Arch Toxicol* 2021;95:283–298.
7. Gotts JE, Jordt S-E, McConnell R, Tarran R. What are the respiratory effects of e-cigarettes? *BMJ* 2019;366:l5275.
8. Polosa R, O'Leary R, Tashkin D, Emma R, Caruso M. The effect of e-cigarette aerosol emissions on respiratory health: a narrative review. *Expert Rev Respir Med* 2019;13:899–915.





## Reply to Campagna and Caci: Taking for Granted Conclusions from Studies that Cannot Prove Causality of Respiratory Symptoms and Vaping

*From the Authors*:

Campagna and Caci raised the concern that smoking history was insufficiently adjusted for in our study (1). Although we appreciate



Supported by the American Lung Association Public Policy Research Award, NHLBI grant 1K01HL154130-01, and American Heart Association Tobacco Center for Regulatory Science grants P50HL120163, U54HL120163, 2U54HL120163, and R01HL092577. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Originally Published in Press as DOI: 10.1164/rccm.202207-1452LE on August 3, 2022

their interest in our work, their concerns were, however, unfounded. To evaluate whether e-cigarette use was associated with respiratory symptoms, we started the analyses with assessing an e-cigarette use status (never, former, current) adjusted for cigarette smoking, other tobacco product use, and secondhand smoke exposure, along with other sociodemographic and behavioral covariates. Rather than a binary measure of current smoking status (as the letter suggested), cigarette smoking was specified as never, former, current some days, or current every day. The letter failed to acknowledge that the analyses in our paper were repeated among respondents who had never smoked combustible cigarettes. All respondents in this subgroup analysis would have zero pack-years of cigarette smoking, virtually eliminating the influence of cigarette smoking history. The positive associations between e-cigarette use and respiratory symptoms remained in this subgroup analysis, and the magnitude of the associations was even stronger, presumably due to lower incidence rates in the reference group.

The letter compared our results with those from the Sargent and colleagues study (2) indicating that exclusive e-cigarette use was not significantly associated with respiratory symptoms after adjustment for pack-years of smoking. However, the null associations after adjustment for pack-years of smoking apply only to cross-sectional associations between e-cigarette use and respiratory symptoms, both measured at wave 2. When evaluating worsening of respiratory symptoms over time (i.e., asymptomatic at wave 2 to symptomatic at wave 3), a more similar approach to our analyses, Sargent and colleagues actually showed a significant positive association of exclusive e-cigarette use with respiratory symptoms (relative risk [RR], 1.63; 95% confidence interval [CI], 1.02–2.59) when a respiratory index cutoff $\geqslant$2 was applied and a similar, albeit statistically nonsignificant, result for a cutoff $\geqslant$3 (RR, 1.58; 95% CI, 0.84–2.96). Moreover, Sargent and colleagues reported that the RRs for exclusive cigarette smoking only and dual cigarette and e-cigarette use were 1.93 (95% CI, 1.50–2.50) and 2.20 (95% CI, 1.67–2.89), respectively. These estimations of longitudinal association were, in fact, very similar to what we found in our study examining joint cigarette and e-cigarette smoking patterns (exclusive e-cigarette use, RR, 1.62; 95% CI, 1.23–2.12; cigarette smoking only, RR, 2.07; 95% CI, 1.75–2.46; dual use, RR, 1.88; 95% CI, 1.41–2.51). ■

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

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## References

1. Xie W, Tackett AP, Berlowitz JB, Harlow AF, Kathuria H, Galiatsatos P, et al. Association of electronic cigarette use with respiratory symptom development among U.S. young adults. *Am J Respir Crit Care Med* 2022;205:1320–1329.
2. Sargent JD, Halenar MJ, Edwards KC, Woloshin S, Schwartz L, Emond J, *et al.* Tobacco use and respiratory symptoms among adults: findings from the longitudinal Population Assessment of Tobacco and Health (PATH) study 2014–2016. *Nicotine Tob Res* 2022;24:1607–1618.





## Reply to Campagna and Caci: Taking for Granted Conclusions from Studies that Cannot Prove Causality of Respiratory Symptoms and Vaping

*To the Editor*:

We thank Drs. Campagna and Caci for their letter in response to the article by Xie and colleagues (1) and my commentary about the need to prioritize a tobacco endgame (2). They cite two reviews of the effects of electronic cigarettes on lung health published in 2019 in support of their challenge to the evidence for e-cigarette harm. However, this omits evidence published in the 3–4 years after those reviews were written, which clearly and significantly demonstrates adverse cardiovascular and respiratory effects from use of these products. Recent studies report biomarkers of pulmonary disease and other toxic effects of vaping in adolescents and young adults (3, 4). My editorial comment pointed out that continued artificial "scientific debate" about potential harms of these products is detrimental, especially because both actual harm and significant addiction have been demonstrated, current marketing and product design are deliberately formulated to attract and addict youth, and the products do not promote cessation of combustible tobacco use (5). This letter reflects exactly that point. The correct comparison for addiction and exposure of new smokers' lungs to e-cigarettes is not with combustible cigarettes; it is with air—with no inhaled tobacco or nicotine exposure at all. Public health policies built on this growing evidence base are equally clear about the need to remove e-cigarettes from commercial markets to protect nonsmokers and to prevent addiction (6, 7). Additional years of Population Assessment of Tobacco and Health (PATH) Study data or more accurate pack-year measures of exposure for correlation to short-term symptom measurement will neither resolve the false "debate" nor protect the next generation from addiction and harm. ■

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

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Originally Published in Press as DOI: 10.1164/rccm.202207-1432LE on August 3, 2022