

## Conclusions

This novel ultrasensitive expression platform can be used for studies of the microbiota and host signatures in respiratory infections and pave the way for the identification of new biomarkers and pathways that can be targeted for treatment. ■

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## Taking for Granted Conclusions from Studies that Cannot Prove Causality of Respiratory Symptoms and Vaping



To the Editor:

In general, cross-sectional analyses of population-based data are inconclusive with respect to health effects outcomes. Consequently, we were glad to see the longitudinal study by Xie and colleagues (1) investigating the respiratory health effect of e-cigarette (EC) use in a nationally representative cohort of young adults in the United States. Using data derived from PATH (The Population Assessment of Tobacco and Health [PATH] Study) Waves 2, 3, 4, and 5, Xie and colleagues showed that both former and current EC use was associated with higher odds of developing any respiratory symptom (adjusted

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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). ■

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## 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

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