Taking for granted conclusions from studies that cannot prove causality of respiratory symptoms and vaping.

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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 et al. (1) investigating the respiratory health effect of e-cigarette (EC) use in a nationally representative cohort of US young adults. Using data derived from PATH Waves 2, 3, 4, and 5, Xie et al. showed that both former and current EC use was associated with higher odds of developing any respiratory symptom (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 et al. is no exception. Better self-reported measures exist, such as those taking into account 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 for exposure to tobacco cigarettes and 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

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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 published by Sargent et al. (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 non-significance in their analyses (e.g. from OR=1.53 [95% CI 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 that is necessary to explain health risks – and Sargent et al. demonstrate this using the same dataset that Xie et al. use.

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

In Xie et al. 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 recognise the limitations of Xie et al. and similar work using PATH datasets. The recent commentary by Klein (4) for example takes for granted that respiratory

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symptoms are causally linked to vaping, when they are not. In spite of 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 matter of debate (7,8).

REFERENCES

1. Xie W, Tackett AP, Berlowitz JB, Harlow AF, Kathuria H, Galiatsatos P, Fetterman JL, Cho J, Blaha MJ, Hamburg NM, Robertson RM, DeFilippis AP, Hall ME, Bhatnagar A, Benjamin EJ, Stokes AC. 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; 121:1428-34.
3. Sargent JD, Halenar MJ, Edwards KC, Woloshin S, Schwartz L, Emond J, Tanski S, Taylor KA, Pierce JP, Liu J, Goniewicz ML, Niaura R, Anic G, Chen Y, Callahan-Lyon P, Gardner LD, Thekkudan T, Borek N, Kimmel HL, Cummings KM, Hyland A, Brunette M. Tobacco use and respiratory symptoms among adults: Findings from the Longitudinal Population Assessment of Tobacco and Health (PATH) Study 2014-16. Nicotine Tob Res. 2022 Apr 2:ntac080. doi: 10.1093/ntr/ntac080. Epub ahead of print. PMID: 35366322.
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 Apr 5;14(4):382. doi: 10.3390/ijerph14040382.
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 Jan;95(1):283-298. doi: 10.1007/s00204-020-02924-x.
7. Gotts JE, Jordt S-E, McConnell R, Tarran R. What are the respiratory effects of e-cigarettes? BMJ. 2019; doi:10.1136/bmj.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; doi: 10.1080/17476348.2019.1649146.

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