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### Authors

Pierce, John P

Leas, Eric C

Benmarhnia, Tarik

et al.

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## **E-cigarettes and cessation: the introduction of substantial bias in analyses of PATH Study**

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John P. Pierce<sup>a,b</sup>, PhD,  
Eric C. Leas<sup>a,b</sup>, PhD,  
Tarik Benmarhnia<sup>a,b,c</sup>, PhD,  
Sara B. McMenamin PhD<sup>a</sup>, MPH  
David R. Strong<sup>a,b</sup>, PhD,  
Ruifeng Chen<sup>a</sup>, MS,  
Karen Messer<sup>a,b</sup>, PhD

### **Affiliations**

<sup>a</sup>Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego

<sup>b</sup>Moore's Cancer Center, University of California San Diego

<sup>c</sup>Scripps Institution of Oceanography, University of California San Diego

**Corresponding author:** John P. Pierce PhD, Professor Emeritus, Moore's UCSD Cancer Center, 3855 Health Sciences Drive, La Jolla CA 92093-0901 e-mail: [jppierce@ucsd.edu](mailto:jppierce@ucsd.edu).

A recent publication by Glasser et al.<sup>1</sup> reports a series of analyses on the associations of e-cigarette use and cigarette abstinence. Of interest, the two senior authors were also co-authors on another recent publication<sup>2</sup> reporting on e-cigarette use and cigarette abstinence that came to a strikingly different conclusion, despite using the same data set from the Population Assessment of Tobacco and Health (PATH) cohort study.

Herein we present potential reasons for this discrepancy that stem from not adhering to the best practices outlined in the National Academies of Science, Engineering and Medicine (NASEM) report on the public health consequences of e-cigarettes.<sup>3</sup> Specifically, NASEM emphasized two key analytic design issues necessary to avoid introducing bias into cohort study findings that were not adhered to in Glasser et al.'s paper: 1) studying "a large cohort of smokers *who want to quit or are making a quit attempt*," and 2) using an analytic design that can "assess e-cigarette exposure in detail *before* the smoking cessation outcome is assessed" (emphasis added).

On the first NASEM guideline regarding motivation to quit cigarettes, we note that Glasser et al.'s study cohort contains all baseline smokers, including many smokers not interested in quitting. Including these smokers uninterested in quitting will overestimate the benefit of e-cigarette use for cigarette cessation. Over 70% of smokers who had used e-cigarettes in the PATH Study indicated that a reason for e-cigarette use was to help them quit smoking cigarettes<sup>4</sup> -- thus e-cigarette users are more likely to be interested in quitting and to make quit attempts than those smokers who don't use e-cigarettes. We checked the PATH data and can report that among Glasser et al.'s "stable never e-cigarette users," only 25% reported a recent quit attempt at Wave 1, while 45% of e-cigarette users reported a recent quit attempt at Wave 1. This substantial baseline difference alone is sufficient to explain many of the positive associations in Glasser et al., including all rows in Table 3 with the exception of the one labeled "used e-cigarette to quit."

On the second NASEM guideline related to assessing e-cigarette exposure before smoking cessation outcome, we note that Glasser et al. included data where e-cigarette use and cigarette abstinence were measured on the same survey. This introduces the possibility that the association could be in the opposite direction to that hypothesized (reverse causality): those who were abstinent from cigarettes were potentially more likely to start using e-cigarettes. We are particularly concerned with Glasser et al.'s column titled "quit < 1 year" in Table 3. Given the PATH Study design, all entries in this column reflect contemporaneous measurement of both e-cigarette and cigarette use at Wave 3. The extent of the bias can be seen in the "used e-cigarette to quit" row of the Table. For those who had e-cigarette use and cigarette abstinence measured contemporaneously (i.e. the quit < 1 year

column), they report that those who were quit were more likely to use e-cigarettes. However, when e-cigarette use was measured before cigarette abstinence (i.e. the column “quit 1+ years at follow”), the adjusted relative rate ratio (between those who reported e-cigarette use to aid quitting and others who did not) was 1.17 (95% CI 0.84-1.63). Thus, their conclusion should be that using e-cigarettes to aid a quit attempt does not lead to increased cessation, a finding concordant with another PATH Study paper that was recently published by the senior authors. (2)

In summary, the Glasser et al. paper reports many associations between e-cigarette use and abstinence from cigarette smoking, but their analytic design introduced two important sources of potential confounding that invalidate their conclusions. In the one analysis that did follow NASEM guidelines, their findings are consistent with the other PATH Study paper that was co-authored by the senior authors of this paper - it found no association between e-cigarette use and smoking cessation. The PATH Study data do not support the Glasser et al. publication conclusions nor the suggested implications of this research.

## References

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