American Journal of
Preventive Medicine

LETTERS TO THE EDITOR

Cross-Sectional Analyses Can Evaluate the Plausibility of, but Not Validate, Causal Accounts

Alzahrani et al.[1] documented a cross-sectional association between survey respondents' current behavior (daily e-cigarette use) and medical history (having suffered a myocardial infarction [MI]). Robust associations signal the presence of causal forces; they do not identify the nature of the causal model. Imagine if Glantz had not posted to his professional blog, "First evidence of long-term damage from ecigs: Smoking e-cigarettes daily doubles risk of heart attacks,"[2] but instead "Health scares push smokers to try ecigs: Smokers who suffered heart attacks overrepresented among e-cigarettes' regular users." What if *The New York Times* had quoted Glantz not as saying, "If you switch it's almost the same as continuing to smoke,"[3] but instead, "Too many smokers are switching too late, only after instead of before suffering smoking-related harm?"

All of these statements are consistent with but none logically follow from the reported association. Without Glantz's spin, it is unlikely that >190 news outlets would have reported on Alzahrani and colleagues[1] with mischaracterizations such as, "They found that vaping leads to an increased risk of heart attack regardless of the user's other lifestyle choices."[4] Such researcher conduct raises difficult questions for scientific societies and journals whose processes and procedures are better equipped to inspect the quality of research submissions than the accuracy of authors' public promotions of them.

Glantz[5] ignores these issues and instead focuses on our cross-sectional analyses of the 2014–2019 National Health Interview Survey data. We wrote that our analyses could "lend more plausibility to certain causal accounts than others," but our pursuit was "undertaken with full appreciation that such nuanced analyses remain correlational and thus cannot definitively address causality."[6]

Estimating the association between e-cigarette use and MI using National Health Interview Survey data is essentially just a test of how these variables co-occur in current and former smokers. Although 60% of the 175,546 respondents were never smokers, only 8% of daily vapors were. Of the 90 daily vapers who had suffered an MI, only 3 had never smoked. Glantz is correct[a] that 3 is 1.65 times what would be expected if daily e-cigarette use is not associated with MI (1.81 respondents). This comparison—3 vs 1.81—is essentially meaningless, as reflected in the extreme unreliability of the AOR point estimate (95% CI=0.51, 5.32; p=0.377).[b] For the same reasons, we discourage any conclusions to be drawn from the point estimate that among never smokers, former e-cigarette users are 28% less likely to have had an MI than never users (p=0.208).

If the data provide no basis for drawing conclusions about the MI–vaping link in never smokers, why care whether the association varied by smoking history? Testing for such a dependency helps to evaluate the plausibility of Alzahrani and colleagues' take that the associations reflect the independent causal contributions of smoking and vaping on MI. Alzahrani et al.[1] tested for 1 specific deviation from the independent-effects model. We instead preserved all 4 levels of combustible and e-cigarette use and conducted an omnibus test that rejected the null hypothesis that the independent-effects model was reasonable.

We then moved to stratified analyses that illustrated how the MI–vaping links varied in strength and statistical significance across the 4 levels of smoking status. These analyses showed varied patterns of statistical significance (Table 2[5]) not merely because of the observed variation in the strength of the MI–vaping link (as reflected by the significant interaction) but also because of variation in statistical power that depends on how many respondents fit different vaping–smoking profiles. Glantz[5] focuses on the AORs associated with daily e-cigarette use in particular and highlights the aberrantly low MI risk for some-days smokers. Most daily e-cigarette users were former smokers. These former smokers were 57% more likely to have had an MI than those who had never vaped. One possibility is that their switch to daily vaping caused their greater likelihood of having had an MI. But if so, why would daily e-cigarette use show no hint of an association with MI among some-days smokers (AOR=0.53, 95% CI=0.20, 1.39)? One could accommodate this finding by (unreasonably) positing that

[a]Actually, Glantz misreports this AOR as 1.57, which described the association between daily e-cigarette use and MI in former smokers, not never smokers.

[b]Figure 1 of Glantz[5] implies that Alzahrani et al.[1] demonstrated a significant association between daily e-cigarette use and MI among never smokers. In actuality, 1 such MI sufferer was observed, whereas 0.59 were expected under the null hypothesis. The figure uses the wrong CIs on the bars depicting the results from Alzahrani et al.,[1] ones that apply to an estimate of the daily e-cigarette use—MI association in the overall sample (from which the AOR was estimated), not (as depicted) to any specific subsample (e.g., never smokers).

Table 1. Associations Between Lifetime Occurrence of MI and Both E-Cigarette Use and Combustible Cigarette Use, by Year

Variables	Year(s)							
	2014	2015	2016	2017	2018	2019	2014–2016	2017–2019
E-cigarette use								
Every day	2.24 (0.99, 5.07)	**2.28** ** **(1.25, 4.14)**	**2.22** * **(1.17, 4.21)**	1.26 (0.44, 3.59)	0.79 (0.35, 1.84)	0.94 (0.44, 2.02)	**2.23** *** **(1.47, 3.38)**	0.99 (0.58, 1.70)
Some days	**1.82**[b] **(1.09, 3.02)**	**2.12** ** **(1.23, 3.67)**	0.77 (0.43, 1.39)	**1.93** * **(1.07, 3.50)**	1.41 (0.67, 2.97)	1.09 (0.58, 2.05)	**1.55** * **(1.11, 2.18)**	1.48 (1.00, 2.18)
Former	1.16 (0.83, 1.62)	**1.45** * **(1.05, 2.00)**	1.02 (0.73, 1.41)	1.01 (0.75, 1.37)	**1.53** ** **(1.16, 2.00)**	1.33 (1.00, 1.78)	1.16 (0.96, 1.41)	**1.28** * **(1.09, 1.51)**
Never	ref	ref	ref	ref	ref	ref	ref	ref
Combustible cigarette use								
Every day	**3.20** *** **(2.36, 4.33)**	**2.20** *** **(1.66, 2.93)**	**2.84** *** **(2.16, 3.73)**	**3.17** *** **(2.43, 4.12)**	**2.44** *** **(1.87, 3.20)**	**2.37** *** **(1.86, 3.04)**	**2.76** *** **(2.35, 3.23)**	**2.64** *** **(2.29, 3.05)**
Some days	**2.57** *** **(1.61, 4.10)**	**1.92** ** **(1.21, 3.06)**	**1.96** ** **(1.29, 2.99)**	**2.67** *** **(1.76, 4.06)**	**2.31** *** **(1.54, 3.47)**	**1.69** * **(1.06, 2.71)**	**2.13** *** **(1.64, 2.78)**	**2.23** *** **(1.74, 2.86)**
Former	**1.83** *** **(1.50, 2.23)**	**1.46** *** **(1.20, 1.77)**	**1.64** *** **(1.37, 1.95)**	**1.70** *** **(1.40, 2.07)**	**1.52** *** **(1.26, 1.83)**	**1.43** *** **(1.20, 1.71)**	**1.64** *** **(1.47, 1.82)**	**1.55** *** **(1.39, 1.72)**
Never	ref	ref	ref	ref	ref	ref	ref	ref

Note: Boldface indicates statistical significance (*$p<0.05$, **$p<0.01$, ***$p<0.001$).
AORs (95% CI)—modeling e-cigarette use and combustible cigarette use as independent effects, accounting for the full set of covariates from both Critcher and Siegel[6] and Alzahrani et al.[1]
MI, myocardial infarction.

smoking on some days serves as a protective factor against the risks of daily e-cigarette use. A more reasonable explanation is that current e-cigarette use is a marker of heavy current (daily) and former smokers who have experienced smoking-related health decline.

We tested whether the primary finding of Alzahrani et al.[1] —the association between daily e-cigarette use and MI—has changed with time. If this association reflected daily e-cigarette use causing MI, it might be expected to strengthen following more years for vaping's consequences to become clearly observable. Instead, it declined, consistent with the possibility that health-compromised smokers—like the general public—have grown skeptical of e-cigarettes' harm reduction potential.[7–9] Glantz[5] notes that we tested for 6 secular trends (across the 3 levels of e-cigarette use and 3 levels of cigarette smoking), which increased the chances that any one of those tests would emerge as significant. But none of the other 5 tests addressed whether the central finding reported by Alzahrani and colleagues[1] has varied with time. Had Glantz similarly (mis)applied his proposed rule to his own work (by adjusting for the 16 tested associations in Alzahrani and colleagues' full model), Alzahrani et al.[1] would not have concluded that daily e-cigarette use is associated with MI.

A more apt critique is that there is little reason to expect the annual rate of change in the association between daily vaping and MI to have been constant. Table 1 documents the precise observed trajectory. If Alzahrani et al.[1] had run their analyses not on the 2014 and 2016 data but on the most recent 2018 and 2019 data, they would have found that neither daily e-cigarette use (AOR=0.87, 95% CI=0.49, 1.54) nor some-days e-cigarette use (AOR=1.24, 95% CI=0.76, 2.06) but only former e-cigarette use (AOR=1.43, 95% CI=1.18, 1.75) is associated with ever having had an MI. For those inclined to think that these associations reflect the causal effect of e-cigarette use on MI, they may conclude that e-cigarettes once posed a cardiac risk but no longer do. Instead, we suspect that the disappearance of the MI—vaping association merely reflects the effectiveness with which scientific research on e-cigarettes has been distorted to evoke fear instead of cautious optimism about vaping's public health potential.[10]

ACKNOWLEDGMENTS

No financial disclosures were reported by the authors of this paper.

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https://doi.org/10.1016/j.amepre.2021.09.009

REFERENCES

1. Alzahrani T, Pena I, Temesgen N, Glantz SA. Association between electronic cigarette use and myocardial infarction [published correction appears in *Am J Prev Med*. 2019;57(4):579–584]. *Am J Prev Med*. 2018;55(4):455–461. https://doi.org/10.1016/j.amepre.2018.05.004.
2. Glantz SA. *First evidence of long-term health damage from ecigs: smoking e-cigarettes daily doubles risk of heart attacks*. San Francisco, CA: UCSF Center for Tobacco Control Research and Education. https://tobacco.ucsf.edu/first-evidence-long-term-health-damage-ecigs-smoking-e-cigarettes-daily-doubles-risk-heart-attacks. Published February 24, 2018. Accessed September 14, 2021.
3. Bakalar N. E-cigarettes may raise risk for heart attack. *The New York Times*. August 23, 2018 https://www.nytimes.com/2018/08/23/well/live/e-cigarettes-may-raise-risk-for-heart-attack.html. Accessed September 14, 2021.
4. Fletcher J. Vaping: is it bad for you? *Medical News Today*. December 20, 2019 https://www.medicalnewstoday.com/articles/327374. Accessed September 14, 2021.
5. Glantz SA. The perils of drawing strong conclusions based on underpowered analyses (Letter to the Editor). *Am J Prev Med*. In press.
6. Critcher CR, Siegel M. Re-examining the association between e-cigarette use and myocardial infarction: a cautionary tale. *Am J Prev Med*. 2021;61(4):474–482. https://doi.org/10.1016/j.amepre.2021.05.003.
7. Kahn C. More Americans say vaping is as dangerous as smoking cigarettes: Reuters poll. *Reuters*. September 24, 2019 https://www.reuters.com/article/us-health-vaping-poll/more-americans-say-vaping-is-as-dangerous-as-smoking-cigarettes-reuters-poll-idUSKBN1W9136. Accessed September 23, 2021.
8. Malt L, Verron T, Cahours X, et al. Perception of the relative harm of electronic cigarettes compared to cigarettes amongst U.S. adults from 2013 to 2016: analysis of the Population Assessment of Tobacco and Health (PATH) study data. *Harm Reduct J*. 2020;17(1):65. https://doi.org/10.1186/s12954-020-00410-2.
9. Nyman AL, Huang J, Weaver SR, Eriksen MP. Perceived comparative harm of cigarettes and electronic nicotine delivery systems. *JAMA Netw Open*. 2019;2(11):e1915680. https://doi.org/10.1001/jamanetworkopen.2019.15680.
10. Balfour DJK, Benowitz NL, Colby SM, et al. Balancing consideration of the risks and benefits of e-cigarettes. *Am J Public Health*. 2021;111(9):1661–1672. https://doi.org/10.2105/AJPH.2021.306416.