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LETTERS TO THE EDITOR

E-Cigarette Use and Myocardial Infarction: Importance of a Sound Evidence Base in the E-Cigarette Risks–Benefits Debate

We read with interest the recent paper by Alzahrani et al.[1] on the association between e-cigarette use and myocardial infarction (MI), as well as the subsequent letter[2] and response.[3] We echo the concerns raised by Middlekauf and Gornbein[2] and note several additional limitations and methodological discrepancies that undermine the conclusions of this study.

First, we attempted to replicate the results presented in Tables 1 and 2 in Alzahrani et al., as well as the supplemental tables,[1] but we obtained similar results only by using unweighted analysis methods; the use of appropriate complex survey procedures yielded different results. Therefore, contrary to what the authors described in their methods, the published tables may present unweighted results. If this is the case, then the results are not nationally representative, do not account for the complex sampling design, and underestimate variance. In addition, the authors examined data from the 2014 and 2016 National Health Interview Surveys, omitting 2015 without mention or explanation despite it being readily available in the cancer control supplement.[4]

The authors' use of effect estimates to calculate the odds of MI for cigarette smokers who switched to e-cigarettes treats all former smokers equally with respect to the risk of MI and the opportunity to try e-cigarettes, an unreasonable assumption given the negative association between the risk of MI and time since quitting smoking[5] and that e-cigarettes became available circa 2010. Our own analysis of 2014 and 2015 National Health Interview Survey data found that e-cigarette experimentation was extremely low for smokers who had quit at or before 2010[6]; thus, analyses of former smokers should separate those who quit before versus those who quit after 2010.[7]

The authors inferred that the effect of e-cigarette use is "independent of and in addition to" the effect of cigarettes[1] but contended that "limiting the analysis to e-cigarette-only users is not a good idea because most e-cigarette users are dual users."[3] Conversely, given the high rates of dual use, we argue that an analysis of e-cigarette use among never smokers is necessary to assess an independent association between e-cigarettes and MI. Should a positive effect exist, one would expect to see increased odds of MI for e-cigarette users who never smoked cigarettes or a synergistic effect for those who use both products. However, the authors did not present an analysis restricted to never smokers and found no significant interaction between e-cigarette and cigarette use, making it impossible to distinguish an "independent effect" of e-cigarettes from the residual effects of smoking among most e-cigarette users.

Finally, the authors used the term "increased risk" several times to describe their observed association between e-cigarette use and MI. This is an incorrect interpretation of OR, especially in the context of a cross-sectional analysis, and may also imply causation to those unfamiliar with statistics.

As the debate on the risks—benefits of electronic-cigarettes continues, a rigorous evidence base is critical. Although determining whether the use of e-cigarettes carries excess risk for future MI is important, it is not possible through the analysis of cross-sectional data, such as the National Health Interview Survey data, from which temporality cannot be inferred. Equally important, we were unable to replicate the authors' findings. Given the importance of this topic to public health, we request that the authors provide a full and comprehensive explanation for the discrepancies noted and temper their conclusions about "increased risk of myocardial infarction" to reflect the limitations of cross-sectional data.

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Adding Data From 2015 Strengthens the Association Between E-Cigarette Use and Myocardial Infarction

Manderski et al. stated that our conclusion that e-cigarette use was associated with having had a myocardial infarction[1] was erroneous because we did not use population weights in our analysis. We did not use weights when presenting the descriptive statistics for the sample (Table 1 in our paper[1]) because we were describing the actual (unweighted) sample characteristics as opposed to presenting population estimates based on the sample (which would have used the weights). The logistic regression analyses of the association between e-cigarette use and having had a myocardial infarction (Table 2 in our paper[1]) used the National Health Interview Survey (NHIS) weights, accounted for the complex survey design, and followed NHIS procedures to combine the 2014 and 2016 data sets.[2] Our multivariable analysis is nationally representative and does not underestimate variance.

There are several differences in the way that Manderski and colleagues did their analysis compared with what we did. (At our request, the editor obtained the SAS code so that we could understand precisely what they did.) First, Manderski et al. used the NHIS "Weight - Final Annual" (WTFA) in their analysis. WFTA is based on design and ratio (including nonresponse and post-stratification) adjustments. This weight was designed mainly for the analysis of the family and person data. By contrast, we used "Sample Adult Weight - Final Annual" (WTFA_SA) because it includes design, ratio, nonresponse, and post-stratification adjustments for sample adults. According to the Centers for Disease Control and Prevention, "National estimates of all sample adult variables can be made using these weights."[2] We used WTFA_SA because all variables that we used in our analysis were from the adult sample except for race/ethnicity. Second, Manderski and colleagues used age as a continuous variable in their logistic regression model, and then used the "ESTIMATE" function to measure the effect of a 10-year interval. We used age in 10-year intervals as a variable (i.e., age/10 years); the resulting roundoff errors in the calculations contribute to the small differences between our results. Third, Manderski et al. treated BMI=99.99 as a missing value, whereas we incorrectly treated this as a real value. We updated the results in this letter, treating BMI=99.99 as a missing value. This change did not substantially alter the results. Most importantly, despite the differences in the analytic approach of Manderski and colleagues, they obtained essentially the same results that we did for the combined data for 2014 and 2016, namely a significant association between daily e-cigarette use and myocardial infarction (OR=1.74, 95% CI=1.14, 2.64 in their analysis; OR=1.79, 95% CI=1.20, 2.66 in ours).

We did not use the 2015 data in our paper because we did not realize that e-cigarette use was available, as it was buried in the cancer control supplement. Table 1 in this letter shows that the 2015 data reveal significantly increased odds of having had a myocardial infarction for both some-day and everyday e-cigarette use. The overall risks including 2015 are higher than we originally reported[1] based on just 2014 and 2016 (OR=1.49 for all 3 years vs 1.16 for 2014 and 2016, for e-cigarette use on some days; OR=2.14 vs 1.78 for everyday e-cigarette use). Moreover, with the additional 2015 data, some-day e-cigarette use became statistically significant.

Manderski et al. argued that an analysis of e-cigarette use among people who never smoke is necessary to assess an independent association between e-cigarettes and myocardial infarction. As we explained in our response to the first letter written about our paper,[3] we do not need to perform this type of analysis to estimate the association between e-cigarette use and having a myocardial infarction because we used multivariable analysis which is adjusted for confounding factors including smoking. Because about two thirds of e-cigarette users also smoke cigarettes (dual users), excluding these people would severely limit the sample size and reduce power to detect a true effect. In addition, because dual use is the dominant pattern for e-cigarette users, it is important to include them in the analysis to obtain the most relevant results.

Similar to the second letter written about our paper, Manderski and colleagues argued that use of the term