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LETTERS TO THE EDITOR

E-cigarette Use and Myocardial Infarction: Association Versus Causal Inference

We read with particular interest the study by Alzahrani et al.,[1] who examined the association between e-cigarette use and myocardial infarction (MI). With this letter, we would like to express our concern about the study conclusions.

Although annual data sets of the National Health Interview Survey (NHIS) have been released consistently, the authors chose to pool non-consecutive years (2014 and 2016) and did not mention any particular reason for this. According to the National Center for Health Statistics (NCHS), a new sampling design was implemented in 2016.[2] Therefore, 2014 and 2016 fall into different sampling design periods. The NCHS guidance clearly states that the different sample design periods should be treated as statistically independent. It is unclear whether this may have affected the outcome of their logistic regression analysis, which was based on treating the pooled data as one sample.

More importantly, Alzahrani and colleagues[1] concluded that daily e-cigarette use is associated with increased risk of MI. This is a misinterpretation and misrepresentation of the study findings. The "increased risk" claim clearly implies causality and a specific temporal definition of events (i.e., that e-cigarette use precedes MI and e-cigarette use caused the MI). This disagrees with what Alzahrani and colleagues mention in the Limitations section of their article: the study cannot permit identifying causal relationships in part because it is not known when the MIs occurred relative to e-cigarette use. It also violates a basic principle of epidemiology that no causal inference can be derived from any cross-sectional study, such as the NHIS.

To more clearly demonstrate the perils of such an approach, we performed logistic regression analyses of the 2016 and 2017 (pooled) NHIS to examine if ever taking prescribed medicine to lower cholesterol is associated with MI and coronary heart disease (CHD). Both years fall into the same sampling design period and thus the data can be pooled.[2] Weighting was performed according to NCHS guidelines.[2] The dependent variables in the two models were MI and CHD; independent variables were age, BMI, gender, race/ethnicity, risk factors for MI/CHD (smoking, hypertension, diabetes, and hypercholesterolemia), and ever taking prescribed medicine to lower cholesterol. Data were collected in 2016 and 2017 and analyzed in 2018. No significant collinearity was observed (all variance inflation factors $\leq$3.22).[3,4] Ever taking prescribed medicine to lower cholesterol was independently associated with increased odds of having had an MI (OR=2.15, 95% CI=1.65, 2.80, $p<0.001$) and having CHD (OR=2.05, 95% CI=1.65, 2.55, $p<0.001$). Having hypercholesterolemia was also associated with both MI (OR=1.31, 95% CI=1.01, 1.71, $p=0.044$) and CHD (OR=1.42, 95% CI=1.15, 1.75, $p=0.001$). Obviously, it would be inappropriate to conclude that ever taking prescribed medicine to lower cholesterol, adjusted for having hypercholesterolemia as well as other risk factors, is associated with increased risk of MI and CHD. Our findings show the well-established limitations of cross-sectional studies, which cannot justify any claims about causal inference, as mentioned in the conclusion by Alzahrani and colleagues.[1] Therefore, the conclusion of their study is incorrect and should be revised.

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The Association Between E-cigarette Use and Myocardial Infarction Is What One Would Expect Based on the Biological and Clinical Evidence

Farsalinos and Niaura[1] state that because we identify e-cigarettes as a "risk factor" for myocardial infarction, we imply "causality" when we clearly only used terms consistent with "associations" when reporting the findings of our study.[2] In particular, "risk factor" is established terminology for describing such associations in cross-sectional studies.[3–5]

In our study, we did not use the 2015 National Health Interview Survey (NHIS) data set because respondents were not asked about e-cigarette use that year. Farsalinos and Niaura ignore the fact that we combined the 2014 and 2016 data in accordance with the Centers for Disease Control and Prevention procedures (reference 18 in our paper[2]). They also ignore the fact that, in addition to the pooled analysis, we reported the analyses of the 2014 and 2016 NHIS data sets separately; the overall conclusion is the same.

It is not surprising that Farsalinos and Niaura found an association between taking medicines to lower cholesterol with having had a myocardial infarction because these drugs are recommended and routinely prescribed for people who have had myocardial infarctions.[6,7] Likewise, it is not surprising that we found an association between using e-cigarettes and having had a myocardial infarction because of the adverse biological and clinical effects that e-cigarettes have on the cardiovascular system that we summarize in our paper.[2]

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