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The proper approach to assessing the impact of the fact that e-cigarettes were not available before 2007

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Abstract

In a cross-sectional study, one computes the association between exposures (in this case e-cigarette and cigarette use) and an outcome (in this case having had an acute myocardial infarction) among data observed at a fixed point in time. In this case the specific issue is whether the myocardial infarctions may have occurred before e-cigarette use. Rodu & Plurphanswat provided an alternative analysis of the Population Assessment of Tobacco and Health (PATH) data set to one we published, that found an association between having had a myocardial infarction and e-cigarette use. Their analysis selectively changes data for e-cigarette users who started using e-cigarettes before their myocardial infarction, which is inappropriate in a cross-sectional study. Their inappropriate analysis led to the biologically implausible result that non-daily e-cigarette use was protective against myocardial infarction. A standard cross-sectional analysis that treats all exposure groups the same is the appropriate way to do such studies.

Rodu & Plurphanswat's [1] re-analysis of our cross-sectional study of the association between e-cigarette and cigarette use and having had an acute myocardial infarction [2] does not follow standard epidemiological procedures for analysis of cross-sectional data.

In a cross-sectional study, one computes the association between exposures (in this case e-cigarette and cigarette use) and an outcome (in this case having had an acute myocardial infarction) among data observed at a fixed point in time. As we note in our paper, temporality and reverse causality (i.e. which event occurred first) are limitations in all cross-sectional studies. In this case, the specific issue is whether the myocardial infarctions may have occurred before e-cigarette use.

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Author contributions

Dharma N. Bhatta and Stanton A. Glantz: Conceptualization; methodology.

Declaration of interests

None.

Contrary to Rodu & Plurphanswat's assertion, we did address these possibilities.

First, we conducted a supplemental analysis in which we excluded all cases when the myocardial infarctions occurred before 2007, when e-cigarettes first appeared on the US market (Table S6 in our paper and the associated text in the Discussion section). This is the appropriate approach because it treated respondents in both the exposed (e-cigarette and cigarette smoking) groups and the control group (never e-cigarette or smoking) the same, thereby maintaining the cross-sectional design of the analysis. As we pointed out in our paper, when we did so, the point estimates for the adjusted odds ratios (ORs) between e-cigarette use and myocardial infarction stayed approximately the same, but the associations became non-significant, probably due to the reduced number of myocardial infarctions among the e-cigarette users. The associations for cigarette smoking also remained approximately the same, with the effects remaining significant, probably because of the larger numbers of smokers. This information was reported in the paper and available for readers to judge.

Second, we used the longitudinal data in PATH to test for reverse causality (Table 4) and found that having had a myocardial infarction at wave 1 of PATH did not predict subsequent adoption of e-cigarettes.

In contrast to our approach, Rodu & Plurphanswat selectively changed the data for current e-cigarette users who had their myocardial infarctions before starting to use e-cigarettes. They did not treat former e-cigarette users or current former smokers comparably, leaving all the former e-cigarette user and smoker data as recorded in the data set. Similarly, they did not change the data for the people in the control group who had myocardial infarctions. This selective manipulation of the data is not appropriate and inconsistent with a cross-sectional analysis.

The way in which Rodu & Plurphanswat selectively manipulated the data led to the biologically implausible result that non-daily e-cigarette use was protective against myocardial infarction, reducing the odds of myocardial infarction in this group by more than a factor of 5 [OR = 0.18, 95% confidence interval (CI) = 0.05–0.66]. Rodu & Plurphanswat do not address this finding, mischaracterizing their results as 'our re-analysis did not find an association of e-cigarette use and heart attack'.

Rodu & Plurphanswat criticized our exclusion of non-daily experimental e-cigarette users (people who only tried e-cigarettes a few times but did not become regular users) as well as non-daily experimental cigarette smokers from our analysis. We excluded these cases because earlier critics of e-cigarette epidemiological research had argued that people who only briefly experimented with e-cigarettes (and cigarettes) should not be counted as 'users' (see, for example, 'Inclusion of experimenters in e-cigarette prevalence studies of "questionable" value' [3]). This approach is a strength, not a weakness, of our analysis because it avoids this potential criticism.

Recognizing that some might disagree with this approach, we conducted a sensitivity analysis that included these cases. Specifically, our paper said: 'The sensitivity analysis including non-daily experimental e-cigarette user with some-day e-cigarette user and non-

daily experimental cigarette smokers (had not smoked 100 cigarettes) with some-day cigarette smokers yielded similar results as the main analysis (Table S3)’.

In both the main cross-sectional analysis in our paper (Table 3) and the sensitivity analysis (Table S6) there is the likelihood that some myocardial infarctions occurred before respondents used e-cigarettes (including in the main analysis, because they were not yet available). However, in a cross-sectional analysis this corresponds to misclassifying some of the e-cigarette non-users as users. The effect of this misclassification will be to bias the estimate of the effect of e-cigarette use on risk of myocardial infarction towards the null.

Rodu & Plurphanswat also criticize us for not reporting how missing data were handled. While we did not explicitly state that we used list-wise deletion, that is the default approach for missing data. If we had used a non-default approach, such as multiple imputation, that would have been stated. They are correct that we reported the total sample sizes after dropping the experimental e-cigarette and cigarette users and following list-wise deletion. When our access to the PATH data set is restored we will be happy to report the sample sizes after list-wise deletion. The way that the sample sizes were reported does not affect the results.

Rodu & Plurphanswat state that they reproduced our results. Careful examination of their Table 1 shows that this is not the case; had they accurately reproduced our analysis the numbers would have been identical.

Rodu & Plurphanswat cite a blog post from Dr. Glantz [4] as saying: ‘This finding was promoted by the senior author as evidence that e-cigarette use causes heart attacks’. This statement is misleading. Neither the paper nor the blog claim that our *Journal of the American Heart Association (JAHA)* paper [2] by itself demonstrated causality. The blog post placed the paper in the context of other epidemiological and biological studies and presented it as part of the overall evidence base. Our paper [2] does not use the word ‘caused’, but discussed the ‘associations’, as is appropriate.

A question concerning Rodu & Plurphanswat’s paper is whether they violated the confidentiality requirements associated with access to the PATH restricted-use data set. Those rules require that any results reported be first cleared by the Interuniversity Consortium for Political and Social Research (ICPSR) before being disseminated to anyone. In particular, they state: ‘The analyses in this manuscript were approved for release by ICPSR on November 12, 2019’. In contrast, they cite two letters they sent to the *JAHA* on 11 and 18 July 2019 (references 5 and 7 of their paper) as well as a 17 July 2019 article in *USA Today* [6] reporting the same criticisms of our work they report in their paper. In addition, their paper reports unweighted sample sizes, something that ICPSR prohibits.

Finally, Rodu & Plurphanswat cite unnamed ‘researchers at another university’ being asked to re-run the analysis following their selectively changing the data set to reclassify e-cigarettes users who had heart attacks before using e-cigarettes as unexposed. It violates fundamental tenants of scientific transparency to report such results anonymously. It is not disclosed whether these unnamed other investigators were properly granted access to, and clearance to disseminate findings from, the PATH restricted-use data set.

Rodu & Plurphanswat's statement that: 'The analysis presented here supports the decision by editors of the *JAHA* to retract BG's article on February 18 2020' is not surprising, because the *Journal of the American Heart Association* retracted the paper because we did not have access to PATH to conduct an analysis similar to that which Rodu & Plurphanswat were pressing the *JAHA* to require us to do [5]. In their retraction statement, however, the *JAHA* editors did not endorse Rodu & Plurphanswat's approach, but rather noted: 'The authors agreed to comply with the editor's request [to conduct the analysis in the way that Rodu & Plurphanswat did]. The deadline set by the editors for completion of the revised analysis was not met because the authors are currently unable to access the PATH database. Given these issues, the editors are concerned that the study conclusion is unreliable' [5].

Now that Rodu & Plurphanswat have provided the details and results of their analysis, even without access to the PATH restricted-use data set, it is clear that they selectively manipulated their data and did not discuss their surprising finding that non-daily e-cigarette use was protective against having a myocardial infarction, their results should be rejected. An analysis in which e-cigarette use, smoking and the control (never-users of either product) are treated differently is not appropriate or standard statistical methodology. The analysis published in Table S6 of our *JAHA* paper that drops cases in which acute myocardial infarctions occurred before 2007 in all groups is the appropriate way to address this issue.

We completely and accurately reported our results, including several sensitivity analyses and a longitudinal analysis of the association between e-cigarette use and incident heart attacks (which did not find a significant association, probably due to low power). We stand behind our paper.

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