Author’s response to reviews

Title: The association between e-cigarette use and asthma among never combustible cigarette smokers: Behavioral Risk Factor Surveillance System (BRFSS) 2016 & 2017

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Author’s response to reviews:

Dear Dr. Luppi,

Thank you for the time and consideration. We have modified our paper according to comments of your editorial team and reviewer’s comments. We think the manuscript is significantly improved. Here you can find a point-to-point response to each comment. Comments are bold and highlighted in grey highlighting. Responses are highlighted in yellow. We also copied the corresponding part of the manuscript/table/figures and presented in italic, and blue font.

Editor’s comments

1. Specific Comments

Riccardo Polosa (Reviewer # 1): MAJOR POINTS

Comment 1. I appreciate the authors' effort at trying to address referees' concerns. However, this revised draft does not provide convincing explanation for the observed associations. Authors
acknowledge the impossibility of establishing causality from this cross-sectional survey, and yet they allude to highly improbable conclusions. In this specific case, it cannot be established temporality (i.e. whether the diagnosis of asthma is prior or subsequent to the use of ECs). However, considering that onset of asthma occurs mostly during childhood, it is reasonable to argue that EC use has started AFTER the diagnosis - thus discounting causality. How can e-cigarette use increase the risk of asthma that happened years before using e-cigarettes? That asthma precedes EC use should be emphasized in the Discussion.

Response 1: We appreciate the reviewer’s comment and understand the need to document that it reasonable to argue that EC use has started after asthma diagnosis considering the age range of the study respondents. The discussion section of the manuscript has been revised accordingly as shown below:

“Also, due to the cross-sectional nature of our study, we cannot infer causality. Additionally, considering that the age range of the study respondents who are current e-cigarette users is 18-24 years and that asthma prevalence is higher mostly during childhood, it reasonable to argue that for some individuals e-cigarette use may have started after asthma diagnosis, discounting causality. However, e-cigarette use may be associated with acute exacerbations of respiratory symptoms.”

Comment 2. In interpreting the study findings, one has also to consider the lack of biological plausibility. It is unlikely that many of the study's respondents had been using ECs for more than 1-2 years and therefore it is biologically implausible to expect development of disease in such a short period of time; even in predisposed allergic individuals it would have taken several years - if not decades - of regular daily EC use to cause asthma. If asthma is correctly diagnosed, this could only result from prolonged exposure to environmental irritants. It is very odd to expect that individuals who start vaping will go on and develop asthma in only a few years. This does not even happen with tobacco smoking. The strength of the association of smoking conventional cigarettes and onset of asthma is known to be very strong, being approximately 5 times stronger than the risk of the association reported with EC use in this study. And yet, there is no evidence that a few years of conventional smoking could lead to asthma epidemics. Of note 1) even in the BRFSS 2016 & 2017 population of never smokers, asthma prevalence is very high at 8.5% and similar to the general population in the US; 2) countries with extremely low prevalence for conventional smoking - e.g. Sweden/Australia/NZ/Hong Kong still have very high asthma prevalence; 3) conversely, countries with extremely high smoking prevalence - e.g. Bulgaria/Russia/China/Indonesia do not have much higher asthma prevalence compared to other countries in their respective regions. Last but not least, no sign of asthma epidemics has been reported in countries with high prevalence of EC use in recent years - e.g. UK, Greece and France. This is all very confusing and inconclusive and long from being helpful in understanding the impact of smoking/vaping on respiratory diseases. All these notions should be included in the Discussion.

Response 2: Thank you for this suggestion. We have tried to incorporate all of the above thoughts into the manuscript. We have tried to reinforce the questionable biologic plausibility of
our findings, and framed our results as hypothesis-generating in need of further study. The manuscript has been revised appropriately to capture the current controversies in the field.

“In interpreting our hypothesis-generating findings, it is important to consider other arguments that may be of concern in this rapidly evolving field of e-cigarettes. For example, while it is known that asthma development may result after prolonged exposure to environmental irritants, many of the BRFSS study respondents may not have used e-cigarettes for extended time periods, thus challenging the plausibility of e-cigarettes leading to disease in a very short period of time. However, some studies have reported associations between e-cigarette exposure, asthma symptoms, and asthma exacerbations in susceptible individuals. E-cigarette vapor may also serve as a non-selective trigger unmasking an underlying subclinical asthma.

It is also useful to frame the biologic plausibility of our results in the context of what is known about smoking and asthma. A study on ten-year prevalence trends in respiratory symptoms and asthma in relation to smoking showed a high prevalence of physician-diagnosed asthma despite a decline in traditional smoking over the same period. In addition, some countries with extremely high smoking prevalence such as Russia do not have much higher asthma prevalence compared to other countries in their respective regions. Also, asthma epidemics are yet to be reported in countries with high prevalence of e-cigarette use in recent years. These arguments highlight current controversies in the field, supporting further biologic plausibility studies and longitudinal studies to assess the population-level and long-term health impact of these novel tobacco products.”

Comment 3. Given that it is highly unreasonable to conclude that EC use may cause asthma, it is mandatory that authors provide a number of plausible alternative explanations for the observed association between asthma and EC use. In my previous review of the earlier draft I proposed some plausible alternative explanations (e.g. selection bias of individuals with asthma self-selecting to a less harmful nicotine containing product for their disease; self-reported diagnosis of asthma is confused with dry cough / wheeze secondary to irritant effect from PG/VG/nicotine inhalation; diagnosis of asthma is the results of the EC vapour acting as an unspecific trigger - such as methacholine or cold dry air - unmasking an underlying subclinical condition of asthma/BHR).

Response 3: We appreciate the suggestions of the reviewer. We have now more thoroughly captured these important thoughts in our discussion to address the suggestion that a number of plausible alternative explanations could account for the observed association between asthma and e-cigarette use. This has been appropriately captured in the manuscript as shown below.

“The possibility of a self-selection based on a pre-existing condition cannot be discounted because individuals with a prior asthma diagnosis might avoid taking up smoking and self-select to e-cigarette use instead, which may be perceived as a less harmful nicotine containing product for their disease. Also, it is possible that report of cough/wheeze associated with vaping may be erroneously self-reported as a diagnosis of asthma as it is known that inhalation of Propylene Glycol (PG) / Vegetable Glycerin (VG) mixtures can cause irritation and trigger the physiological reflex of cough/wheeze. To minimize this confusion, participants in this study
were asked to self-report only diagnoses of asthma made from a doctor, nurse, or other health professional. Also e-cigarette vapor may serve as a non-selective trigger unmasking an underlying subclinical asthma.”

Comment 4. In the Abstract, Main text and Conclusions the use of strong policy claims such as must be avoided given that study findings are confusing and far from being conclusive.

Response 4: Thank you for the suggestion. We have minimized the of strong policy claims in the abstract, main text and conclusion.

“In conclusion, our findings from a large, nationally representative survey suggest increased odds of asthma among never combustible smoking e-cigarette users. This may have potential public health implications, providing a strong rationale to support future longitudinal studies of pulmonary health in young e-cigarette using adults.”

Comment 5. I appreciate the Authors' effort with propensity score matching, but inclusion of important risk factors for asthma (Hx of allergic disease, family hx of allergy etc.) has not been considered when matching the two study groups.

Response 5: Thanks for the comment. We considered propensity score (matched and then adjusted) models for the secondary analysis of these two groups. Age, sex and race were incorporated in constructing the propensity score. In the propensity score adjusted model, we adjusted for propensity score, income, education and body mass index. We agree with the reviewer that important risk factors such as history of allergic disease and family history of allergy have not been considered in the matching process. The BRFSS does not provide data on these risk factors. The propensity score (matched and then adjusted) models for the secondary analysis are shown below:

<table>
<thead>
<tr>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3103</td>
<td>3103</td>
<td>1.40 (1.06-1.86)</td>
</tr>
</tbody>
</table>

Propensity score matched model

Asthma§

OR (95% CI)

Never Smokers (N=402,822)

E-cigarette use status
Never E-cigarette users Ref

Current E-cigarette users 1.35 (1.12-1.65)
- Occasional Use 1.29 (1.04-1.60)
- Daily Use 1.66 (1.15-2.38)

Propensity score adjusted model adjusted for propensity score, income, education and body mass index

Comment 6. Acute changes described here are not specific and simply due to hyperosmolarity of EC aerosols indicating a physiologic defensive reflex response. In particular, the effects described are consistent with the generic well-known increased sensitivity of 'asthmatic' lungs to inhaled respiratory irritants and do not indicate EC vapour emission specific effects. These findings are at variance with results from several trials by different research groups. I am aware of at least three acute studies consistently showing NO changes in respiratory symptoms, lung function (using either spirometry or forced oscillation technique) as well as in signs of inflammation (by measuring FeNO and serum CRP levels) in response to 1-hour use of e-cigarette in both healthy and asthmatic subjects (1-3).


Response 6: Thanks for the suggestion. We have revised the manuscript to capture these acute exposure studies that reported no changes in respiratory symptoms and mechanics following e-cigarette use. The revision is captured in our discussion and is shown below:

“In a nationally-representative sample of never smokers, we report significantly higher odds of asthma among current e-cigarette users compared to never e-cigarette users. E-cigarettes have been promoted as a less harmful alternative to combustible cigarettes and may play a role in smoking cessation. Study of the health effects of e-cigarettes has been limited by the relatively short time e-cigarettes have been on the market. Some studies have reported e-cigarette related acute toxicity reflected by increased airway resistance, oxidative stress and inflammatory responses, with reported cases of acute respiratory distress after e-cigarette use. However, other acute exposure studies have reported no or minimal changes in respiratory...
symptoms, lung function or inflammatory markers with acute e-cigarette exposures, highlighting current controversy in the field.”20–22

Peter Hiemstra (Reviewer # 2):

Comment 1  The authors have provided detailed and adequate responses to my comments and have made appropriate revisions in the manuscript.

Response 1:  Thanks for your comment.