Reviewer's report

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

Version: 1 Date: 22 Jul 2019

Reviewer: Riccardo Polosa

Reviewer's report:

MAJOR POINTS

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.

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.
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).

MINOR POINTS

Change Title from:

<<The association between e-cigarette use and asthma among never combus\ntible cigarette smokers: Behavioral Risk Factor Surveillance System (BRFSS) 2016 & 2017>>

To:

<<E-cigarette use and self-reported asthma among never combustible cigarette smokers: cross-sectional analysis from Behavioral Risk Factor Surveillance System (BRFSS) 2016 & 2017>>

In the Abstract, Main text and Conclusions the use of strong policy claims such as: <<This may have potential public health and tobacco regulatory implications, providing a strong rationale to support future longitudinal studies of pulmonary health in young e-cigarette-using adults.>> must be avoided given that study findings are confusing and far from being conclusive.

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.

<<However, some studies have reported e-cigarette related acute toxicity reflected by increased airway resistance, oxidative stress and inflammatory responses (4)>> Acute changes described here are not specific and simply due to hyperosmolality 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).


**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

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I recommend additional statistical review

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