

## PEER REVIEW HISTORY

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## ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Motivation and main flavor of use, use with nicotine, and dual use of electronic cigarettes in Barcelona, Spain: a cross-sectional study
<b>AUTHORS</b>	Bunch, Kailey; Fu, Marcela; Ballbè, Montse; Matilla, Nuria; Lidón-Moyano, Cristina; Martin-Sanchez, Juan Carlos; Fernandez, Esteve; Martínez-Sánchez, Jose

## VERSION 1 – REVIEW

<b>REVIEWER</b>	Brian King Centers for Disease Control and Prevention, United States
<b>REVIEW RETURNED</b>	27-Jun-2017

<b>GENERAL COMMENTS</b>	<p>This manuscript presents the findings of a cross-sectional assessment of patterns and characteristics of e-cigarettes use among adult current e-cigarette users in Barcelona, which were recruited and surveyed via a consumer panel in 2015. The findings indicate that the primary motivation for using e-cigarettes was to reduce or quit smoking, tobacco was the most commonly used flavor, a majority of users reported using nicotine containing e-cigarettes, and most users were former tobacco smokers. Younger users were more likely to use flavors other than tobacco and to use e-cigarettes for recreational as opposed to cessation purposes. The authors conclude that policy makers should consider more expansive e-cigarette regulations, including bans on marketing that attracts young people, regulation of flavored e-cigarette products, and the prohibition of e-cigarette use in public indoor environments.</p> <p>Overall, this manuscript is generally well written and presents findings on a timely and relevant topic in the field of public health. The tobacco product landscape has rapidly diversified in recent years, and the use of emerging tobacco products, most notably e-cigarettes, has increased considerably among adults and youth. Although science on the long-term health effects of these products remains uncertain, there is potential for these products to have either a net harm or benefit on public health. The latter scenario could be realized if adult cigarette smokers were to transition completely to e-cigarettes, although existing science doesn't necessarily suggest that is prominently occurring. Nonetheless, continued monitoring of the patterns and characteristics of e-cigarette use are critical to inform efforts to minimize potential harms and to maximize any potential benefits of these products at the population level.</p> <p>Specific comments and recommendations for improvement of the manuscript are described below.</p>
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	<p>1. Page 3. Abstract. In framing the conclusions in the abstract, it's important to ensure that the content is consistent with the actual results presented in the abstract. For example, the conclusions make statements about non-smokers being more likely to use flavors other than tobacco and to use e-cigarettes for recreational purposes; however, those data are not presented in the actual abstract. In the end, the abstract should be able to serve as a standalone document that does not require the reader to reference the main text of the article. Similarly, the conclusion should be restricted to content that relates to the implications of the present study findings; at present, the conclusion references content related to availability of flavors attracting young users who were never conventional cigarette smokers, which cannot be fully gleaned from the present study findings, particularly those presented in the abstract.</p> <p>2. Page 4. Article Summary. As currently framed, the article summary heading notes "strengths and limitations", but there are no real limitations actually noted in the list. The limitations from the Discussion section of the manuscript should be duly noted here as well, most notably the limitation regarding the use of a non-probabilistic consumer panel. The current framing around the panel simply states that it shows greater sample representativeness than other non-probabilistic techniques, but makes no mention of the comparison with regard to probabilistic techniques.</p> <p>3. Page 5. Third paragraph. The second statement of this paragraph doesn't adequately summarize the state of the science on the effectiveness of e-cigarettes for cessation from conventional cigarettes. The science on this issue is still quite mixed, and there is non-conclusive evidence that these products are effective for long-term cessation. At present, the language indicates that some studies have found a positive effect; however, it doesn't balance this statement with an acknowledgment of the inconclusive nature of the existing scientific literature.</p> <p>4. Page 6. Second paragraph. The paragraph beginning "Researchers recognize" is seemingly out of the place and likely not necessary to adequately frame the issue to the reader. Instead of focusing on this nuance, the introduction would segue better if the authors provided a clearer discussion of the explicit gaps in the existing literature and how this study fills those gaps.</p> <p>5. Page 7. First paragraph. It would be helpful if a clear definition of e-cigarette user was provided to the reader. It's not clear whether this is ever or current use, although it's likely the latter. If so, further clarity is warranted; for example, was it defined as use within the past 30 days, everyday or someday use, or some other standard measure? At present, this definition isn't clear, and should ideally come before the various patterns of use are defined.</p> <p>6. Page 8. Motivations for Use. It would be helpful if further nuance was provided on how this question was asked. More specifically, was it an open ended question or were there specific categories that the respondent could select from? At present, it appears that there were a small percentage of respondents who did not fall within these three categories. As such, some clarity on the primary reasons for use beyond these three major responses would be useful; at the least, simply mentioning all the available response categories on the</p>
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	<p>questionnaire would help put the findings into better context.</p> <p>7. Pages 8-9. Data Analysis. It's not clear whether the data were weighted in any way to enhance representativeness of the target population of interest. Although a non-probabilistic approach was used, the data could still be weighted to enhance external validity. If that was not done, it should be clearly articulated in the Methods, and also duly acknowledged in the statement of limitations in the Discussion.</p> <p>8. Page 12. Results. In the narrative of the results, it would be useful to provide an overall estimate of the proportion of respondents who reported using a flavor. The various types of flavor use is very helpful, but understanding the magnitude of any flavored use is critical, particularly to inform efforts to broach flavors through population based interventions, such as sales and advertising prohibitions. Perhaps this information is contained somewhere in the report, but it wasn't readily identifiable as currently framed.</p> <p>9. Paged 10-13. Results. It's not clear whether the authors calculated any estimate of error (e.g. relative standard error) to assess the statistical robustness of their estimates. In some cases, the sample sizes for certain estimates are quite small, suggesting large standard errors and wide confidence intervals. A standard in the literature is usually suppression of the point estimate if the relative standard error is greater than 30%.</p> <p>10. Page 15. Second paragraph. As mentioned in a previous comment, a more careful summary of the existing science is warranted on the efficacy of e-cigarettes for the purposes of cessation. At present, there are only a handful of longitudinal studies, including only a few trials, that have assessed this issue. Moreover, the findings from these studies are mixed, with some studies actually finding that e-cigarette users are less likely to quit at follow-up. As presently framed, the discussion of the manuscript appears to only highlight the positive findings without duly acknowledging the full scope of the existing scientific literature on this matter.</p> <p>11. Page 16. First paragraph. The statement that "a high proportion of users prefer tobacco as their main flavor" is not entirely accurate. The study in question, which this reviewer co-authored, did account for tobacco flavor. Tobacco flavor was not listed specifically as a response option because prevalence was so low among respondents from other studies. Moreover, respondents had the ability to enter "tobacco" in the open ended response option for this question, which very few did. Although the current study may have found prominent tobacco flavor use among heavier users, the existing evidence on this issue is not supportive of the broader claim that a "high proportion of users prefer tobacco flavor." In the case of the United States, preference of tobacco flavor is so low, as documented by retail sales and self-reported data, that it's not even worth including it as a response option on surveys because it won't yield sufficiently robust or presentable point estimates. That being said, it's reasonable to cite the current findings from this study to help put the content into context; however, suggesting that tobacco flavor is most prominent among users more broadly, and actually preferred, is not consistent with the preponderance of existing research on this matter.</p>
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	<p>12. Page 17. First paragraph. When framing the rationale for including e-cigarettes in indoor smoking prohibitions, it's also critical to acknowledge the health risks of exposure to e-cigarette aerosol. Although the aerosol does not have the same level of harmful ingredients as tobacco smoke, this does not mean that it is risk free. Environmental studies of aerosol have documented many harmful and potentially harmful ingredients, including heavy metals, ultrafine particulate, volatile organic compounds, and others. Prohibiting the use of these products in indoor environments protect bystanders from these harmful ingredients and the associated health risks of exposure.</p> <p>13. Page 17. Limitations. As noted earlier, the limitations should provide a clearer articulation of the external validity (i.e. generalizability) of the sample. In the end, a non-probabilistic technique was used, and the data don't appear to be weighted. Although it may afford greater sample representativeness than other non-probabilistic sampling methods, it's not nearly as accurate as a probabilistic approach. This could introduce bias, which should be duly and clearly noted in the statement of limitations.</p> <p>14. Page 18. Last paragraph. When framing the rationale and importance for regulation, it's important to reference factors beyond just dual use. One of the primary purposes of regulation of these products is to minimize use among young people and never users of conventional tobacco products. In order for these products to have a net benefit on public health, they need to successfully aid in transitioning current smokers to exclusive e-cigarette use, while also not leading to greater nicotine or tobacco product use among young people and never users. In the end, the importance of regulation is more expansive than what is necessarily alluded to in the first sentence of this paragraph.</p> <p>15. Page 18. Last sentence. As noted earlier, the rationale for prohibiting e-cigarette use in indoor public areas is not merely to prevent normalization. It's to prevent bystanders, particularly children, from being exposed to the harmful ingredients of the aerosol – a fact that has been established in the scientific literature through laboratory and environmental studies.</p>
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<b>REVIEWER</b>	Konstantinos Farsalinos Onassis Cardiac Surgery Center, Greece University of Patras, Greece
<b>REVIEW RETURNED</b>	21-Jul-2017

<b>GENERAL COMMENTS</b>	<p>General comments</p> <p>This study is a survey of e-cigarette users, with a small sample and no added information compared to any previous survey published until now. The authors found that the vast majority of e-cigarette users are current or former smokers, and the main motivation is to quit smoking or reduce cigarette consumption. This information is consistent with the large number of surveys published until now, and provides no new information.</p> <p>Although conducting the survey with face-to-face interviews is a plus, the authors provide no information about the methodology for recruitment (they cite a Spanish article which I am unable to understand since I don't speak Spanish). Also, there is no information on how this recruitment method is more representative</p>
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	<p>of the population of e-cigarette users. For example, are users who buy e-cigarette online represented proportionally with this recruitment method?</p> <p>The measure of consumption (nr of cartridges per week) is problematic (see below for more details).</p> <p>The question on flavors requested a single response only, while we know a large proportion of e-cigarette users use more than 1 type of flavoring regularly.</p> <p>The logistic regression analysis seems to be separate models for each variable, with each model adjusted for age, gender and education. It seems they did not include all variables into a single model, which would make more sense. Although flavor use and motivation are analyzed according to patterns of use and past and current smoking status, the univariate nature of the analysis does not provide a comprehensive view of the interactions between different factors.</p> <p>Conclusions in the abstract and full text about restrictive regulations are not supported by the study findings which show that the majority of e-cigarette users are current and former smokers. Also, discouraging dual use makes little sense since dual use is a necessary step towards quitting (it is unreasonable to expect that initiation of e-cigarette use will immediately result in quitting smoking). Studies have shown that dual use can lead to smoking cessation, while quitting e-cigarette use can lead to relapse to smoking.</p> <p>Specific comments</p> <p>Please remove the term “smoking” when discussing about e-cigarette use. There is no such thing as “smoking” of e-cigarettes.</p> <p>Page 5, line 53-55. “Their advertising and availability of fruit and other non-tobacco flavors may also specifically appeal to young people (15-16) and non-smokers. (17)”</p> <p>Reference 17 only assessed prevalence of use and had no information on the effects of flavors on e-cigarette use prevalence or patterns of use. Additionally, only 12.6% of e-cigarette users in that study were never smokers. Thus, this reference should be removed from the statement about flavors.</p> <p>Page 6, lines 6-11. “Some short-term studies have found negative pulmonary and cardiovascular effects in users such as lung and airway obstruction and increased heart rate, cough and sore throat. (18-19)”</p> <p>Reference 18 is a conference abstract. The authors should find other studies to support their statement. Also, the increase in heart rate is not a negative cardiovascular effect but the acute effect of nicotine intake. Same acute effects are observed for approved nicotine replacement therapies.</p> <p>Page 6, lines 10-17. “Furthermore, chemicals such as carcinogenic tobacco specific nitrosamines, carcinogenic carbonyls, volatile organic compounds and formaldehyde (20–24) have been found in e-cigarette liquid. The long-term effects of these chemicals must continue to be evaluated.”</p> <p>Again I would advise the authors to avoid citing conference abstracts</p>
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	<p>(reference 24). Also, formaldehyde is a carbonyl (carbonyls are mentioned in the same sentence). "Volatile organic compounds" is a generalized term and includes chemicals which are not harmful in any form. The authors should be more specific in their discussion about potentially toxic compounds.</p> <p>Page 7, Methods. "The market research technique known as 'consumer panels' was used to enroll e-cigarette users as described previously elsewhere. (27)" The authors provide no details about the consumer panel technique, and they cite a study which is "in press". In fact, the manuscript is available but it is in Spanish. The authors need to present information on the technique they used in this manuscript.</p> <p>Page 7, Methods The authors should mention how many participants were approached and agreed to participate initially, and which proportion of them was included in the final sample. Also, I don't understand why they were interviewed twice (2015 and 2016). What if someone was an e-cigarette user in 2015 but had quit in 2016? Was he excluded from the study?</p> <p>Page 7, Patterns of use. The authors ask "nr of cartridges" used by the participants, and the median response was 2 per week. I think responders mentioned the number of bottles they were using weekly, and this creates a lot of problems because bottles can have different volume (10-30 mL or even more). In that aspect, the information on liquid consumption is highly inaccurate.</p> <p>Page 8, Flavors used. I think there is a problem in the question asking about the "primary" flavor. Primary is not necessarily the only flavor participants were using. It is quite common for such questions to allow multiple answers because it is quite common for e-cigarette users to use multiple flavors (see Farsalinos et al. Int J Environ Res Public Health. 2013 Dec 17;10(12):7272-82).</p> <p>Page 9, Data analysis. It seems to me that the logistic regression analysis model did not include all factors into one model but created separate models for each variable, with each model adjusted for age, gender and education. This is not a true multivariate regression analysis.</p> <p>Page 11, line 20. I don't understand what the terms "past non-smoker" and "current non-smoker" mean.</p>
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	<p>Page 12, lines 23-33. The authors discuss about statistical differences with some ORs being not statistically significant. They cannot discuss about differences since such differences did not reach statistical significance.</p> <p>Page 12, table 3. The last column of table 3 is not visible in the pdf file.</p> <p>Page 13. Lines 43-45. "...there was a relatively high percentage of people who were nonsmokers before beginning use of e-cigarettes (13%)." I am not sure with what criterion is the 13% of participants considered "relatively high percentage". They definitely constitute a minority.</p> <p>Page 14, lines 36-41. "On the other hand, if users continue dual use, they may be at greater risk for adverse health effects, as studies show that even light smoking can have significant negative health impacts and there is potential for long-term health effects of e-cigarette use. (31)" I don't understand what the authors mean with "greater" risk for adverse health effects. Greater than being exclusive smokers? What if a dual user has reduced smoking from 20 cigarettes per day to 2 cigarettes per day? This is defined as dual use, but does this represent a greater risk compared to smoking 20 cigarettes per day only? Dual use represents a normal pathway towards complete cessation. NRTs are also used together with smoking initially, and are approved for long-term use even as partial substitutes for smoking (MHRA, UK). Studies have shown that dual use can lead to future quitting (Etter, Nicotine Tob Res. 2017 Jun 7. doi: 10.1093/ntr/ntx132). In fact, the study by Etter found that quitting e-cigarette use was associated with relapse to smoking.</p> <p>Page 15, lines 16-35. This paragraph is a bit puzzling. It seems that the authors are criticizing the fact that motivation for e-cigarette use is to quit or reduce smoking. Do the authors think there is another reason for e-cigarettes to exist? Irrespective of whether the evidence supports or not the value of e-cigarettes in quitting smoking (which I think it does), it is entirely desirable from a public health perspective that e-cigarettes are used as smoking cessation or reduction aids.</p> <p>Discussion section. The authors do not mention important information derived from a large survey of e0cigarette users concerning flavors (Farsalinos et al., Int J Environ Res Public Health. 2013 Dec 17;10(12):7272-82). There is a transition from tobacco flavors at e-cigarette use initiation to other types of flavors over time. The authors had participants with low duration of e-cigarette use, so this transition may not have happened yet. Again, I should stress that the question seems to accept only 1 response about primary flavor used, which does not take into account the possibility that participants may use more than</p>
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	1 type of flavor.
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## VERSION 1 – AUTHOR RESPONSE

bmjopen-2017-018329

"Motivation and main flavor of use, use with nicotine, and dual use of electronic cigarettes in Barcelona, Spain: a cross-sectional study"

Point-by-point reply to reviewers' Comments

We would like to thank to the reviewers for the useful comments.

Please see enclosed a point-by-point reply to the issues raised. The modifications in the text of the manuscript have been highlighted.

Editorial Requirements:

- Please work to improve the quality of the English throughout your manuscript. We encourage you to ask a native English speaking colleague to assist you.

A native English speaking colleague has assisted in the revision of the English throughout the manuscript. Moreover, the first author of the manuscript is a native English speaker (from USA).

Reviewer 1

Reviewer Name: Brian King

This manuscript presents the findings of a cross-sectional assessment of patterns and characteristics of e-cigarettes use among adult current e-cigarette users in Barcelona, which were recruited and surveyed via a consumer panel in 2015. The findings indicate that the primary motivation for using e-cigarettes was to reduce or quit smoking, tobacco was the most commonly used flavor, a majority of users reported using nicotine containing e-cigarettes, and most users were former tobacco smokers. Younger users were more likely to use flavors other than tobacco and to use e-cigarettes for recreational as opposed to cessation purposes. The authors conclude that policy makers should consider more expansive e-cigarette regulations, including bans on marketing that attracts young people, regulation of flavored e-cigarette products, and the prohibition of e-cigarette use in public indoor environments.

Overall, this manuscript is generally well written and presents findings on a timely and relevant topic in the field of public health. The tobacco product landscape has rapidly diversified in recent years, and the use of emerging tobacco products, most notably e-cigarettes, has increased considerably among adults and youth. Although science on the long-term health effects of these products remains uncertain, there is potential for these products to have either a net harm or benefit on public health. The latter scenario could be realized if adult cigarette smokers were to transition completely to e-cigarettes, although existing science doesn't necessarily suggest that is prominently occurring. Nonetheless, continued monitoring of the patterns and characteristics of e-cigarette use are critical to inform efforts to minimize potential harms and to maximize any potential benefits of these products at the population level.

Thank you very much for the kind comments to our work.

Specific comments and recommendations for improvement of the manuscript are described below.

1. Page 3. Abstract. In framing the conclusions in the abstract, it's important to ensure that the content is consistent with the actual results presented in the abstract. For example, the conclusions make statements about non-smokers being more likely to use flavors other than tobacco and to use e-cigarettes for recreational purposes; however, those data are not presented in the actual abstract. In the end, the abstract should be able to serve as a standalone document that does not require the reader to reference the main text of the article. Similarly, the conclusion should be restricted to content that relates to the implications of the present study findings; at present, the conclusion references content related to availability of flavors attracting young users who were never



conventional cigarette smokers, which cannot be fully gleaned from the present study findings, particularly those presented in the abstract.

Thank you for your comments. We have modified the abstract so that the conclusions are consistent with the presented results. We have deleted the conclusion about flavors attracting young users. The new section states:

**“Results:**

The most prevalent motivation for using e-cigarettes was to reduce tobacco smoking (48%, n=288), followed by quitting smoking (39.2%, n=235), and to use in places where tobacco was prohibited (10.2%, n=61). The most prevalent primary flavor used was tobacco (49%, n=294), followed by fruit (19.5%, n=117). People younger than 25 years old (OR=4.36, 95%CI 1.99-9.57) were more likely than older people to use them where cigarettes were prohibited. A greater proportion of those in the youngest age group preferred fruit flavor compared with older individuals (29.3%, n=41).

**Conclusions:**

Younger users of e-cigarettes and non-smokers are more likely to use flavors other than tobacco and to use e-cigarettes mainly for recreational purposes. Policy makers should consider more expansive e-cigarette regulations on flavors and their use in smoke-free areas. Furthermore, although many people use e-cigarettes to quit or reduce tobacco smoking, the current evidence on their effectiveness is inconclusive; thus their marketing highlighting their usefulness as a tobacco cessation tool should be more strongly regulated.”

2. Page 4. Article Summary. As currently framed, the article summary heading notes “strengths and limitations”, but there are no real limitations actually noted in the list. The limitations from the Discussion section of the manuscript should be duly noted here as well, most notably the limitation regarding the use of a non-probabilistic consumer panel. The current framing around the panel simply states that it shows greater sample representativeness than other non-probabilistic techniques, but makes no mention of the comparison with regard to probabilistic techniques.

Thank you for your comment. The following limitations were added to this section:

- “The sample was recruited using a non-probabilistic sampling method which could affect the external validity of the study.
- The use of a questionnaire in data collection allows for possible recall and response biases.”

3. Page 5. Third paragraph. The second statement of this paragraph doesn’t adequately summarize the state of the science on the effectiveness of e-cigarettes for cessation from conventional cigarettes. The science on this issue is still quite mixed, and there is non-conclusive evidence that these products are effective for long-term cessation. At present, the language indicates that some studies have found a positive effect; however, it doesn’t balance this statement with an acknowledgment of the inconclusive nature of the existing scientific literature.

Thank you for your comment. We completely agree with the reviewer’s comment. We have added to the sentence and cited a systematic review that found e-cigarettes not to be effective in smoking cessation as follows:

“Some studies show that e-cigarettes can be an effective tool for cessation or reduction of tobacco consumption and for the improvement of tobacco-related disease conditions (7–13) while a recent systematic review and meta-analysis concluded that they have no effect or even a negative effect. (14)”

Reference added:

14. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respir Med* 2016;4(2):116-28.  
<http://www.thelancet.com/article/S2213260015005214/fulltext>14. (accessed 7 August 2017).

4. Page 6. Second paragraph. The paragraph beginning “Researchers recognize” is seemingly out of the place and likely not necessary to adequately frame the issue to the reader. Instead of focusing on

this nuance, the introduction would segue better if the authors provided a clearer discussion of the explicit gaps in the existing literature and how this study fills those gaps.

We have deleted the above mentioned paragraph and changed the paragraph that followed to state:

"Gaps in information on e-cigarette users' patterns and characteristics of use still exist. Monitoring these patterns of use is necessary to inform decisions aimed at minimizing the potential negative effects of e-cigarettes and at maximizing their potential benefits. Therefore, the objective of this study is to describe current e-cigarette users' patterns of use, including primary motivation for use, dual use, use with nicotine, and main flavor used, according to individuals' sociodemographic characteristics and conventional tobacco consumption."

5. Page 7. First paragraph. It would be helpful if a clear definition of e-cigarette user was provided to the reader. It's not clear whether this is ever or current use, although it's likely the latter. If so, further clarity is warranted; for example, was it defined as use within the past 30 days, everyday or someday use, or some other standard measure? At present, this definition isn't clear, and should ideally come before the various patterns of use are defined.

We have defined that the participants had to be current e-cigarette users at the moment of the interview, independently of the time of use of e-cigarettes. Unfortunately, our questionnaire does not allow us to differentiate between daily and occasional e-cigarettes users. We have added the following sentence to clarify that all participants were "current e-cigarette users":

"The sensors walked around Barcelona neighborhoods and when they identified an individual using or carrying an e-cigarette in public, the interviewee was approached and asked if they were current e-cigarette users and if they would take part in the study. All participants were current e-cigarette users at the moment of the interview independent of whether they used it daily or occasionally."

6. Page 8. Motivations for Use. It would be helpful if further nuance was provided on how this question was asked. More specifically, was it an open ended question or were there specific categories that the respondent could select from? At present, it appears that there were a small percentage of respondents who did not fall within these three categories. As such, some clarity on the primary reasons for use beyond these three major responses would be useful; at the least, simply mentioning all the available response categories on the questionnaire would help put the findings into better context.

Thank you for the comment. We have included this information to state:

"Motivation for use: Users were asked about their primary motivation for using e-cigarettes. The possible responses were: "to quit tobacco smoking", "to reduce tobacco smoking", "to smoke in places where tobacco is prohibited" and "other reasons". This last category was open-ended and the interviewers wrote the literal response of the participants."

7. Pages 8-9. Data Analysis. It's not clear whether the data were weighted in any way to enhance representativeness of the target population of interest. Although a non-probabilistic approach was used, the data could still be weighted to enhance external validity. If that was not done, it should be clearly articulated in the Methods, and also duly acknowledged in the statement of limitations in the Discussion.

Thank you very much for the interesting comment. In a previous work (Matilla-Santander et al., 2017), we compared this sample of e-cigarette users obtained by means of a non-probabilistic method with other samples of e-cigarette users obtained in other studies conducted in Barcelona (Martínez-Sánchez et al., 2014) and Spain (Lidón-Moyano et al., 2016) using a probabilistic method of sampling. In that work, we have concluded that this non-probabilistic sample was representative of the current e-cigarette users of the city of Barcelona according to sex and age (Matilla-Santander et al., 2017). Moreover, we could have used the information from the aforementioned studies (Martínez-Sánchez et al., 2014; Lidón-Moyano et al., 2016) to weight these data, but they have small sample sizes and a big limitation of external validity (Matilla-Santander et al., 2017). For this reason, we have decided not to weight this sample. We have clarified this aspect in the Methods section as follows:

"Although we used a non-probabilistic sampling method to recruit the e-cigarette users, our sample was representative of current e-cigarette users according to sex and age (23). For this reason, analyses were not weighted"

And in the Discussion section:

"Our study has some limitations. First, we recruited study participants using the method of 'consumer panels', a non-probabilistic sampling technique, which calls into question the external validity of the sample. However, our sample was representative of current e-cigarette users according to sex and age (23). Despite our sampling method being a non-probabilistic technique itself, it has been shown in another study to provide greater sample representativeness than other commonly used non-probabilistic sampling methods. (23) Moreover, previous studies (4, 40) which we could use to weight our study have a small sample size and a big limitation of external validity (23). For this reason, the data were not weighted."

Moreover, we believe there are not appropriate data in Spain (due to the external validity limitation of the previous studies) to performance the weighting. However, if the editor thinks it is appropriate to weight the sample using previous studies, the authors would have no objection in doing so.

References:

23. Matilla-Santander N, Fu M, Ballbè M, et al. Using consumer panels in public health observational studies. *Gac Sanit*. 2017. Available from: <http://www.gacetasanitaria.org/es/linkresolver/uso-paneles-consumidores-estudios-observacionales/S0213911117301280/> (Accessed 17 August 2017).
4. Martínez-Sánchez JM, Ballbè M, Fu M, et al. Electronic cigarette use among adult population: a cross-sectional study in Barcelona, Spain (2013 – 2014). *BMJ Open*. 2014;4: e005894. Available from: <http://bmjopen.bmj.com/content/4/8/e005894> (Accessed 19 June 2017).
40. Lidón-Moyano C, Martínez-Sánchez JM, Fu M, Ballbè M, Martín-Sánchez JC, Fernández E. [Prevalence and user profile of electronic cigarettes in Spain (2014)]. *Gac Sanit*. 2016 Nov - Dec;30(6):432-437. Available from: <http://www.gacetasanitaria.org/es/linkresolver/prevalencia-perfil-uso-del-cigarrillo/S0213911116300395/> (Accessed 23 August 2017).

8. Page 12. Results. In the narrative of the results, it would be useful to provide an overall estimate of the proportion of respondents who reported using a flavor. The various types of flavor use is very helpful, but understanding the magnitude of any flavored use is critical, particularly to inform efforts to broach flavors through population based interventions, such as sales and advertising prohibitions. Perhaps this information is contained somewhere in the report, but it wasn't readily identifiable as currently framed.

As the reviewer mentioned, we have added the percentage of respondents as follows:

"Of the overall sample, 99% reported using an e-cigarette flavor."

9. Paged 10-13. Results. It's not clear whether the authors calculated any estimate of error (e.g. relative standard error) to assess the statistical robustness of their estimates. In some cases, the sample sizes for certain estimates are quite small, suggesting large standard errors and wide confidence intervals. A standard in the literature is usually suppression of the point estimate if the relative standard error is greater than 30%.

We did not assess the robustness of our estimation; moreover, in some stratification of the data the sample size are quite small and the confidence intervals may be very wide as the reviewer mentioned, thank you very much. We have decided to keep all point estimates and mentioned this limitation in the Discussion section as follows:

"However, we used a face-to-face questionnaire to collect data, which, compared to many studies of e-cigarette users in which data was obtained using other methods such as online questionnaires (31) or mail-in surveys, (41) our study has more internal validity. Furthermore, the estimates in stratification with small samples could be considered with caution due to the wide confidence intervals."

If the editor thinks it is appropriate to delete the point estimate if the relative standard error is greater than 30%, the authors would have no objection in doing so.

10. Page 15. Second paragraph. As mentioned in a previous comment, a more careful summary of the existing science is warranted on the efficacy of e-cigarettes for the purposes of cessation. At present, there are only a handful of longitudinal studies, including only a few trials, that have assessed this issue. Moreover, the findings from these studies are mixed, with some studies actually finding that e-cigarette users are less likely to quit at follow-up. As presently framed, the discussion of the manuscript appears to only highlight the positive findings without duly acknowledging the full scope of the existing scientific literature on this matter.

We agree with the reviewer's comment. We tried to be neutral in our discussion due to the polarization of the researchers and evidence. Following the recommendation of the reviewer, we have added a reference highlighting the negative findings as follows:

"This signifies that e-cigarette use with nicotine could contribute to cigarette smokers reducing consumption, which has been supported by past studies, (7,8,10,28) but contradicted by others. (14)"

11. Page 16. First paragraph. The statement that "a high proportion of users prefer tobacco as their main flavor" is not entirely accurate. The study in question, which this reviewer co-authored, did account for tobacco flavor. Tobacco flavor was not listed specifically as a response option because prevalence was so low among respondents from other studies. Moreover, respondents had the ability to enter "tobacco" in the open ended response option for this question, which very few did. Although the current study may have found prominent tobacco flavor use among heavier users, the existing evidence on this issue is not supportive of the broader claim that a "high proportion of users prefer tobacco flavor." In the case of the United States, preference of tobacco flavor is so low, as documented by retail sales and self-reported data, that it's not even worth including it as a response option on surveys because it won't yield sufficiently robust or presentable point estimates. That being said, it's reasonable to cite the current findings from this study to help put the content into context; however, suggesting that tobacco flavor is most prominent among users more broadly, and actually preferred, is not consistent with the preponderance of existing research on this matter.

Thank you very much for the comment. We have modified the paragraph according with the comment as follows:

"Despite wide bans on flavored cigarettes, bans on flavored e-cigarettes are scarce. Research on flavors is necessary to provide evidence on the potential harms of certain e-cigarette flavors to inform related policy decisions. 50% of our sample preferred tobacco flavor, followed by fruit, menthol and others. Our findings coincide with one study's findings (30) but differ from other studies which found fruit or menthol to be the preferred flavors (31, 33–34) and another that found users were more likely to use tobacco flavor at e-cigarette initiation but to switch to other flavors like fruit with continued use.(35) These differences could be related to the trend of e-cigarette use not having caught on in Spain like it has in countries such as the US, to differences in restrictions on e-cigarettes marketing, or to the relatively short duration of use among our study participants. To our knowledge, no other study has been published that compares preferred flavor of e-cigarettes among individuals' sociodemographic characteristics, patterns of use and tobacco consumption. One comprehensive study from the US was recently published that assessed preferred non-cigarette tobacco product (NCTP) flavors and stratified by sociodemographic characteristics. (34) Although the study provided information on the proportion of e-cigarette users who use with flavors in general, it did not stratify by the flavors themselves."

12. Page 17. First paragraph. When framing the rationale for including e-cigarettes in indoor smoking prohibitions, it's also critical to acknowledge the health risks of exposure to e-cigarette aerosol.

Although the aerosol does not have the same level of harmful ingredients as tobacco smoke, this does not mean that it is risk free. Environmental studies of aerosol have documented many harmful and potentially harmful ingredients, including heavy metals, ultrafine particulate, volatile organic compounds, and others. Prohibiting the use of these products in indoor environments protect bystanders from these harmful ingredients and the associated health risks of exposure.

We agree with the reviewer and have modified the paragraph to include the following:

“The act of using e-cigarettes indoors is problematic since environmental studies of their aerosol document harmful and potentially harmful ingredients such as formaldehyde, acetaldehyde, ultrafine particulate, polyaromatic hydrocarbons (PAHs), tobacco-specific nitrosamines (TSNAs) and heavy metals including cadmium, copper, lead and nickel, among others. (36) Individuals exposed to second-hand aerosol may be at risk of adverse health effects.”

13. Page 17. Limitations. As noted earlier, the limitations should provide a clearer articulation of the external validity (i.e. generalizability) of the sample. In the end, a non-probabilistic technique was used, and the data don't appear to be weighted. Although it may afford greater sample representativeness than other non-probabilistic sampling methods, it's not nearly as accurate as a probabilistic approach. This could introduce bias, which should be duly and clearly noted in the statement of limitations.

Thank you very much for the comment. Please see the response to comment #7 of this reviewer.

14. Page 18. Last paragraph. When framing the rationale and importance for regulation, it's important to reference factors beyond just dual use. One of the primary purposes of regulation of these products is to minimize use among young people and never users of conventional tobacco products. In order for these products to have a net benefit on public health, they need to successfully aid in transitioning current smokers to exclusive e-cigarette use, while also not leading to greater nicotine or tobacco product use among young people and never users. In the end, the importance of regulation is more expansive than what is necessarily alluded to in the first sentence of this paragraph.

We have changed the conclusion according to reviewer's comment as follows:

“More expansive regulations on e-cigarettes are important to minimize use by non-smokers, and young people and to protect people from second-hand aerosol and their potentially dangerous long-term effects. Until more evidence exists on long-term adverse effects of e-cigarettes and their effectiveness in helping smokers completely transition from dual use to use of e-cigarettes exclusively, regulations should be considered to discourage dual use. Furthermore, marketing that targets young people should be banned, including the promotion of novel flavors that are known to appeal to youth. Moreover, measures should be taken to discourage non-smokers from initiating e-cigarette use to prevent nicotine addiction that could lead to future tobacco product use. Next, flavored e-liquid, such as fruit and menthol flavors, should be more strongly regulated since they are more likely to be preferred by tobacco non-smokers. Finally, e-cigarette use in smoke-free areas should be banned, so as not to normalize their use and potentially renormalize smoking and to protect against passive exposure to the aerosol, particularly children.”

15. Page 18. Last sentence. As noted earlier, the rationale for prohibiting e-cigarette use in indoor public areas is not merely to prevent normalization. It's to prevent bystanders, particularly children, from being exposed to the harmful ingredients of the aerosol – a fact that has been established in the scientific literature through laboratory and environmental studies.

As included in the response to the previous comment, we have modified this sentence to state:

“Finally, e-cigarette use in smoke-free areas should be banned, so as not to normalize their use and potentially renormalize smoking and to protect against passive exposure to the aerosol, particularly children.”

## Reviewer 2

Reviewer Name: Konstantinos Farsalinos

This study is a survey of e-cigarette users, with a small sample and no added information compared to any previous survey published until now. The authors found that the vast majority of e-cigarette users are current or former smokers, and the main motivation is to quit smoking or reduce cigarette consumption. This information is consistent with the large number of surveys published until now, and provides no new information.



Although conducting the survey with face-to-face interviews is a plus, the authors provide no information about the methodology for recruitment (they cite a Spanish article which I am unable to understand since I don't speak Spanish). Also, there is no information on how this recruitment method is more representative of the population of e-cigarette users. For example, are users who buy e-cigarette online represented proportionally with this recruitment method? The measure of consumption (nr of cartridges per week) is problematic (see below for more details).

The question on flavors requested a single response only, while we know a large proportion of ecigarette users use more than 1 type of flavoring regularly.

The logistic regression analysis seems to be separate models for each variable, with each model adjusted for age, gender and education. It seems they did not include all variables into a single model, which would make more sense. Although flavor use and motivation are analyzed according to patterns of use and past and current smoking status, the univariate nature of the analysis does not provide a comprehensive view of the interactions between different factors.

Conclusions in the abstract and full text about restrictive regulations are not supported by the study findings which show that the majority of e-cigarette users are current and former smokers.

Also, discouraging dual use makes little sense since dual use is a necessary step towards quitting (it is unreasonable to expect that initiation of e-cigarette use will immediately result in quitting smoking).

Studies have shown that dual use can lead to smoking cessation, while quitting ecigarette use can lead to relapse to smoking.

Thank you very much for your comments and suggestions. Following, we have enclosed a point-by-point reply to all of them.

Specific comments

1. Please remove the term "smoking" when discussing about e-cigarette use. There is no such thing as "smoking" of e-cigarettes.

We have removed any reference to "smoking" e-cigarettes.

2. Page 5, line 53-55. "Their advertising and availability of fruit and other non-tobacco flavors may also specifically appeal to young people (15-16) and non-smokers. (17)". Reference 17 only assessed prevalence of use and had no information on the effects of flavors on e-cigarette use prevalence or patterns of use. Additionally, only 12.6% of e-cigarette users in that study were never smokers. Thus, this reference should be removed from the statement about flavors.

Thank you for your comment. We have removed that reference, changed the sentence and added a new reference as follows:

"Their advertising and availability of fruit and other non-tobacco flavors may also specifically appeal to young people (16,17) and fruit and other sweet flavors have been shown to be perceived as less harmful and more likely to be used by young, non-smokers. (18)"

New reference:

18. Ford A, MacKintosh AM, Bault L, Moodie C, Hastings G. Adolescents' responses to the promotion and flavouring of e-cigarettes. *Int J Public Health* 2016;61:215-224.

3. Page 6, lines 6-11. "Some short-term studies have found negative pulmonary and cardiovascular effects in users such as lung and airway obstruction and increased heart rate, cough and sore throat. (18-19)" Reference 18 is a conference abstract. The authors should find other studies to support their statement. Also, the increase in heart rate is not a negative cardiovascular effect but the acute effect of nicotine intake. Same acute effects are observed for approved nicotine replacement therapies. We have removed the above reference, as the reviewer suggested, and changed the sentence to state:

"Some short-term studies have found negative pulmonary effects in users such as lung and airway obstruction. (19)"

4. Page 6, lines 10-17. "Furthermore, chemicals such as carcinogenic tobacco specific nitrosamines, carcinogenic carbonyls, volatile organic compounds and formaldehyde (20–24) have been found in e-



cigarette liquid. The long-term effects of these chemicals must continue to be evaluated.” Again I would advise the authors to avoid citing conference abstracts (reference 24). Also, formaldehyde is a carbonyl (carbonyls are mentioned in the same sentence). “Volatile organic compounds” is a generalized term and includes chemicals which are not harmful in any form. They authors should be more specific in their discussion about potentially toxic compounds.

We have removed the reference and have changed the sentence to state:

“Furthermore, chemicals such as carcinogenic tobacco specific nitrosamines (TSNAs) and carcinogenic carbonyls including formaldehyde and acetaldehyde (19–22) have been found in e-cigarette liquid.”

5. Page 7, Methods. “The market research technique known as ‘consumer panels’ was used to enroll e-cigarette users as described previously elsewhere. (27)” The authors provide no details about the consumer panel technique, and they cite a study which is “in press”. In fact, the manuscript is available but it is in Spanish. The authors need to present information on the technique they used in this manuscript.

We have provided more information on the sampling technique used:

“Due to limited resources and a necessary sample size that was large relative to the prevalence of e-cigarette use in the population, a probabilistic sampling technique was infeasible. Therefore, the technique known as ‘consumer panels’ was used to enroll e-cigarette users as described previously elsewhere. (23) Briefly, this technique is often used in market research to recruit users of uncommonly found products. For this study, e-cigarette users were recruited in all neighborhoods of the city of Barcelona between February and June of 2015 by sensors (specifically trained personnel for the recruitment of uncommon product consumers, in this case, e-cigarette users). The sensors walked around Barcelona neighborhoods and when they identified an individual using an e-cigarette in public, the individual was approached and asked if they would take part in the study.”

6. Page 7, Methods The authors should mention how many participants were approached and agreed to participate initially, and which proportion of them was included in the final sample. Also, I don't understand why they were interviewed twice (2015 and 2016). What if someone was an e-cigarette user in 2015 but had quit in 2016? Was he excluded from the study?

In this study, we only use the baseline information of the cohort study. This is a cross-sectional study. Currently, we are in the field-work of the follow-up of this survey and recruitment of more e-cigarettes users. For this reason, we do not have information about the e-cigarette users who quit smoking or continued using the e-cigarette in 2016.

As the reviewer suggested, we have added in the Methods section information about the participation rate and the reason for interviewing participants twice:

“To recruit the 600 participants, 665 individuals were approached (a rejection rate of 9.7%).” Moreover, we have clarified that we only use the baseline survey of the cohort study.

“A brief face-to-face interview was conducted with the individuals who agreed to participate at that point and again in 2016 since this was the baseline survey of a cohort study.”

7. Page 7, Patterns of use. The authors ask “nr of cartridges” used by the participants, and the median response was 2 per week. I think responders mentioned the number of bottles they were using weekly, and this creates a lot of problems because bottles can have different volume (10-30 mL or even more). In that aspect, the information on liquid consumption is highly inaccurate.

Thank you very much for the interesting comment. We agree with the reviewer about the potential bias of the questionnaire in measuring the information of e-liquid. Moreover, we asked the participants only about the milligrams of nicotine not the volume of the e-liquid and this could be another source of bias due to the different volumes of e-liquid, as the reviewer mentioned. We have mentioned this limitation in the discussion section as follows:

“We asked participants to recall information about their past smoking habits, such as the number of cigarettes they smoked before use of e-cigarettes. Therefore, there is a possibility of recall bias.

Moreover, the information about the milligrams of nicotine of the cartridges should be considered with caution because there are several volumes of e-liquid (from 10 to 30 or more mL) and the milligrams of nicotine could vary.”

Although the information about milligrams of nicotine of the cartridges could be biased we prefer to keep them included in the above limitations because we believe that it is interesting. However, if the editor thinks it is appropriate to delete, the authors would have no objection in doing so.

8. Page 8, Flavors used. I think there is a problem in the question asking about the “primary” flavor. Primary is not necessarily the only flavor participants were using. It is quite common for such questions to allow multiple answers because it is quite common for e-cigarette users to use multiple flavors (see Farsalinos et al. *Int J Environ Res Public Health*. 2013 Dec 17;10(12):7272-82). Thank you very much for the comment, we agree with it. For this reason, we did collect information on users’ secondary and tertiary flavor preferences. However, for this study, we only utilized the responses to the survey question of the flavor they use most habitually. In future studies we will focus in this interesting topic.

9. Page 9, Data analysis. It seems to me that the logistic regression analysis model did not include all factors into one model but created separate models for each variable, with each model adjusted for age, gender and education. This is not a true multivariate regression analysis. As the reviewer mentioned, we only performed separate multivariate models adjusted by age, sex, and education. We did not include all factors because we only adjusted by the potential socio-demographic confounders. We have clarified this in the Methods section as follows: “We also fit separate multivariate logistic regression models to calculate the odds ratios (OR) with their 95% confidence intervals (CI) of e-cigarette users’ use with nicotine, motivation for use and flavor used adjusted for sex, age, and educational level.

10. Page 11, line 20. I don’t understand what the terms “past non-smoker” and “current non-smoker” mean. We asked all participants about their smoking status before and after using e-cigarettes as we mentioned in the Methods section. We talked about their smoking before using e-cigarettes. We agree with the reviewer’s comment that it was not clear in the previous version. We have clarified this as follows: “Individuals whose main motivation was to use in places where tobacco was prohibited were more likely to use fruit flavor (OR=8.72, 95%CI 3.76-20.26) and to have been non-smokers before initiating e-cigarette use (OR=36.15, 95%CI 18.36-71.18) or non-smokers after initiating their use (OR=10.60, 95%CI 5.40-20.82) (Table 2).”

11. Page 12, lines 23-33. The authors discuss about statistical differences with some ORs being not statistically significant. They cannot discuss about differences since such differences did not reach statistical significance. Thank you for the comment. We have deleted reference to the non-statistically significant results, as the reviewer suggested, and modified the sentence to state: “Fruit flavor was more prevalent among women (women, 23.9%; men, 11.9%  $p<0.001$ ) and the youngest age group, showing a negative dose-response pattern with increasing age (<25, 29.3%; 25-44, 17.7%; 45-64, 14.4%; ≥65, 12.5%  $p=0.008$ ) (Table 3), although OR did not yield statistically significant results.”

12. Page 12, table 3. The last column of table 3 is not visible in the pdf file. We are sorry for that. We believed it would appear in the generation of the pdf file. We have corrected this.

13. Page 13. Lines 43-45. "...there was a relatively high percentage of people who were nonsmokers before beginning use of e-cigarettes (13%)." I am not sure with what criterion is the 13% of participants considered "relatively high percentage". They definitely constitute a minority. Following the comment of the reviewer, we have only provided the information, deleting the perception of high or low prevalence, as follows:

"We also found a high proportion (65%) of users smoke conventional cigarettes (dual use), and nearly one in seven (13%) were non-smokers before beginning use of e-cigarettes."

14. Page 14, lines 36-41. "On the other hand, if users continue dual use, they may be at greater risk for adverse health effects, as studies show that even light smoking can have significant negative health impacts and there is potential for long-term health effects of e-cigarette use. (31)" I don't understand what the authors mean with "greater" risk for adverse health effects. Greater than being exclusive smokers? What if a dual user has reduced smoking from 20 cigarettes per day to 2 cigarettes per day? This is defined as dual use, but does this represent a greater risk compared to smoking 20 cigarettes per day only? Dual use represents a normal pathway towards complete cessation. NRTs are also used together with smoking initially, and are approved for long-term use even as partial substitutes for smoking (MHRA, UK). Studies have shown that dual use can lead to future quitting (Etter, *Nicotine Tob Res.* 2017 Jun 7. doi:10.1093/ntr/ntx132). In fact, the study by Etter found that quitting e-cigarette use was associated with relapse to smoking.

We agree that dual use would represent a normal pathway towards cessation if e-cigarettes were found effective in doing this. We acknowledged this in the previous sentence, "On one hand, if a longer duration of use eventually leads to complete tobacco cessation, public health implications may be positive." We are also aware that studies have shown that dual use can lead to future quitting, but that other studies show no relation. Also, that many of the studies that have found dual use leading to future quitting have been rated 'Low' or 'Very low' by GRADE standards because of non-representative samples and low response rates, like the article mentioned above (Etter, *Nicotine Tob Res.* 2017 Jun 7. doi:10.1093/ntr/ntx132).

We have changed the sentence referenced in the comment above to state:

"On the other hand, if users continue dual use they may still be at risk of the negative health outcomes of tobacco, as studies show that even light cigarette smoking can have significant negative health impacts (27) and at risk of the potential long-term health effects of e-cigarette use."

15. Page 15, lines 16-35. This paragraph is a bit puzzling. It seems that the authors are criticizing the fact that motivation for e-cigarette use is to quit or reduce smoking. Do the authors think there is another reason for e-cigarettes to exist? Irrespective of whether the evidence supports or not the value of e-cigarettes in quitting smoking (which I think it does), it is entirely desirable from a public health perspective that e-cigarettes are used as smoking cessation or reduction aids.

We are sorry for the misunderstanding. We are not criticizing that quitting or reducing smoking are the main motivations for using e-cigarettes. Moreover, if the e-cigarette is useful for doing this, we recognize the public health perspective of their desirability. However, we realize that, while it is desirable that tobacco smokers quit smoking, the evidence supporting the value of e-cigarettes is inconclusive and since long-term studies of their adverse effects do not yet exist (but evidence does exist of carcinogenic chemicals they contain), the precautionary principle should be adhered to until there is more definitive evidence. If and when e-cigarettes are proven to be effective in quitting smoking and the long term health effects negligible, they would be considered valuable from a public health perspective to be used by current smokers who want to quit smoking.

16. Discussion section. The authors do not mention important information derived from a large survey of e-cigarette users concerning flavors (Farsalinos et al., *Int J Environ Res Public Health.* 2013 Dec 17;10(12):7272-82). There is a transition from tobacco flavors at e-cigarette use initiation to other types of flavors over time. The authors had participants with low duration of e-cigarette use, so this transition may not have happened yet. Again, I should stress that the question seems to accept only 1

response about primary flavor used, which does not take into account the possibility that participants may use more than 1 type of flavor.

As mentioned above (please see response to point 8 of this reviewer), although we did collect information on users' secondary and tertiary flavor preferences, for this study we only utilized the responses to the survey question of the flavor they use most habitually. We will take in to consideration the analysis of other flavors for future studies.

We have also added reference to the above article recommended by the reviewer as follows:

"Our findings coincide with one study's findings (30) but differ from other studies which found fruit or menthol to be the preferred flavors (31, 33–34) and another that found users were more likely to use tobacco flavor at e-cigarette initiation but to switch to other flavors like fruit with continued use. (35) These differences could be related to the trend of e-cigarette use not having caught on in Spain like it has in countries such as the US, to differences in restrictions on e-cigarettes marketing or to the relatively short duration of e-cigarette use among our study participants."

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Brian King Centers for Disease Control and Prevention, United States of America
<b>REVIEW RETURNED</b>	15-Sep-2017

<b>GENERAL COMMENTS</b>	The authors have made a concerted and adequate effort to address the comments of both original reviewers, and have provided sufficient narrative in instances where comments were not fully addressed in the revised draft. This study still has several inherent limitations, not the least of which is the sampling approach; however, these items are duly noted and described in the manuscript, thus making the reader aware of these critical caveats. This original reviewer is satisfied with the revised version and recommends publication of the manuscript in its present form.
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<b>REVIEWER</b>	Konstantinos Farsalinos Onassis Cardiac Surgery Center, Greece University of Patras, Greece National School of Public Health, Greece
<b>REVIEW RETURNED</b>	15-Oct-2017

<b>GENERAL COMMENTS</b>	The authors need to balance the manuscript and make it more relevant to the study findings instead of an overview of the theoretical concerns about potential harms from e-cigarettes. In some parts of the manuscript there is strong bias against e-cigarettes, presenting theoretical (and of course understandable) concerns as evidence (e.g. renormalization, addiction among non-smokers, adoption of use by kids, gateway to smoking etc). The discussion is too long and in most part irrelevant to the study findings. The issues of smoking renormalization and kids being attracted to e-cigarettes are mentioned repeatedly although all participants were adults. Suggestions about marketing are made although marketing and health claims are banned in the EU through the TPD. There is nothing stricter that can be implemented. The discussion should be shortened and be relevant to the study findings. An important issue is that about 21% of participants who were non-
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	<p>smokers before e-cigarette use said that the reason to use e-cigarettes was to reduce or quit smoking!! This makes the analysis particularly problematic. There is almost no discussion about the findings that smokers were reduced by 22% after e-cigarette use initiation (from 87% to 65%, relative reduction of 25%). This is in fact the main finding of the study and must be discussed, and the potential benefit in these participants by far outweighs any harm from adoption of use by non-smokers.</p> <p>Some recommendations simply make no sense. E.g., “regulations should be considered to discourage dual use”. This is unrealistic and could also be dangerous for smokers who have substantially reduced their consumption with e-cigarette use.</p> <p>Finally, the conclusions and recommendations are unsubstantiated by the study findings and largely irrelevant. Again, the authors ignore that a substantial proportion of users were current non-smokers while they were smokers before e-cigarette use initiation (obviously with the limitations relevant to the cross-sectional design of the study).</p> <p>Finally, it is not mentioned anywhere if the participants signed an informed consent to participate to the study. I suppose they did, but the authors should mention it.</p> <p>Please see some more detailed comments below.</p> <p><b>Abstract conclusions</b></p> <p>The conclusion section has only one sentence relevant to the study, while the rest are recommendations by the authors about strict regulations that are neither supported nor justified by the study. All the sentences besides the first one should be removed. Conclusions should be relevant to the study findings. See more details below, in relation to similar statements mentioned in the text.</p> <p>Page 5 lines 50-55. “There is also evidence e-cigarettes may harm public health gains in tobacco reduction by renormalizing smoking and creating and sustaining nicotine addiction, since their use, sale and marketing are less regulated than tobacco products.”</p> <p>There is no evidence that e-cigarettes renormalize smoking. There is no country where e-cigarette use has led to increased smoking prevalence (whether in adults or in adolescents). This is a theoretical concern, which has not been demonstrated by any study. The authors should present it either as a theoretical concern or remove the sentence. Below I provide more details about use by non-smoking adolescents and adults.</p> <p><b>References 16 and 17.</b></p> <p>Reference 17 is a news report on BMJ about a congressional hearing in the US. This is not a scientific document and should be removed. Reference 16 is also completely outdated and should be removed. It is a viewpoint at a time when no regulation existed (2013). Europe now has regulated e-cigarettes (prohibiting advertising and marketing), so the reference is irrelevant to the present situation.</p> <p>Page 39, lines 27-29. “... our sample was representative of current e-cigarette users according to sex and age.(23)”</p> <p>I don't understand how this conclusion was made and how a reference discussing in general about consumer panels (in Spanish) can provide proof that the sample in this study is representative of the current e-cigarette users in Barcelona. The authors need to</p>
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	<p>explain how this is substantiated.</p> <p>Table 2. The authors mention total sample n = 600, however they have analyzed 584 participants (235 quit smoking, 288 reduce smoking, 61 use in places where smoking is prohibited). Obviously they omitted the participants who responded "other". This should be mentioned in the manuscript and the number mentioned in the table should be corrected to 584. A major issue of the study is related to the responses of past non-smokers about reasons for using e-cigarettes. 21% of the 69 past non-smokers included in the table said they use e-cigarettes to quit smoking. Additionally, 8.9% said they use e-cigarettes to reduce smoking. A total of 21 non-smokers said they used e-cigarettes to quit or reduce smoking. How is that possible? Were they misreporting the reasons of use or their past smoking status? How can the authors distinguish which is the case? This represents 27% of all non-smoking participants (21 of 79) and is a substantial proportion. This creates substantial problems with the presentation of findings for non-smokers. All the proportions mentioned in the results and discussion section may be based on false reports by the participants.</p> <p>Page 42, lines 54-56. "...users of menthol and fruit flavors were more likely to be past and current non-smokers" For menthol the OR of being current non-smoker is 1.44 (0.94-2.21) so it is not statistically significant. The same applies for fruit flavors. The p values which refer to proportions should be interpreted as more current non-smokers compared to current smokers use fruit and menthol flavors, but the regression analysis showed that they were NOT more likely to use these flavors. Therefore, it should be removed from the sentence.</p> <p>Discussion. The discussion should be substantially shortened. Many parts are irrelevant to the study itself. The potential theoretical risk for adolescents initiating e-cigarette use or even transitioning to smoking is mentioned while no adolescents were recruited in this study. The authors discuss about second -hand exposure based on the small proportion of participants who said they initiated e-cigarette use to avoid smoking bans. There is a lot of discussion about marketing while marketing is completely banned in Spain (and in the whole EU) through the 2014 TPD.</p> <p>Discussion, page 44 lines 33-38. "This discrepancy in average time of e-cigarette use could quite possibly be due to their recent growth in popularity in Spain at the time of data collection and many users having newly initiated their use." There is no substantiation for this argument. In fact, e-cigarette use was quite high in Spain until 2014, where a case of lipoid pneumonia which was attributed to e-cigarettes led to a strong media campaign that virtually extinguished the e-cigarette market. Here is an article from Spanish media dated November 2014 saying that the market was reduced by 90%: <a href="https://www.thelocal.es/20141103/spain-turns-back-on-e-cigarettes-ance-who">https://www.thelocal.es/20141103/spain-turns-back-on-e-cigarettes-ance-who</a></p>
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	<p>Discussion, page 45, lines 52-57. "The contradictory evidence on whether or not this is true and lack of long term studies on the health effects of e-cigarettes give reason for policy makers to consider stronger regulations on their marketing until there is more definitive evidence."</p> <p>Again this is an outdated statement. E-cigarette marketing has been banned throughout the EU. There cannot be any stronger regulation than that.</p> <p>Discussion, page 47, lines 13-21. "It is feared that the normalization of e-cigarettes among young people will increase the prevalence of their use, contributing to dual use in smokers and nicotine addiction and subsequent use of other tobacco products in non-smokers"</p> <p>I understand that this may be a legitimate fear, but the authors should at the same time mention that this is not happening. A recent study in the UK found that e-cigarette use among adolescents is mainly experimentation (Bauld et al., Int J Environ Res Public Health. 2017 Aug 29;14(9) . pii: E973). Also, in the US, the increased ever and current e-cigarette use among adolescents has been accompanied by the highest rates of smoking decline ever observed. Finally, all data from 2016 from the US (NYTS 2016 and MTF 2016 surveys) have shown that even experimentation with e-cigarettes has dropped by 20% among adolescents. So, the concerns raised by the authors have been rejected by all the current evidence. The authors need to make the manuscript more balanced and mention all the above.</p> <p>Discussion, page 47, lines 39-49.</p> <p>This is another case of exaggerated claims about second hand exposure effects. Even in studies where some compounds exceeded background levels, the post-use levels measured were by far lower than indoor air quality limits. Characteristically, NIOSH did a study in the environment of vapes shops, which are most likely the places with the highest burden of e-cigarette emissions. They found no chemical present at levels above safety limits. (<a href="https://www.cdc.gov/niosh/hhe/reports/pdfs/2015-0107-3279.pdf">https://www.cdc.gov/niosh/hhe/reports/pdfs/2015-0107-3279.pdf</a>)</p> <p>Discussion, page 48 lines 13-15. "E-cigarette companies take advantage of this by marketing fruity flavors to youth. (17)"</p> <p>Again the authors use reference 17 which was a totally unsubstantiated conclusion from a congressional report in the US.</p> <p>Discussion, page 48, lines 13-15. "Bans on certain characterizing flavored cigarettes have had a positive impact on reducing the number of young people who smoke (39) and similar bans on flavored e-cigarettes should be considered."</p> <p>The authors present the case for e-cigarette flavors as similar to tobacco cigarettes. However, the two cases are not at all comparable. E-cigarettes are used as smoking substitutes, studies have shown that flavors exist because of adult vapers' demand, and use by non-smoking adults and kids is minimal. Therefore, the current situation shows potential benefit for the group of smokers</p>
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	<p>from switching to e-cigarettes and no harm to other groups. Contrary to that, tobacco cigarettes cause only harm and provide no potential benefit to anyone. While it is totally justifiable to ban flavored tobacco cigarettes, there is currently no justification to ban flavored e-cigarettes.</p> <p>Discussion, page 49, lines 30-58. The whole paragraph is problematic and should be removed. The discussion about kids (again, as in previous sections) is irrelevant to the study. Discussion about marketing is outdated because there is no marketing allowed according to the EU TPD, while sales of any e-cigarettes (irrespective of flavor) to kids has been banned.</p> <p>Discouraging dual use is:</p> <ol style="list-style-type: none"> <li>1. Unfeasible, unless the authors believe that use of e-cigarettes should lead to smoking cessation on the first day of initiation. All users of smoking cessation medications are essentially dual users initially, and the majority eventually becomes exclusive smokers because they fail to quit with medications.</li> <li>2. Dangerous, for those who have substantially reduced smoking but have not completely quit. Discouraging dual use will lead to relapse to smoking at the same consumption as before.</li> </ol> <p>I agree with discouraging use by non-smokers (for both nicotine and non-nicotine e-cigs), but the restrictions the authors suggest apply to a small proportion (13%, if that is accurate) of the study sample (even smaller when considering the non-smokers using nicotine e-cigarettes) but will likely hurt the majority.</p> <p>The discussion about potential harm from e-cigarettes is also emotional. There is no doubt that e-cigarettes are by far less harmful than smoking. Of course long term epidemiological studies are needed, but they are needed to accurately quantify the level of risk reduction.</p> <p>The public health benefit of any intervention is not determined only by the effects on kids but on the overall effects on the whole population. The concern about kids is of course reasonable, but the discussion is too emotional. Finally, I will mention once again that this discussion is irrelevant to the study because no kids were included in the study, while the non-smoking adults who were using e-cigarettes were a very small minority (13%, if that is accurate).</p>
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## VERSION 2 – AUTHOR RESPONSE

bmjopen-2017-018329

"Motivation and main flavor of use, use with nicotine, and dual use of electronic cigarettes in Barcelona, Spain: a cross-sectional study"

Point-by-point reply to reviewers' Comments

We would like to thank Reviewer #1 (Dr. Brian King) for the kind comments about our work and who recommends publication of the manuscript in its present form. However, we are a bit surprised that

Reviewer #2 (Dr. Farsalinos). We have revised the manuscript again according to the new comments of Dr. Farsalinos in order to improve the level of quality of the manuscript and we are following all his recommendations (see response below). However, we do not know whether the potential conflicts of interest that Dr. Farsalinos has now declared (not declared in his initial review) may be biasing his judgment.

Reviewer: 1

Reviewer Name: Brian King

Institution and Country: Centers for Disease Control and Prevention, United States of America Please state any competing interests: None declared.

Please leave your comments for the authors below The authors have made a concerted and adequate effort to address the comments of both original reviewers, and have provided sufficient narrative in instances where comments were not fully addressed in the revised draft. This study still has several inherent limitations, not the least of which is the sampling approach; however, these items are duly noted and described in the manuscript, thus making the reader aware of these critical caveats. This original reviewer is satisfied with the revised version and recommends publication of the manuscript in its present form.

Thank you very much for the kind comments to our work and the recommendation to publish the manuscript.

Reviewer: 2

Reviewer Name: Konstantinos Farsalinos

Institution and Country: Onassis Cardiac Surgery Center, Greece, University of Patras, Greece, National School of Public Health, Greece Please state any competing interests: In the past 36 months, 2 studies were performed using unrestricted funds from the non-profit association AEMSA and 1 study by the non-profit association Tennessee Smoke-Free Association.

The authors need to balance the manuscript and make it more relevant to the study findings instead of an overview of the theoretical concerns about potential harms from e-cigarettes. In some parts of the manuscript there is strong bias against e-cigarettes, presenting theoretical (and of course understandable) concerns as evidence (e.g. renormalization, addiction among nonsmokers, adoption of use by kids, gateway to smoking etc). The discussion is too long and in most part irrelevant to the study findings. The issues of smoking renormalization and kids being attracted to e-cigarettes are mentioned repeatedly although all participants were adults.

Suggestions about marketing are made although marketing and health claims are banned in the EU through the TPD. There is nothing stricter that can be implemented. The discussion should be shortened and be relevant to the study findings.

An important issue is that about 21% of participants who were non-smokers before e-cigarette use said that the reason to use e-cigarettes was to reduce or quit smoking!! This makes the analysis particularly problematic. There is almost no discussion about the findings that smokers were reduced by 22% after e-cigarette use initiation (from 87% to 65%, relative reduction of 25%). This is in fact the main finding of the study and must be discussed, and the potential benefit in these participants by far outweighs any harm from adoption of use by non-smokers.

Some recommendations simply make no sense. E.g., "regulations should be considered to discourage dual use". This is unrealistic and could also be dangerous for smokers who have substantially reduced their consumption with e-cigarette use.

Finally, the conclusions and recommendations are unsubstantiated by the study findings and largely irrelevant. Again, the authors ignore that a substantial proportion of users were current non-smokers while they were smokers before e-cigarette use initiation (obviously with the limitations relevant to the cross-sectional design of the study).

Finally, it is not mentioned anywhere if the participants signed an informed consent to participate to the study. I suppose they did, but the authors should mention it.

We would like to thank the Reviewer for the second revision that was performed. As the reviewer suggested, we have balanced the manuscript and shortened the discussion. We have also highlighted the percentages of former smokers after use of e-cigarettes. Please see the detailed answers to the comments below. As the Reviewer mentioned, the participants signed the informed consent and the project was approved by the Ethics Committee. We have mentioned this in the Methods section.

Please see some more detailed comments below.

#### Abstract conclusions

The conclusion section has only one sentence relevant to the study, while the rest are recommendations by the authors about strict regulations that are neither supported nor justified by the study. All the sentences besides the first one should be removed. Conclusions should be relevant to the study findings. See more details below, in relation to similar statements mentioned in the text.

As the Reviewer suggested, we have only kept the first sentence of the Discussion section of the abstract.

Page 5 lines 50-55. "There is also evidence e-cigarettes may harm public health gains in tobacco reduction by renormalizing smoking and creating and sustaining nicotine addiction, since their use, sale and marketing are less regulated than tobacco products."

There is no evidence that e-cigarettes renormalize smoking. There is no country where e-cigarette use has led to increased smoking prevalence (whether in adults or in adolescents). This is a theoretical concern, which has not been demonstrated by any study. The authors should present it either as a theoretical concern or remove the sentence. Below I provide more details about use by non-smoking adolescents and adults.

We agree with the reviewer that it is a theoretical concern and there is scarce evidence. In this sense, a recent study published in JAMA Pediatric (Goldenson NI et al., 2017) has shown that a high concentration of nicotine of e-cigarettes was associated with the frequency and intensity of smoking and vaping.

As the reviewer suggested, we have included that it is a theoretical concern.

#### References 16 and 17.

Reference 17 is a news report on BMJ about a congressional hearing in the US. This is not a scientific document and should be removed. Reference 16 is also completely outdated and should be removed. It is a viewpoint at a time when no regulation existed (2013). Europe now has regulated e-cigarettes (prohibiting advertising and marketing), so the reference is irrelevant to the present situation.

As the reviewer suggested, we have deleted both references and the sentence in the Introduction section.

Page 39, lines 27-29. "... our sample was representative of current e-cigarette users according to sex and age.(23)"

I don't understand how this conclusion was made and how a reference discussing in general about consumer panels (in Spanish) can provide proof that the sample in this study is representative of the current e-cigarette users in Barcelona. The authors need to explain how this is substantiated.

This aspect was replied to in the first response to comments by the Reviewer (please see comment #7 of Reviewer #1).

Table 2.

The authors mention total sample  $n = 600$ , however they have analyzed 584 participants (235 quit smoking, 288 reduce smoking, 61 use in places where smoking is prohibited). Obviously they omitted the participants who responded "other". This should be mentioned in the manuscript and the number mentioned in the table should be corrected to 584.

Thank you very much for the comment. We have corrected the mistake in the table and mentioned it in the Methods section as the reviewer suggested.

A major issue of the study is related to the responses of past non-smokers about reasons for using e-cigarettes. 21% of the 69 past non-smokers included in the table said they use e-cigarettes to quit smoking. Additionally, 8.9% said they use e-cigarettes to reduce smoking. A total of 21 non-smokers said they used e-cigarettes to quit or reduce smoking. How is that possible? Were they misreporting the reasons of use or their past smoking status? How can the authors distinguish which is the case? This represents 27% of all non-smoking participants (21 of 79) and is a substantial proportion.

This creates substantial problems with the presentation of findings for non-smokers. All the proportions mentioned in the results and discussion section may be based on false reports by the participants.

Thank you very much for the comment. We have checked the database and the results are corrected. This could be due to a recall bias or information bias.

We have mentioned this limitation in the Discussion section as follows:

"We asked participants to recall information about their past smoking habits, such as the number of cigarettes they smoked before use of e-cigarettes. Therefore, there is a possibility of recall bias or information bias. In this sense, around 30% of the participants who declared to be non-smokers before use of e-cigarettes also declared used it to quit or reduce tobacco smoking. For this reason, the information collected about users' characteristics before using e-cigarettes should be considered with caution due to the potential for response bias."

Page 42, lines 54-56. "...users of menthol and fruit flavors were more likely to be past and current non-smokers"

For menthol the OR of being current non-smoker is 1.44 (0.94-2.21) so it is not statistically significant. The same applies for fruit flavors. The p values which refer to proportions should be interpreted as more current non-smokers compared to current smokers use fruit and menthol flavors, but the regression analysis showed that they were NOT more likely to use these flavors. Therefore, it should be removed from the sentence.

As the reviewer suggested, we have deleted this sentence due to it not being statistically significant.

#### Discussion.

The discussion should be substantially shortened. Many parts are irrelevant to the study itself. The potential theoretical risk for adolescents initiating e-cigarette use or even transitioning to smoking is mentioned while no adolescents were recruited in this study. The authors discuss about second-hand exposure based on the small proportion of participants who said they initiated e-cigarette use to avoid smoking bans. There is a lot of discussion about marketing while marketing is completely banned in Spain (and in the whole EU) through the 2014 TPD.

As the reviewer suggested, we have shortened the Discussion section following his comments.

Discussion, page 44 lines 33-38. "This discrepancy in average time of e-cigarette use could quite possibly be due to their recent growth in popularity in Spain at the time of data collection and many users having newly initiated their use."

There is no substantiation for this argument. In fact, e-cigarette use was quite high in Spain until 2014, where a case of lipoid pneumonia which was attributed to e-cigarettes led to a strong media campaign that virtually extinguished the e-cigarette market. Here is an article from Spanish media dated November 2014 saying that the market was reduced by 90%:

<https://www.thelocal.es/20141103/spain-turns-back-on-e-cigarettes-ance-who>

We have deleted this sentence as the reviewer recommended.

Discussion, page 45, lines 52-57. "The contradictory evidence on whether or not this is true and lack of long term studies on the health effects of e-cigarettes give reason for policy makers to consider stronger regulations on their marketing until there is more definitive evidence."

Again this is an outdated statement. E-cigarette marketing has been banned throughout the EU. There cannot be any stronger regulation than that.

We have deleted this sentence as the reviewer recommended.

Discussion, page 47, lines 13-21. "It is feared that the normalization of e-cigarettes among young people will increase the prevalence of their use, contributing to dual use in smokers and nicotine addiction and subsequent use of other tobacco products in non-smokers"

I understand that this may be a legitimate fear, but the authors should at the same time mention that this is not happening. A recent study in the UK found that e-cigarette use among adolescents is mainly experimentation (Bauld et al., Int J Environ Res Public Health. 2017 Aug 29;14(9) . pii: E973). Also, in the US, the increased ever and current e-cigarette use among adolescents has been accompanied by the highest rates of smoking decline ever observed. Finally, all data from 2016 from the US (NYTS 2016 and MTF 2016 surveys) have shown that even experimentation with e-cigarettes has dropped by 20% among adolescents. So, the concerns raised by the authors have



been rejected by all the current evidence. The authors need to make the manuscript more balanced and mention all the above.

We have deleted this sentence due to it being a theoretical concern (please see previous answer to the second comment of the Reviewer). Moreover, we have balanced the discussion adding the reference recommended by the reviewer and another recently published in JAMA pediatrics as follows:

“A recent study conducted among US high school students (16) showed that a high concentration of nicotine of e-cigarettes was associated with frequency and intensity of smoking and vaping. Moreover, another study conducted in adolescents in the UK (34) showed that the main motivation for using e-cigarettes was for experimentation.”

Discussion, page 47, lines 39-49.

This is another case of exaggerated claims about second hand exposure effects. Even in studies where some compounds exceeded background levels, the post-use levels measured were by far lower than indoor air quality limits. Characteristically, NIOSH did a study in the environment of vapes shops, which are most likely the places with the highest burden of e-cigarette emissions. They found no chemical present at levels above safety limits.  
(<https://www.cdc.gov/niosh/hhe/reports/pdfs/2015-0107-3279.pdf>)

As the Reviewer suggested, we have deleted the sentence about passive exposure of aerosol from e-cigarettes.

Discussion, page 48 lines 13-15. “E-cigarette companies take advantage of this by marketing fruity flavors to youth. (17)”

Again the authors use reference 17 which was a totally unsubstantiated conclusion from a congressional report in the US.

As the Reviewer suggested, we have deleted the sentence and the reference.

Discussion, page 48, lines 13-15. “Bans on certain characterizing flavored cigarettes have had a positive impact on reducing the number of young people who smoke (39) and similar bans on flavored e-cigarettes should be considered.”

The authors present the case for e-cigarette flavors as similar to tobacco cigarettes. However, the two cases are not at all comparable. E-cigarettes are used as smoking substitutes, studies have shown that flavors exist because of adult vapers’ demand, and use by non-smoking adults and kids is minimal. Therefore, the current situation shows potential benefit for the group of smokers from switching to e-cigarettes and no harm to other groups. Contrary to that, tobacco cigarettes cause only harm and provide no potential benefit to anyone. While it is totally justifiable to ban flavored tobacco cigarettes, there is currently no justification to ban flavored e-cigarettes.

We have deleted this sentence as the Reviewer suggested.

Discussion, page 49, lines 30-58.

The whole paragraph is problematic and should be removed. The discussion about kids (again, as in previous sections) is irrelevant to the study. Discussion about marketing is outdated because there is no marketing allowed according to the EU TPD, while sales of any e-cigarettes (irrespective of flavor) to kids has been banned.

Discouraging dual use is:

1. Unfeasible, unless the authors believe that use of e-cigarettes should lead to smoking cessation on the first day of initiation. All users of smoking cessation medications are essentially dual users initially, and the majority eventually becomes exclusive smokers because they fail to quit with medications.

2. Dangerous, for those who have substantially reduced smoking but have not completely quit.

Discouraging dual use will lead to relapse to smoking at the same consumption as before.

I agree with discouraging use by non-smokers (for both nicotine and non-nicotine e-cigs), but the restrictions the authors suggest apply to a small proportion (13%, if that is accurate) of the study sample (even smaller when considering the non-smokers using nicotine e-cigarettes) but will likely hurt the majority.

The discussion about potential harm from e-cigarettes is also emotional. There is no doubt that e-cigarettes are by far less harmful than smoking. Of course long term epidemiological studies are needed, but they are needed to accurately quantify the level of risk reduction.

The public health benefit of any intervention is not determined only by the effects on kids but on the overall effects on the whole population. The concern about kids is of course reasonable, but the discussion is too emotional. Finally, I will mention once again that this discussion is irrelevant to the study because no kids were included in the study, while the non-smoking adults who were using e-cigarettes were a very small minority (13%, if that is accurate).

As the Reviewer suggested, we have removed the last paragraph of the Discussion section. We have also included the conclusion recommended by the Reviewer in the abstract as follows:

"In conclusion, according to our results, younger users of e-cigarettes and non-smokers are more likely to use flavors other than tobacco and to use e-cigarettes mainly for recreational purposes. More studies are needed to verify the different theories about e-cigarettes."