PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risky Business: A longitudinal study examining cigarette smoking initiation among susceptible and non-susceptible e-cigarette users in Canada
AUTHORS	Aleyan, Sarah; Cole, Adam; Qian, Wei; Leatherdale, Scott

VERSION 1 – REVIEW

REVIEWER	Stanton Glantz and Shannon Lea Watkins University of California San Francisco USA
REVIEW RETURNED	25-Jan-2018

GENERAL COMMENTS	The study contributes to the literature that investigates the gateway effect that e-cigarettes have on cigarette initiation. The study stratifies youth by cigarette susceptibility, and finds that e-cigarettes are related to progression of non-susceptible youth to both susceptibility and cigarette trial, and that they are also related to progression of susceptible youth to cigarette trial. The fact that e-cigarettes use is a stronger predictor of subsequent cigarette smoking in the non-susceptible (to cigarette smoking) youth is an important finding that adds to the case that e-cigarettes are expanding the cigarette market by bringing low-risk youth into the market is important and deserves more emphasis in the Abstract and Conclusions section of the Discussion. SPECIFIC COMMENTS BACKGROUND Page 4 Line 5-15. The authors again offer to cursory a take on this research and should offer more details in order to establish why their paper contributes something new. Page 4 Line 18-23. This sentence is a bit unclear for readers outside of this field. It might require a couple of sentences. Page 4 Line 20. The phrase “it is likely that smoking initiation among youth in these studies primarily occurs among those that are already at risk of future smoking” however a number of those studies control for cigarette risk indicators and still find evidence of a gateway effect. The authors again cannot hang their originally hat on looking at risk. They might make the argument that they address it in a more direct way. Indeed, the authors’ own data shows that this is not a correct assumption. Page 5 Line 3-6. Authors should specify the comparison group in the sentence…“Grade 11 and 12 non-susceptible never smokers that used e-cigarettes at baseline were more likely to initiate cigarette smoking at follow-up [than who?].” See also missing comparison groups on Page 5 Line 38 and Page 9 Line 47. Page 5 Line 9. Authors write “It is evident that additional longitudinal

	data that use younger students and a longer follow-up period are needed" but they haven't actually made that evident. Authors should explain this need more clearly. METHODS Page 6 Line 6. This is the first mention of Canada in the body of the manuscript. Consider emphasizing earlier in the text, and at least specifying that Ontario and Alberta are Canadian provinces. Does a Canadian study offer any advantages compared to previous studies? If so, authors could mention as well. Page 6. The discussion of the data structure is unclear. The paper implies that the study is longitudinal in the Data Linkage section (page 6) but mentions that both years gather data on 9th-12th graders. Is Year 4 a combination of longitudinal observations for the kids who were in 9th and 10th grade, and a set of new 9th and 10th grade recruits? Please clarify the research design and what data are used in the present analysis. ANALYSES Page 7 Line 40. The authors conduct separate analyses for low-risk and high risk kids. Did the authors consider using an interaction term between risk and e-cigarette use or some other way of including all of the data in the same model? Was the sample weighted in any way to better reflect the school population? What is the author's assessment of the external validity of this sample to other high school students in Canada? RESULTS Page 8 Line 6. The discussion of table 1 results is unclear. The way it is written now sounds like more than 50% of males were e-cigarette users. But I think the authors mean that the proportion of e-cigarette users that were male is higher than the proportion of non-e-cigarette users that were male. Or in even clearer terms, males were more likely to be e-cigarette users than females. Please clarify and consider restructuring the table to improve clarity. Page 9 Line 3. Here and elsewhere, authors should be clearer about which variables were measured at baseline and which were measured at follow-up. For example, one approach might be "Figure 1 presents the smoking status at follow-up for baseline non-smokers. Results are stratified by e-cigarette use and cigarette susceptibility at baseline." Page 9 Line 27. The phrase "non-current users" is awkward. Consider "current non-users." DISCUSSION Page 10 Line 11-25. I understand the authors' intentions in this section to emphasize that even though the proportion of youth who are e-cigarette users is small, we should still care about increased risk of future cigarette use for those kids. As written, however, this paragraph is unclear. Please revise. Page 10 Line 42. Remove the phrase "to limit their attractiveness" to eliminate redundancy. Page 11 15. The sentence "E-cigarettes may potentially lead to a rise in tobacco initiation rates" is unclear because e-cigarettes are often referred to as a tobacco product. Please clarify. I also think it behooves the authors to mention in their discussion somewhere that e-cigarettes, even in absence of progression to cigarettes, pose health risks to youth. Page 11 Line 32. I suggest the authors provide an example from Bill S-5 in order to illuminate for a non-Canadian audience.

REVIEWER	Maria Cooper University of Texas Health Science Center at Houston (UTHealth), School of Public Health, Austin Campus, USA

REVIEW RETURNED	26-Feb-2018

GENERAL COMMENTS	This is a longitudinal analysis of a large cohort of Canadian youth exploring current use of e-cigarettes with trying cigarettes 2 years later. The hypothesis, analysis and results are clearly written, and important implications for policy and prevention among Canadian youth are discussed. This study primarily confirms what several previous studies have already found: youth who use e-cigarettes in the past 30 days are more likely to progress to trying cigarettes than those who have not. This study also confirms 2 previous studies in its finding that the magnitude of that relationship is larger among low risk, non-susceptible youth. As authors state, this study has a younger sample and longer follow up period than previously conducted studies. Importantly, consistent with only two of the previous studies, the authors separate findings by cigarette susceptibility. In addition, this is one of the few studies documenting this pattern in adolescents conducted outside the U.S. While it does seem important to confirm findings among different populations, I was disappointed the manuscript did not extend our knowledge to currently unanswered questions, such as examining potential bidirectional relationships between cigarettes and e-cigarettes, transitions to sustained smoking, or use of nicotine vs. non-nicotine e-cigarettes. In fact, authors described a multi-wave study, so it would be interesting to understand the cigarette smoking outcome in Wave 3 (not included) or perhaps a measure of "sustained use" which could draw from both Waves 3 and 4. This struck me as a missed opportunity to not examine all 3 times points (Waves 2, 3 and 4). In a revised manuscript, the authors could consider examining this transition across 3 time points. In addition to that primary concern, addressing the following points are suggested to strengthen this manuscript: 1) Page 3-4 (intro) and page 11 (discussion): consider updating the introduction and discussion to include the new report from the National Academies of Sciences [1], which concludes that e-cigarettes might help cigarette smokers quit, but also might attract new smokers in youth and young adults. A consensus is emerging in the tobacco control community that both of those conclusions can be true, but the challenge is in developing and implementing policies given the evidence for both of these scenarios. 2) Page 5, top of page: reference 18 doesn't appear to be correct 3) Other covariates: Socioeconomic status, or some proxy variable for it like parental educational attainment, is commonly used in the tobacco literature as a control variable. Did study authors consider including SES or a similar construct as a covariate? 4) At least 3 of the previous studies [2, 3, 4] have included a control variable for sensation seeking, delinquency, or risk taking, to further address the concern that these youth are "high risk" and would go on to use cigarettes due to these intrapersonal factors regardless of e-cigarette status. It seems important to me to control for this in this type of analysis. If the authors have these items available to them, consider adding them to strengthen their findings and conclusions. 5) It appears that student-level clustering within schools was included as a covariate in the regression model. It is more statistically valid to use a multilevel model to account for the nested data structure (clustering within schools). Consider using multilevel regression models instead.

	6) Discussion: Consider adding to the section on strengths. I think there are only a few studies documenting the e-cigarette to cigarette transition in youth outside of the U.S., such as Lozano et al, [5], but there could be others. This means the phenomenon is not unique to U.S. youth and could represent a new generation of smokers globally. 7) Figure 2: The graph of odds ratios should be on the logarithmic scale. See: [6] Minor concerns: 1) Page 3: Consider substituting the term "constituent" for "chemical," as the other constituent not described is vegetable glycerin. 2) Page 6: "on a spare" in an unfamiliar term to me, perhaps it is regional. Consider replacing with a term familiar to a wide range of audiences. 3) Page 6: Consider replacing "measures" with "3-item measure" as the measure of susceptibility is made up of 3 items. 4) Consider adding the alpha level for the statistical analyses. 5) Figure 2: There is a typo in the title should read Figure 2, not Figure 3. References: [1] "Public Health Consequences of E-cigarettes" (http://nationalacademies.org/hmd/Reports/2018/public-health-consequences-of-e-cigarettes.aspx) [2] Leventhal, A. M., et al. (2015). "Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence." JAMA 314(7): 700-707. [3] Primack BA, Soneji S, Stoolmiller M, Fine MJ, Sargent JD. Progression to traditional cigarette smoking after electronic cigarette use among US adolescents and young adults. JAMA Pediatr. 2015;169(11):1018–1023 [4] Primack B, Shensa A, Sidani JE, et al. Initiation of cigarette smoking after e-cigarette use: a nationally representative study [abstract] http://www.sbm.org/UserFiles/file/2016AbstractSupplement.pdf. Accessed July 15, 2016. [5] Lozano, P., Barrientos-Gutierrez, I., Arillo-Santillan, E., Morello, P., Mejia, R., Sargent, J. D., & Thrasher, J. F. (2017). A longitudinal study of electronic cigarette use and onset of conventional cigarette smoking and marijuana use among Mexican adolescents. Drug & Alcohol Dependence, 180, 427-430 [6] Levine, M. A., El-Nahas, A. I., & Asa, B. (2010). Relative risk and odds ratio data are still portrayed with inappropriate scales in the medical literature. Journal of clinical epidemiology, 63(9), 1045-1047.

VERSION 1 – AUTHOR RESPONSE

EDITORIAL REQUIREMENTS:

- Please revise your title to include the setting (location). This is the preferred format for the journal.
RESPONSE:
This has been added to the revised manuscript.

REVIEWER 1 COMMENTS:

Reviewer Name: Stanton Glantz and Shannon Lea Watkins
Institution and Country: University of California San Francisco, USA

Comment 1:
The study contributes to the literature that investigates the gateway effect that e-cigarettes have on cigarette initiation. The study stratifies youth by cigarette susceptibility, and finds that e-cigarettes are related to progression of non-susceptible youth to both susceptibility and cigarette trial, and that they are also related to progression of susceptible youth to cigarette trial. The fact that e-cigarettes use is a stronger predictor of subsequent cigarette smoking in the non-susceptible (to cigarette smoking) youth is an important finding that adds to the case that e-cigarettes are expanding the cigarette market by bringing low-risk youth into the market is important and deserves more emphasis in the Abstract and Conclusions section of the Discussion.

RESPONSE:

We appreciate the comments provided and agree with the reviewer that this study contributes important findings by demonstrating the relationship observed between e-cigarette use and cigarette smoking initiation is even stronger among low risk youth. We also agree that these results support growing concerns that e-cigarettes may be attracting low-risk youth into the cigarette market. These points have been added to both the Abstract and Conclusions of the revised manuscript.

Comment 2:
BACKGROUND
Page 4 Line 5-15. The authors again offer to cursory a take on this research and should offer more details in order to establish why their paper contributes something new.

RESPONSE:
Additional details have been provided within the revised manuscript to help establish what this paper adds to the current knowledge base.

Comment 3:
Page 4 Line 18-23. This sentence is a bit unclear for readers outside of this field. It might require a couple of sentences.

RESPONSE:
This sentence has been clarified in the revised manuscript.

Comment 4:
Page 4 Line 20. The phrase “it is likely that smoking initiation among youth in these studies primarily occurs among those that are already at risk of future smoking” however a number of those studies control for cigarette risk indicators and still find evidence of a gateway effect. The authors again cannot hang their originally hat on looking at risk. They might make the argument that they address it in a more direct way. Indeed, the authors’ own data shows that this is not a correct assumption.

RESPONSE:
We agree with the reviewers’ comment and have removed this phrase from the revised manuscript.

Comment 5:

Page 5 Line 3-6. Authors should specify the comparison group in the sentence…"Grade 11 and 12 non-susceptible never smokers that used e-cigarettes at baseline were more likely to initiate cigarette smoking at follow-up [than who?]." See also missing comparison groups on Page 5 Line 38 and Page 9 Line 47.

RESPONSE:
This has been amended in the revised manuscript to clarify which comparison groups were used in the study.

Comment 6:
Page 5 Line 9. Authors write "It is evident that additional longitudinal data that use younger students and a longer follow-up period are needed" but they haven't actually made that evident. Authors should explain this need more clearly.

RESPONSE:
This has been clarified in the revised manuscript.

Comment 7:
METHODS
Page 6 Line 6. This is the first mention of Canada in the body of the manuscript. Consider emphasizing earlier in the text, and at least specifying that Ontario and Alberta are Canadian provinces. Does a Canadian study offer any advantages compared to previous studies? If so, authors could mention as well.

RESPONSE:
This has been amended in the revised manuscript to draw attention to the fact that this was a Canadian study and that the study sample comprised of high school students located within the Canadian provinces of Ontario and Alberta.

Additional detail has also been added regarding the advantages provided by a Canadian study in both the Background and Discussion sections of the revised manuscript.

Comment 8:
Page 6. The discussion of the data structure is unclear. The paper implies that the study is longitudinal in the Data Linkage section (page 6) but mentions that both years gather data on 9th-12th graders. Is Year 4 a combination of longitudinal observations for the kids who were in 9th and 10th grade, and a set of new 9th and 10th grade recruits? Please clarify the research design and what data are used in the present analysis.

RESPONSE:
The current study used a longitudinal design. The sample consisted of a longitudinal sample of students that could be linked between Year 2 (2013-2014) and Year 4 (2015-2016) of the COMPASS study. In other words, the linked sample comprised of students that could be followed across both time points. We could not link the set of new 9th and 10th grade recruits (in Y4), as we only had follow-up data available on these students. Similarly, we could not link the 11th and 12 grade students that had already graduated at follow-up, as we only had baseline data available for this set of students. A sample of 11,215 students who were in grade 9, 10 and 11 at baseline were linked across both time points and were used in the present analysis. Grade 11 students within the linked sample

represented students who had not graduated high school with their peers at follow-up and as such were available to participate in the study at both time points.

The research design and data used in the present analysis have been clarified in the revised manuscript. Furthermore, an additional reference by Qian and colleagues that delves in further depth on the process used to link multiple waves of student-level data has been added to the revised manuscript [1].

Comment 9:
ANALYSES
Page 7 Line 40. The authors conduct separate analyses for low-risk and high risk kids. Did the authors consider using an interaction term between risk and e-cigarette use or some other way of including all of the data in the same model?

RESPONSE:
Given that the sample consisted of distinct sub-populations (i.e., susceptible and non-susceptible never smokers) and that the aim of this study was to assess the differential effects of current (past-30 day) e-cigarette use on subsequent smoking initiation within these two sub-populations, running stratified models was considered the most suitable strategy for addressing our research question. Furthermore, different modelling approaches were needed to assess the effect of baseline e-cigarette use among non-susceptible versus susceptible never smokers. To examine whether baseline use of e-cigarettes predicted smoking susceptibility and initiation at follow-up among non-susceptible never smokers, multinomial logistic regression models were used. In contrast, to examine whether baseline use of e-cigarettes predicted smoking initiation among susceptible never smokers, binary logistic regression models were used. Given that distinct modelling approaches were used for different sub-populations (i.e., strata), stratified models was considered an appropriate analysis approach to answer our research questions. If the outcomes being examined in both models had been identical, we may have considered a combined model because it would increase estimation efficiency and allow us to test the effect of an interaction (i.e., e-cigarette use*susceptibility). However, in our case, one response is binary and another is multinomial, which makes combining the models difficult.

Comment 10:
Was the sample weighted in any way to better reflect the school population? What is the author's assessment of the external validity of this sample to other high school students in Canada?

RESPONSE:
Given that this study used non-probability sampling methods (specifically, convenience sampling), weighting the sample examined was not considered appropriate, as the study was not designed to be representative [2]. As such, the study findings are not generalizable to other Canadian high schools outside of the study sample.
This point has been added as a study limitation within the revised manuscript. Furthermore, an additional citation by Leatherdale and colleagues that describes the methods used within the COMPASS study in greater detail has been added to the References List of the revised manuscript.

Comment 11:

RESULTS
Page 8 Line 6. The discussion of table 1 results is unclear. The way it is written now sounds like more than 50% of males were e-cigarette users. But I think the authors mean that the proportion of e-

cigarette users that were male is higher than the proportion of non-e-cigarette users that were male. Or in even clearer terms, males were more likely to be e-cigarette users than females. Please clarify and consider restructuring the table to improve clarity.

RESPONSE:

The discussion of Table 1 has been clarified within the Results section of the revised manuscript.

Comment 12:

Page 9 Line 3. Here and elsewhere, authors should be clearer about which variables were measured at baseline and which were measured at follow-up. For example, one approach might be “Figure 1 presents the smoking status at follow-up for baseline non-smokers. Results are stratified by e-cigarette use and cigarette susceptibility at baseline.”

RESPONSE:
These points have been clarified in the revised manuscript.

Comment 13:

Page 9 Line 27. The phrase “non-current users” is awkward. Consider “current non-users.”

RESPONSE:
We believe that the phrase “current non-users” is misleading given that students reported not using e-cigarettes within the last 30 days and were not necessarily never users. Instead, we have referred to these individuals as “students who had not used e-cigarettes in the past 30 days”.

Comment 14:

DISCUSSION
Page 10 Line 11-25. I understand the authors’ intentions in this section to emphasize that even though the proportion of youth who are e-cigarette users is small, we should still care about increased risk of future cigarette use for those kids. As written, however, this paragraph is unclear. Please revise.

RESPONSE:
This paragraph has been amended in the revised manuscript to improve the clarity of points presented.

Comment 15:

Page 10 Line 42. Remove the phrase “to limit their attractiveness” to eliminate redundancy.

RESPONSE:
This phrase has been removed from the revised manuscript to limit redundancy.

Comment 16:

Page 11 15. The sentence “E-cigarettes may potentially lead to a rise in tobacco initiation rates” is unclear because e-cigarettes are often referred to as a tobacco product. Please clarify. I also think it behooves the authors to mention in their discussion somewhere that e-cigarettes, even in absence of progression to cigarettes, pose health risks to youth.

RESPONSE:
This sentence has been clarified in the revised manuscript. In addition, a sentence has been added discussing the health risks posed by e-cigarettes to youth.

Comment 17:
Page 11 Line 32. I suggest the authors provide an example from Bill S-5 in order to illuminate for a non-Canadian audience.

RESPONSE:
Examples of measures included within Bill S-5 have been provided within the revised manuscript to provide greater context for a non-Canadian audience.

REVIEWER 2 COMMENTS:
Reviewer Name: Maria Cooper
Institution and Country: University of Texas Health Science Center at Houston (UTHealth), School of Public Health, Austin Campus, USA

Comment 1:

This is a longitudinal analysis of a large cohort of Canadian youth exploring current use of e-cigarettes with trying cigarettes 2 years later. The hypothesis, analysis and results are clearly written, and important implications for policy and prevention among Canadian youth are discussed. This study primarily confirms what several previous studies have already found: youth who use e-cigarettes in the past 30 days are more likely to progress to trying cigarettes than those who have not. This study also confirms 2 previous studies in its finding that the magnitude of that relationship is larger among low risk, non-susceptible youth. As authors state, this study has a younger sample and longer follow up period than previously conducted studies. Importantly, consistent with only two of the previous studies, the authors separate findings by cigarette susceptibility. In addition, this is one of the few studies documenting this pattern in adolescents conducted outside the U.S.

While it does seem important to confirm findings among different populations, I was disappointed the manuscript did not extend our knowledge to currently unanswered questions, such as examining potential bidirectional relationships between cigarettes and e-cigarettes, transitions to sustained smoking, or use of nicotine vs. non-nicotine e-cigarettes. In fact, authors described a multi-wave study, so it would be interesting to understand the cigarette smoking outcome in Wave 3 (not included) or perhaps a measure of “sustained use” which could draw from both Waves 3 and 4. This struck me as a missed opportunity to not examine all 3 times points (Waves 2, 3 and 4). In a revised manuscript, the authors could consider examining this transition across 3 time points.

RESPONSE:
We appreciate the reviewers’ comments regarding the importance of examining the relationship between e-cigarette use and subsequent smoking susceptibility among distinct populations, in

addition to assessing the differential effects of e-cigarette among different at-risk groups (i.e., low vs. high-risk students).

Though we do agree with the reviewer that examining the potential bi-directional relationships between cigarette use and e-cigarette use would extend the current knowledge base, the current objective of this manuscript was to assess the relationship between baseline e-cigarette use and cigarette smoking susceptibility at follow-up among different risk groups (i.e., susceptible vs. non-susceptible never smokers). To remain in line with the focus on our manuscript, extending the current analysis to the assessment of bidirectional relationships between cigarettes and e-cigarettes would require a measure of e-cigarette smoking susceptibility, which was not available to us within the dataset. Future longitudinal studies that incorporate measures of e-cigarette smoking susceptibility should extend our current analysis to additionally examine the relationship between baseline cigarette use and e-cigarette smoking susceptibility at follow-up among different risk groups.

Though we agree with the reviewers that examining transitions to sustained cigarette smoking using both Waves 3 and 4 would add further depth to this analysis, sustained cigarette smoking was not examined in the current study due to the significantly reduced sample size that would limit our ability to examine these transitions using both waves of data (i.e., Waves 3 and 4). We believe that examining the stability of the transition over a 2-year follow-up period (rather than a one-year follow-up period) would contribute to the literature.

Though we agree with the reviewers that assessing the differential effects of using nicotine vs. non-nicotine e-cigarettes on subsequent smoking initiation would add to the current knowledge base, however the COMPASS study did not include measures that would have allowed us to distinguish between nicotine vs. non-nicotine containing e-cigarette products.

Comment 3:

In addition to that primary concern, addressing the following points are suggested to strengthen this manuscript: Page 3-4 (intro) and page 11 (discussion): consider updating the introduction and discussion to include the new report from the National Academies of Sciences [1], which concludes that e-cigarettes might help cigarette smokers quit, but also might attract new smokers in youth and young adults. A consensus is emerging in the tobacco control community that both of those conclusions can be true, but the challenge is in developing and implementing policies given the evidence for both of these scenarios.

RESPONSE:
This reference has been added to both the Introduction and Discussion sections of the revised manuscript.

Comment 4:
Page 5, top of page: reference 18 doesn’t appear to be correct

RESPONSE:
This has been corrected in the revised manuscript.

Comment 5:

Other covariates: Socioeconomic status, or some proxy variable for it like parental educational attainment, is commonly used in the tobacco literature as a control variable. Did study authors consider including SES or a similar construct as a covariate?

RESPONSE:
Thank you for your suggestion. Though a measure of socioeconomic status was not available to us in the current dataset, we have included a measure of "weekly spending money" as an additional control variable within our modelling procedures. Our Methods and Results sections have been updated to reflect these changes.

Comment 6:
At least 3 of the previous studies [2, 3, 4] have included a control variable for sensation seeking, delinquency, or risk taking, to further address the concern that these youth are "high risk" and would go on to use cigarettes due to these intrapersonal factors regardless of e-cigarette status. It seems important to me to control for this in this type of analysis. If the authors have these items available to them, consider adding them to strengthen their findings and conclusions.

RESPONSE:
Though we do agree with the reviewer that sensation seeking/delinquency are important measures to account for (where possible), measures of sensation seeking or risk-taking were not present within the current dataset.

Comment 7:
5) It appears that student-level clustering within schools was included as a covariate in the regression model. It is more statistically valid to use a multilevel model to account for the nested data structure (clustering within schools). Consider using multilevel regression models instead.

RESPONSE:
Student-level clustering within schools was not included as a covariate within the regression model. Rather, the clustering of students within school was accounted for using Generalized Estimating Equations (GEE) models. The GEE procedure (present on SAS 9.4) estimates population-averaged model parameters, while accounting for the clustered nature of the data (i.e., students clustered within schools) [3]. GEE extends the generalized linear model to allow for the analysis of repeated measures or correlated observations (e.g., clustered data) [3].

These details have been added to the revised manuscript to clarify the analyses that were conducted. In addition, a publication by Zeger and Liang which provides additional details on the GEE procedure has also been added to the References list of the revised manuscript.

Comment 8:
6) Discussion: Consider adding to the section on strengths. I think there are only a few studies documenting the e-cigarette to cigarette transition in youth outside of the U.S., such as Lozano et al, [5], but there could be others. This means the phenomenon is not unique to U.S. youth and could represent a new generation of smokers globally.

RESPONSE:
Thank you for the helpful suggestion that emphasizes a strength of our study. This point has been added within the revised manuscript.

Comment 9:
Figure 2: The graph of odds ratios should be on the logarithmic scale. See: [6]

RESPONSE:

Within our analysis, the confidence interval of the odds ratio was derived by exponentiating the confidence interval of the log odds ratio. As such, it would be equivalent to present either the odds ratio or the log odds ratio. Furthermore, we believe that the odds ratio graphs are better depicted using an arithmetic scale. As noted by Rothman and colleagues [4], logarithmic scales do not scale effects according to risk differences, whereas arithmetic scales do. As such, an arithmetic scale can often be seen as less visually misleading when compared to a logarithmic scale, as an arithmetic scale preserves proportionality with differences in risk.

Comment 10:
Page 3: Consider substituting the term “constituent” for “chemical,” as the other constituent not described is vegetable glycerin.
RESPONSE:
This has been corrected in the revised manuscript.

Comment 11:
Page 6: “on a spare” in an unfamiliar term to me, perhaps it is regional. Consider replacing with a term familiar to a wide range of audiences.

RESPONSE:
This has been clarified in the revised manuscript.

Comment 12:
Page 6: Consider replacing “measures” with “3-item measure” as the measure of susceptibility is made up of 3 items.

RESPONSE:
This has been clarified in the revised manuscript.

Comment 13:
4) Consider adding the alpha level for the statistical analyses.

RESPONSE:
The alpha level for the statistical analyses was 0.05. This detail has been added to the revised manuscript.

Comment 14:
5) Figure 2: There is a typo in the title should read Figure 2, not Figure 3.

RESPONSE:
This has been corrected within the revised manuscript.

References:

1. Qian W, Battista K, Bredin C, Brown KS, Leatherdale ST. Assessing longitudinal data linkage results in the COMPASS study: Technical Report Series. 2015; 3(4). Waterloo, Ontario: University of Waterloo. Available at: https://uwaterloo.ca/compass-system/publications#technical
2. Leatherdale, S.T., Brown, K.S., Carson, V., Childs, R.A., Dubin, J.A., Elliott, S.J., Faulkner, G., Hammond, D., Manske, S., Sabiston, C.M., Laxer, R.E., Bredin, C. & Thompson-Haile, A. The COMPASS study: a longitudinal hierarchical research platform for evaluating natural experiments related to changes in school-level programs, policies and built environment resources. BMC Public Health 2014, 14:331
3. Zeger, S. L., & Liang, K.-Y. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986, 42, 121-130.
4. Rothman, K.J., Wise, L.A., Hatch, E.E.. Should Graphs of Risk or Rate Ratios be Plotted on a Log Scale? Am J Epidemiol 2011,174:3, 376–377.

VERSION 2 – REVIEW

REVIEWER	Maria Cooper University of Texas Health Science Center at Houston (UTHealth), School of Public Health, Austin Campus, USA
REVIEW RETURNED	09-Apr-2018

GENERAL COMMENTS	In their response, the authors have addressed all of my previously mentioned suggestions. I have no further comments.

REVIEWER	Stanton Glantz UCSF USA
REVIEW RETURNED	11-Apr-2018

GENERAL COMMENTS	The authors have done a nice job or responding to the reviewers' comments.