Author's response to reviews

Title: Adverse Childhood Experiences are Associated with the Risk of Lung Cancer: A Prospective Cohort Study

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Author's response to reviews: see over
Response to reviewer comments
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“Adverse Childhood Experiences Are Associated with the Risk of Lung Cancer: A Prospective Cohort Study”

Note that all changes have been highlighted in the revised text.

Editorial requests:
• Please include a 'Competing interests' section between the Conclusions and Authors' contributions. If there are none to declare, please write 'The authors declare that they have no competing interests'.
  RESPONSE: Section added.

• Please include an Authors' contributions section before the Acknowledgements and Reference list.
  RESPONSE: Section added.

• Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include their source(s) of funding. Please also acknowledge anyone who contributed materials essential for the study. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements.
  RESPONSE: Not applicable.

• Informed consent must also be documented. Manuscripts may be rejected if the editorial office considers that the research has not been carried out within an ethical framework, e.g. if the severity of the experimental procedure is not justified by the value of the knowledge gained.
  RESPONSE: As noted in the second sentence of the Methods, the ACE Study has been approved by the institutional review boards of Southern California Permanente Group (Kaiser Permanente) and the Centers for Disease Control and Prevention.
Reviewer #1

This paper addressed an important topic since both exposure and outcome are highly preventable by public health interventions. However, some major revisions are necessary in order to make the paper more readable. Good luck with the revision!

Major Compulsory Revisions

Abstract
1. The result section needs more numbers in order to be self-explanatory to the reader. Please remove some of the last sentences and provide some extra numbers.
RESPONSE: We thank the reviewer for the comment. While we disagree that the results section of the abstract is not self-explanatory, we are glad to work with the Editor to re-work this section. We have included the primary results of the analysis; namely, the presence of a graded relationship to the incidence of lung cancer based on hospital discharge records and mortality records, risk ratios comparing the risk of lung cancer for those with 6 or more ACEs to those without ACEs, a note on the early age at presentation for persons with 6 or more ACEs, and a note on the attributable risk percent.

2. Based on the small number of lung cancer cases and the findings of the study, your conclusion is too strong. There might be an association.
RESPONSE: The conclusion has been toned down.

Methods
1. The methods are clearly written, but way too long. There are too many different analyses included in your paper, which makes it very confusing for the reader. Consider taking out some of the analyses you have done (see also comments for results section) and focus more on those analyses that have an impact on the clinical relevance of your paper. I would suggest that you drop the following analyses:
   • Confidence interval functions
   • Competing risks
In addition, shorten the overall methods section and maybe consider writing a methods appendix. This makes it much easier for the reader to understand your methods and if necessary the reader can find the details in the methods appendix. Your methods section
should not be more than 2 pages (now there are 6!). I think you can drop the competing risk analysis (see also below) and just discuss this possibility in the discussion.

**RESPONSE:** We thank the reviewer for the comment. We are glad to work with the Editor to develop a Methods Appendix should that be the desired way to move forward. We disagree with the notion of a pre-specified length limit to the Methods (2-pages?). We have referenced our prior work when appropriate to reduce length but we also are careful to not refer the reader to prior work too often. I do not think any of us like having to go pull another paper to read the one we are interested in. The issue of the length of the methods has not been a concern of other reviewers as most appear to desire an appropriate description rather than having to refer to prior work. Nonetheless, a fair comment and we are glad to work with the Editor on this issue.

2. Given that smoking is a causal intermediate in the pathway between ACE and lung cancer (as you also mention in your methods section), I think it is impossible to assess the relation between ACE and lung cancer while adjusting for smoking. This biases your results and is incorrect. In this scenario you can only study these associations separately:

ACE #Smoking # Lung cancer

This means that you can study the association between ACE and smoking, Smoking and Lung cancer, and ACE and lung cancer. As written by Rothman and Greenland in “Modern Epidemiology”: “Any factor that represents a step in the causal chain between exposure and disease should not be treated as an extraneous confounding factor, but instead requires special treatment as an intermediate factor”. I suggest you read more information on this topic and rethink your methods. Maybe there is a possibility of using time-dependent exposures and covariates?

**RESPONSE:** We thank the reviewer for the time taken with this comment. The *a priori* hypothesis of this paper is that ACEs are associated with an increased risk of lung cancer with special attention to a causal intermediate (i.e., a variable lying at least in part in the causal pathway between exposure and outcome), smoking. The causal intermediate is in contrast to a confounder, for which the effects of exposure should usually be corrected. The reviewer correctly notes that it is misleading to correct for an intermediate variable; however, as a result, intermediate variables often are ignored. It can nonetheless be useful to ask how much of the effect of the exposure variable on the outcome has been mediated by an intermediate variable. To this end, we have modeled the association between ACEs and risk of lung cancer (Model A). To examine smoking as a causal intermediate in the pathway, we added smoking to the model (Model B). As one can readily observe, the addition of smoking to the model results in a
reduction in the risk ratio for the association between ACEs and risk of lung cancer. To the extent that smoking only partially explains some of the association between ACEs and lung cancer, there is the suggestion of possible other causal mechanisms between ACEs and lung cancer.

From the very outset of the manuscript (last paragraph of the Introduction) we set up our treatment of smoking not as a confounder, as suggested by the reviewer, but rather as a causal intermediate. These are important yet subtle distinctions, and the decision to treat smoking as a causal intermediate was made a priori before any analyses were begun. Thus, it appears that the reviewer has misread and/or misunderstood the analysis.

Results
1. Please create a general “table 1” as available in all other publications on cohort studies. This is essential for an epidemiological paper! At the moment you describe way too much numeric information with words. Create a frequency/mean table that report values for instance ever and never smokers.

   | Ever (N= xxx) | Never (N= xxx) |
--- | --- | --- |
Mean number of ACE (Sd) | |
Age | |
Parental history of smoking | |
SES | |
Etc. | |

This will allow you to reduce for instance the first paragraph of “Incident hospitalization with lung cancer during follow-up” to only one sentence because you can refer to a table. The same is true for the first paragraph of “Death from lung cancer during follow-up”.

RESPONSE: At the Editor’s discretion we would be glad to add another table to the manuscript as described by the reviewer. We have chosen to include the respondent characteristics by presence or absence of the outcome in the text and to focus our tables/figures on the associations between ACEs and lung cancer. This is a matter of style. The reviewer has a very strong preconceived notion as to what should be where, while it is our feeling that what is most important is that the information is present for the reader given restrictions and limitations on space. Nonetheless, we are willing to add a table if the Editor requests such.

2. Drop the graphs in figure 2, 4, and 5

RESPONSE: Thank you for the comment. At the discretion of the Editor, we are willing to move the graphs to an Annex; however, we do not feel they should be moved from their current
location and we certainly argue against their being dropped. While the graphic display is not
essential when considering confidence interval functions, the graph facilitates the readers’ visual
formulation of the curve. Most persons are not familiar enough with confidence interval functions
to take the lower and upper limit of the confidence interval and create the corresponding curve in
their mind and see the range of values consistent with the data.

3. Drop the sentence “A possible association remained between ACE Scores ...” in the
section “Death from lung cancer during follow-up”. As you have said, it is a small number
and so therefore not worth mentioning in the results section. In addition, explanation of
results needs to be in the discussion section. If you want to, you can comment on this in the
discussion section.
RESPONSE: We have edited the sentence to read, “A possible association remained between
ACE Scores of 6 or more and lung cancer although a small number of cases (n=4) among the
exposed pose a challenge to interpretation.”

4. Add the findings with adjustment for baseline history of asthma, COPD, cancer, or TBC
to the table in figure 5. It is much easier for the reader to find numbers in a table!
RESPONSE: Thank you for the comment. We have chosen to leave the findings in the text to
maintain a consistence across tables. This appears to be a matter of style for the reviewer as other
readers have not made similar comment.

5. Premature death from lung cancer # this makes it less easy to follow your results section.
Try to rewrite your results section so that it guides your reader from table to table. So first
describe everything in table 2 (which is now still called figure 2), then table 4, and table 5.
You only have small numbers and so re-analyzing is not always strengthening your
findings. It gives an impression of searching for a method that can find some significant
results. It would be good if you delete the section “premature death from lc” and the
“competing risk” section. You could also add the information of premature death analyses
to the section on table 3.
RESPONSE: Thank you for the comment. We have chosen to leave the premature analysis as is
and have moved text on competing risks to the Discussion. We did notice that our motivation for
conducting the premature mortality analysis was not evident and have added reference to prior
work currently “in press” at the American Journal of Preventive Medicine due to come out in
November 2009.
6. Also, I am not convinced by the methodology you use to address the phenomenon of competing risks. The methods section does not describe any specific method (eg. Grays & Fine competing risk analysis?). If you want to show the possibility of competing risks, you might want to consider a graph that shows the cumulative incidence for lung cancer and death (other than lung cancer death) by using a censor variable (0=no LC, no death, 1=LC, 2=non-LC death). Another possibility is just mentioning the possibility of competing risks in the discussion section.

**RESPONSE:** As noted above, we have moved text on competing risks to the Discussion.

7. It is interesting to show AR%, however it would be good to make this paragraph a bit shorter and more focused.

**Discussion**

1. This is definitely an interesting subject. However, when reading through this paper I get the feeling that this was written as part of a thesis. I think that a lot of the paragraphs can be rewritten – shorter and more focused. Also, the discussion section needs to have a better organized structure:
   a. Summary of findings
   b. What is known about the topic so far?
   c. What do your findings add? How can you explain them
   d. Strengths and limitations
   e. Conclusion

**Minor Essential Revisions**

**Introduction**

1. Please provide a reference for the first paragraph.

**RESPONSE:** Added.

2. The last sentence of the second paragraph (the epidemiological findings parallel ...) is not completely clear. Please rephrase.

**RESPONSE:** This has not been a comment of others. We would defer to the copy Editor if the paper is accepted.
Results

3. ACEs and Smoking Behaviour: Consider rephrasing the second sentence as this is not clear to the reader now (However, the overall prevalence of ...)
RESPONSE: This has not been a comment of others. We would defer to the copy Editor if the paper is accepted.

4. Premature death from lung cancer: on average need to be removed once from sentence

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests
Reviewer #2

This is a very nice manuscript. Very detailed and thorough methodology and statistical procedures. Additionally, you were very thoughtful about some limitations to what you have accomplished - meaning that you presented a very balanced presentation.

Major Compulsory Revisions – None

Minor Essential Revisions - Page 12, end of second paragraph. It is stated - ". . . although a small number of cases (N=4) among the exposed pose a challenge to conclusive statements." - which I think is a huge overstatement. I would suggest the end part be re-stated as " . . . pose a challenge in interpretation." Attempting to make "conclusive statements" with four cases is folly at best.

RESPONSE: Change made.

Page 14, entire second paragraph of discussion section. I would strongly suggest moving that up front to ground your entire thesis in a theoretical model (with references). Here it seems out of place. I think it would strengthen the entire foundation of your paper. (Note: Also, a nice schematic/conceptual model that would help the reader visualize the mechanisms of action of your thesis – would be a good touch).

RESPONSE: Thank you for the comment. We have moved the paragraph (with some shortening) to the Introduction as suggested.

Discretionary Revisions - Also, in your discussion section - Personally, I would have preferred some time devoted to potential ethical problems - with Kaiser Permanente potentially utilizing the findings, with respect to scoring on Adverse Childhood Experiences (ACE) to potentially deny insurance coverage/ increase insurance rates for those with higher scores. That is certainly an extension of the findings that are not touched upon (whether its a risk factor of a risk factor (smoking) or a direct effect (albeit relatively smaller than smoking)- it should be a point of consideration (I think). Its akin to discussions of genetic profiling – where genetic trait relationships with disease outcomes - might lead to discrimination. Here, we have a more 'social-cultural profiling' relationships with disease outcomes. What is a bit unpalatable - is that individuals (whether through inherited genes or exposures to social/ psychological traumas while growing up) - have no choice and no control.
RESPONSE: Thank you for the comment. Given the current length we will reserve discussion of these points for another manuscript.

General questions - Page 6 - description of items to measure various ACE’s. Why have some factors measured with 4 questions (for example), while others only have two? Wouldn’t the smaller number of questions necessarily limit the range of variation of the factor? (minor point).
RESPONSE: Thank you for the comment. No, the fact that one construct uses 4 questions and another uses 2 questions does not in any way limit the range of variation since each component category of the ACE Score is a dichotomous variable.

At points throughout the manuscript you relate that a relationship is 'graded' - which I interpret as saying there is a dose-response gradient.
RESPONSE: We agree with the reviewer in the interpretation, and note that the terms are often used interchangeably in the literature perhaps solely to reduce space by not having to repeat the longer phrase.

For the second paragraph on page 10, starting with " multivariable-adjusted models . . ." - I think you need to mention that you expected such a relationship. (minor point).

In Figure 1 (at bottom) - write out "observations" - and don't have 'obs.' (minor point).
RESPONSE: Change made.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests
Reviewer #3

The manuscript entitled “Adverse Childhood Experiences Are Associated with the Risk of Lung Cancer: A Prospective Cohort Study” aims to examine the adverse childhood experiences (childhood emotional, physical or sexual abuse and household dysfunction) and risk of lung cancers in a cohort study, ACE Study, conducted in California. To date, it appears that few studies have assessed adverse childhood experiences with lung cancer. As there are a limited number of studies, this study adds to the important discussion of this association.

For this analysis, the question posed by the authors is well defined and the methods are appropriate. In general, the authors clearly state the background, methods and results, however a few points should be addressed.

Minor Essential Revisions:

ABSTRACT section
The conclusion statements appear strong for the results that you presented, particularly since most of the estimates have wide confidence intervals and many are not statistically significant. Instead of “Adverse childhood experiences are associated with an increased risk”, it would be better to state “Adverse childhood experiences may be associated with an increased risk”. In addition, the statement re smoking – since you were not able to examine different models adjusting for smoking using duration, etc, “may only be partly explained by smoking”.

RESPONSE: Conclusion has been toned down.

INTRODUCTION section
In the introduction you do not discuss if there is any prior research conducted on ACE or lung CA or ACE with any other types of cancer. Please see Fuller-Thomson E. Cancer 2009 Jul 15: 115(14): 3341-50.

RESPONSE: Thank you for the comment. We have added the citation. We do our best to keep on top of the relevant literature and you have identified a paper that came out after we had submitted our manuscript. Thank you.

METHODS section:
With regards to the population, I am not sure how the population numbers are defined. It appears that initially you start with 18,175 (those who completed the mailed questionnaire) – but some of the following paragraphs/analyses relate to 17,337. Can you show in your methods how you switch from 18,175 to 17,337? Since you show how you go from 17,337 to 15,365 (-1248 – 735)?

RESPONSE: Thank you for the comment. We have made a change to clarify this issue. The confusion arises because there were 754 of the 18,175 baseline observations who responded to both Wave I and Wave II. Thus, the unduplicated number of baseline observations is 17,421; of these, 84 observations had missing data on race and education, leaving a final baseline sample of 17,337. The text has been revised to read, “A total of 17,421 (68%) persons responded; 84 persons had incomplete information on race and educational attainment leaving 17,337 persons available in the baseline cohort [13].”

Instead of just adding smoking as a covariate, are you able to do an analysis stratified by smoking status? Do you see the same results in never smokers? I am not sure if you have the case numbers to be able to do this analysis, if so, I think it would greatly add to the paper.

RESPONSE: Thank you for the comment. The analysis suggested would not be consistent with our hypothesis as we do not add smoking as a covariate. The a priori hypothesis of this paper is that ACEs are associated with an increased risk of lung cancer with special attention to a causal intermediate (i.e., a variable lying at least in part in the causal pathway between exposure and outcome), smoking. The causal intermediate is in contrast to a confounder, for which the effects of exposure should usually be corrected. To this end, we have modeled the association between ACEs and risk of lung cancer (Model A). To examine smoking as a causal intermediate (not as a covariate) in the pathway, we added smoking to the model (Model B). As one can readily see, the addition of smoking to the model results in a reduction in the risk ratio for the association between ACEs and risk of lung cancer. To the extent that smoking only partially explains some of the association between ACEs and lung cancer, there is the suggestion of possible other causal mechanisms between ACEs and lung cancer.

Also, for a number of analyses you have too few cases in the highest category to get meaningful results. Have you done analyses collapsing the highest two categories (4 or 5 with 6, 7 or 8)?

RESPONSE: Thank you for the comment. As one would expect, collapsing the upper two categories provides a value intermediate to the two estimates for each category separately. We
present the information as we do based on more than 50 prior ACE Study papers which have followed similar convention. In this case, we feel that it would be misleading to present the collapsed categories as there is possible heterogeneity in risk present; we just need more years of follow-up to further explore such. We are forthcoming with the limitations of small numbers and leave interpretation of the results to the reader.

**Do you have information on screening practices – it might be interesting to examine those who follow guidelines versus those who do not.**

**RESPONSE:** We do not have this information.

**In addition, have you assessed whether or not the association is linear. If it is linear, you can do analyses of continuous estimate of ACE stratified for other factors of interest (smoking status, SES, screening history)?**

**RESPONSE:** Thank you for the comment. We will consider this for another manuscript. We feel this manuscript has about as much information as one manuscript should without losing focus.

**When you examined competing risks – you might want to state that you excluded lung cancer?**

**RESPONSE:** Thank you for the comment. This was noted in the text and must not have been recognized: “we identified smoking-related disease (other than lung cancer) from…(original manuscript page 10)” and “a total of 707 smoking related deaths other than lung cancer were identified…(original manuscript page 13)”. The reviewer will notice that the competing risk text has been moved to the Discussion at the request of one of the reviewers.

**RESULTS section:**

**How many cases were in the analysis on page 13, paragraph 1 for the estimates 10.48 (1.94-56.64) and 7.90 (1.40-44.61). As these confidence intervals are extremely wide, I think this information should be included.**

**RESPONSE:** Thank you. As we note in the text there were 10 deaths from lung cancer at age 65 years or younger and 55 deaths at age 75 years or younger. Yes, the confidence intervals are wide but they are also consistent with a range of values suggesting an increased risk of premature death from lung cancer that might not be dismissed. This is a good example of the need for graphical displays of confidence interval functions.
DISCUSSION section:
Were your results in line with the same magnitude (similar strength in RR/OR) of prior research? Are any of the biologic plausibility related to lung cancer, or another type of cancer? If so, you might want to include this information in the discussion.

RESPONSE: Thank you for the comment. It is difficult to put these results into the context of the work of others such as Fuller-Thompson because in all instances that we have identified, the outcome of cancer was captured in a cross-sectional fashion and therefore subject to a selection bias. This is, in fact, the first study that we are aware of to prospectively examine the risk of lung cancer associated with childhood traumatic stressors. Prior to this study, we too were limited to look at cross-sectional relationships.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests