Author’s response to reviews

Title: Adverse childhood events and risk of diabetes onset in the 1979 National Longitudinal Survey of Youth Cohort

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Adverse childhood events and risk of diabetes onset in the 1979 National Longitudinal Survey of Youth Cohort

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RESPONSES TO Reviewer reports:

Reviewer 1: no separate comments for authors.

Elva Dolores Arias-Merino, Ph.D. (Reviewer 2): It is an important study for public health that can contribute to direct public policies.

I have some indications: It is convenient that the data of table 1 and the description have the same sequence for better compression of the results. Review all the tables.

Page 13, paragraph 1, line 3, correct digit.

Response:

-Results, section 3.1 p 12 and Table 1: We have edited text to report results following the same sequence as presented in Table 1. We also moved the ACE2+ findings to be directly below the findings related to the individual ACE items for continuity.

-Results, section 3.1, p 13 and Table 2: We edited text to correspond to the sequence presented in Table 2.

-Page 13: We corrected the p value to read <.0001. Thank you for catching that.

Susan Marshall Mason (Reviewer 3): This study examines the association of adverse childhood events with later onset of Type 2 diabetes. Because this association has been examined in several other studies, the major contribution of this analysis is assessing the role of a range of health risk behaviors as possible mediators. This is a significant topic, although I had some questions about the methods and presentation of results. Comments below:

Major

1. The authors state that ACEs were measured in 2012, but then describe their modeling approach as censoring individuals who were lost to follow-up before 2012. Am I correct that those individuals lost to follow-up would not have had info on ACEs? It seems that they should have been excluded. Please clarify.
Response: After reexamining our analysis, we found that we already excluded all individuals who were lost to follow-up before 2012 from the analysis since, in these cases, we would not have ACE information. So we deleted the corresponding paragraph in the original manuscript.

2. Please provide more information on response rates over time and exclusions. Does the analytic sample include all those enrolled in 1982, or just those with ACE reports from 2012? I assume those with diabetes at enrollment were excluded? Any other exclusions?

Response: We include the response rates in Section 2.1 Study Population in which the baseline response rate in 1979 was 90%, then declined over time to 71% (77% excluding decedents) in more recent surveys. As mentioned above for point 1, the analytic sample only includes participants with at least 4 responses to ACE questions from 2012 and diabetes data from the 40+/50+ health modules. In conducting our survival models, we start the risk period in 1982 because questions on risk behaviors began in this survey year and continued to 2012. Those with diabetes at 1982 were not excluded. There were only two cases in participants who were aged 18-20 (see Results, Sec 3.1 para 1, page 12). These cases were unlikely to be T2DM given the young age.

3. Please examine whether there are any interactions between ACEs and risk behaviors in predicting T2DM, because the presence of interaction between the exposure and mediators complicates mediation analysis and interpretation (see, e.g., VanderWeele TJ, Mediation Analysis: A Practitioners Guide. Annu Rev Public Health. 2016;37:17-32).

Response: Although it is very interesting to further include the interaction between the exposure and mediators, it may not be practical in our case. First, the main effects of our mediators are not significant and further investigation of their interaction may not enhance the current findings. Second, the causal mediation and interaction inference by VanderWeele (2010, 2016) didn’t provide a specific way to handle the multiple multi-category mediators-risky health behaviors-in this study. VanderWeele (2016) mentioned that “Sometimes an informal approach is used for multiple mediators by assessing mediation one mediator at a time and then summing the proportion mediated across mediators. If the mediators affect one another, then this approach fails.” Clearly, this is likely to be the case in our study especially considering that the dummy-coded variables for multiple category variables like BMI, smoking and alcohol consumption would not be independent of each other. In addition, VanderWeele’s approach didn’t cover the clustering effect among repeated measured responses and the complex survey sampling with unequal probability as in our longitudinal study. Furthermore, the direct effect after including the exposure and mediator interaction depends on the levels of exposure and covariates. This would make the difference method hard to summarize in assessing the mediation effects. Finally, VanderWeele (2016) stated that “A more challenging setting is to assess the effect mediated...
through one intermediate when there are other mediators that precede and affect the mediator of interest. In this context, direct and indirect effects are generally not identified, even if one has data on all the variables (4, 47), unless one makes further strong modeling assumptions about linearity of the models and the absence of certain interactions (7, 16, 36, 57), as is done in a linear structural equation model”. What VanderWeele described here could be the case for our study especially when you think that BMI, smoking and alcohol consumption are likely to influence each other over time. Given these reasons, we decided not to include an interaction between ACE and the risky behaviors.

4. Change in significance is not a useful metric for assessing mediation, since p-values are driven both by magnitude of effect estimates and power/sample size. In results text, please report differences in ORs in models with and without adjustment for risk factors and base interpretation on the magnitude of differences.

Response: We agree that change in significance may not be the best way to assess mediation. However, in our case, there may not be another better way to evaluate the mediation effect. The difference method for assessing mediation is based on the standardized beta coefficients (rather than ORs; 3 to be valid. However, given the clustering effect among repeated measured responses and the complex survey sampling with unequal probability in the longitudinal data used in this study, the regression-based approach is still understudied. VanderWeele (2010, 2016) provided an approximation as an alternative for the rare event outcome as in our study. However, it would be problematic given the interdependence between mediators like BMI, smoking and alcohol use and between their corresponding dummy-coded variables. On the other hand, given our large sample size, we have enough power to detect any small mediation effects4 so that we still think change in significance could be used here.

5. I am not sure what stratification by race/ethnicity adds, as it is clearly underpowered (overall there is an association of ACEs with T2DM but no one group shows this). I think the authors should either eliminate this analysis or consider it to be exploratory and present ORs and 95% CIs without relying on significance testing to interpret results.

Response: -Section 3.3, para 4. We have reframed this section to be exploratory and included new text to that effect. “Given the significant racial/ethnic differences in T2DM risk among women, we conducted exploratory analyses among women only, stratifying by race (Table 5).” As an exploratory analysis we now focus on the main effects and have deleted material related to other risk factors to simplify and streamline the message and address the critique #7 below.
6. Results would be improved by greater clarity about which models results are from and what these are trying to estimate. For example, Model 1 in Table 4 might be referred to as a 'total effect' or 'confounder-adjusted' estimate as it is adjusting only for covariates thought to be confounders. Model 2 would be estimating the 'direct effect' after adjustment for BMI. Likewise Model 3 would be the 'direct effect' estimate after adjustment for BMI, tobacco, and alcohol. (See Tyler Vanderweele's papers on mediation analyses for information on these terms.)

Response: In Table 4, these new labels have been applied and throughout the results text (Section 3.3, Survival Models- para 1-4) we refer to these new labels.

Minor

7. In results, there are numerous findings presented having to do with how each covariate is associated with T2DM. It would streamline the paper to pare this down, and focus only on the central questions the paper addresses. Specifically, it would be appropriate to examine the ways that the exposure (ACEs) is related to potential mediators, and from mediators to T2DM, and this could be presented as an analysis of the proposed pathways along this mechanism. Information on other covariates is less relevant and somewhat distracting to the flow of the paper.

Response: Section 3.3-Survival Models, end of para 2, includes two sentences summarizing other risk factors for T2DM. While not central to the paper, many of the risks that emerge for women reflect aspects of socio-economic status and we think these risks are important to document since they have implications for interventions. Thus, we elected to keep those sentences. But, the point is a good one and we elected to simply in other places by deleting the final sentence on additional risk factors when reporting Table 4 results for men, since the main effect was not significant, and in the Table 5 results by race/ethnicity, (Section 3.3, Survival Analysis, para 4).

8. The difference between 'current smoker' and 'daily smoker' is not clear, particularly in abstract and results

Response: We edited the section in Methods/Smoking to define the smoking categories more clearly and then referred to the categories consistently throughout the manuscript. Smoking is divided into three categories. These categories were formed based on questions about daily smoking and include: never daily smoker, former daily smoker, or current daily smoker. We have corrected the text to consistently refer to these groups in the abstract and the results as never smoker, former smoker, and current smoker for clarity. The smoking variables can be created for each wave of data where smoking information was collected. The methods/smoking section now says:
“Smoking: A set of smoking questions was asked in 1992, 1994, 1998, 2008, 2010, and 2012, including the age when participants started to smoke daily, current daily smoking, and cigarettes smoked per day. Summarizing the available data, we created an age of onset of daily smoking and carried it forward from that age, and then grouped smoking status for each year into never daily smoker, former daily smoker, and current daily smoker and referred to in the manuscript as never, former, and current smoker.”

9. The p-value for comparison of number of ACEs in women with T2DM versus those without is different in results (bivariate results) than in abstract.

Response: The p value is <.0001 and it is now consistent in the Abstract, Results, and Table 2. Thank you for noticing this.

10. Throughout, it would help to give age at 2012 to better understand T2DM risk.

Response: Section 2.3-Statistical Analysis, para 2. The age range in for NLSY participants in 2012 is 48 to age 55. This is now specified in section 2.3-Statistical Analysis, para 2, line 3.

11. At the top of p 13 the authors present crude ORs instead of confounder-adjusted ORs for individual ACEs. Is there a reason they preferred crude ORs? It seems that seeing the confounder-adjusted ORs would be helpful.

Response: The authors thought it made sense to provide data on each adverse events and to show the simple bivariate relationships first (Table 2) before building more complex models. The confounder adjusted OR’s are presented in Tables 4 and 5 (Section 3.3) using the overall ACE variable. We hoped that bivariate results from Table 2 provide a fuller picture of the impact of ACE and allows the reader to observe the relationships before we introduce the confounders. We believe this is a fairly typical way to present such data.

12. Page 15 - ACEs did not predict T2DM in men. Is this after confounder adjustment? Earlier results say that 4+ ACEs were associated with T2DM in men.

Response: In section 3.3 (Survival Models), para 3. Yes, this is adjusting for confounders. Section 3.3 is describing results from Table 4 which are from multivariate survival models—all of which adjust for confounders. Earlier results describing 4+ACE (Section 3.2-Bivariate Relationships, para 1) are from Table 2 showing bivariate results.
13. In discussion, it should be noted that findings of an ACE-T2DM association only within women is consistent with prior literature finding sex differences in ACE effects with regard to obesity and other outcomes.

Response: Very good point. We have added a sentence in the Discussion Section, at the end of paragraph 1 that says “This finding is consistent with previous studies, 5 noting that physical or sexual abuse predicted T2DM and that the relationship, as in the present study, was partially explained by high BMI in the abused women.6”

REFERENCES


