Replies for “Association of states' marijuana legalization policies for medicinal and recreational use and vaping associated lung injury” (JNO19-4156-T)

Dear Dr. Rubenfeld,

We write to you with a revised version of our article “Association of states' marijuana legalization policies for medicinal and recreational use and vaping associated lung injury” (JNO19-4156-T) for JAMA Network Open. We thank you for the opportunity to resubmit the paper. We believe that addressing the concerns and comments raised by both yourself and the referees have helped us to improve the paper. In our replies below, we describe in detail the changes we have made.

Many of the comments asked us to add to the manuscript length. Given the journal’s word limitations, we revised the manuscript to focus on the edits we deemed most important, ensuring that we keep the word count as low as possible. Although we could not incorporate all suggestions into the manuscript, we have included responses in our reply document to each comment if they were not fully incorporated into the text. We would be happy to further shorten the manuscript text if you would like.

The remainder of the document contains our replies to specific comments. We look forward to hearing from you. Please let us know if you or the referees have any questions or concerns.

Sincerely,

Coady Wing, Ashley Bradford, Aaron Carroll, and Alex Hollingsworth

Comments from Editor

Thank you for your comments and helpful suggestions. We think they have helped improve the manuscript. Below, we describe how we have addressed each of your concerns. Your comments are in italics; our responses are in regular print.

Editor's Specific Comments

1. *It might be difficult in the confines of the letter but the editors really think you need to emphasize the limitations of the databases for case reporting, the potential bias that states that limit cannabis might have different ascertainment and reporting of these cases, ecologic fallacy.*

   RESPONSE:
   We have added, in the discussion section, a list of limitations of our analysis to clarify these points. We have outlined these issues as well other limitations of our work (e.g., it is from a cross-sectional analysis and does not exploit a quasi-experimental research design)

2. *You really need to temper your conclusions particularly the last sentence in the face of a rapidly evolving evidence base.*

   RESPONSE:
   We agree. We altered our language in both the conclusion and throughout the document to better reflect the limitations of the analysis and to reflect

Additional Comments

3. *Change title to, "Association of states' marijuana legalization policies for medicinal and recreational use and vaping associated lung injury"*

   RESPONSE:
   We have made this change. We also request that you consider an alternative title: "Cross sectional association of vaping associated lung disease and state marijuana policies." This alternative title satisfies STROBE guidelines by indicating study design in the title. We are happy with either title.

4. *Methods: please include study type*

   RESPONSE:
   We have added a reference that this is a cross-sectional study to both the introduction and the methods section.

5. *Indicate how this report follows the STROBE reporting guideline for cross-sectional studies. See http://www.equator-network.org/reporting-guidelines/strobe/*

RESPONSE:
We now indicate in our acknowledgements that "Dr. Wing and Dr. Hollingsworth are responsible for ensuring that this report followed the STROBE guidelines for cross-sectional studies." For more detail please see below:

Our proposed alternative title satisfies STROBE 1 by indicating the study design in the title. There is no abstract. Our introduction satisfies STROBE 2 and 3 by explaining background and rational for our question of interest (STROBE 2) and by stating our hypothesis (STROBE 3) that EVALI case rates may be lower in recreational marijuana states. Our data and methods sections satisfy STROBE 4-12. We present our study design early in the paper (STROBE 4), in the title and outline in the first portion of the methods section. We describe our data sources, dates, and relevant time periods (STROBE 5 and 8) throughout the manuscript. Our study uses only observational data and did not involve the recruitment of participants (STROBE 6). We outline variables used and data sources in the data section (STROBE 7 and 8). We discuss limitations of our analysis including potential bias in our discussion section, when we address limitations (STROBE 9). Our sample size is all US states, which is mentioned in the data section (STROBE 10). We discuss the grouping of policy variables as well as the regression used in the analysis in the results section (STROBE 11). We discuss statistical methods in our data, methods, and results sections (STROBE 12). We mention potential confounding, how subgroups were defined, absence of missing data, and all analyses performed. We use the entire sample throughout our analysis and due to space limitations cannot include a flow diagram (STROBE 13). We describe our data in the data section and present means by subgroup in Figure 1, which is discussed in the results section (STROBE 14). These means are reported for both outcomes of interest and explanatory variables (STROBE 15). Our main results, including 95% confidence intervals are reported in the results section and in Figures 1 and 2 (STROBE 16). We mention other analyses performed in Figure 2, and in the results section. We do not include these due to space limitations, but results are included in table form at the end of this reply document (STROBE 17). In our discussion section, we outline the how our results inform our initial hypothesis (STROBE 18). Our discussion section includes a limitations section that outlines our main limitation- that this is not a randomized experiment (STROBE 19). Our discussion section also includes a cautious interpretation of our findings, suggesting that the initial CDC hypothesis may be correct (STROBE 20). We discuss the generalizability of our results in the discussion section (STROBE 21). We also discuss our funding sources (none to disclose) in the acknowledgements (STROBE 22).

6. *Statistical Analysis: Provide a brief description of all statistical tests used in the study and levels of statistical significance at the end of the methods section.*

RESPONSE:
We have expanded and clarified our explanation of the statistical tests used throughout the manuscript. We also added a specific note regarding the statistical significance threshold used in our analyses (where $p < .05$ is deemed to be statistically significant). We also added five tables with expanded results in Table format at the end of this replies document.

7. *Results: For reports of original data, present numerical results (eg, absolute numbers, proportions, rates, ratios, or differences) with appropriate indicators of uncertainty, such as confidence intervals.*

   RESPONSE:
   We have ensured that all means presented follow these guidelines. We have added 95% confidence intervals to our mean estimates presented in Figure 1.

8. *Label Exhibit 1 and 2 as Figures 1, 2*

   RESPONSE:
   We have changed these labels as requested.

9. *Acknowledgement: Provide Access to Data statement: Using the exact language enclosed in the following quotation marks, provide a statement from one author (eg, the principal investigator), or no more than 2 authors, that she or he "had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis" and include this in the Acknowledgment section of the manuscript.*

   RESPONSE:
   We have added this language to the Acknowledgments section.

Reviewer: 1

Thank you for your comments and helpful suggestions. We believe this has improved our manuscript. We describe how we have addressed all of your concerns. Your comments are in italics; our responses are in regular print. Tables at the end of the reply document also incorporate many of your suggested changes.

1. *The analytic methods are not clearly delineated. It appears that a multivariable linear regression model was conducted, but it is unclear if the primary IV in the model is the state level data or the policy level data (or both with a clustering on state level).*

   RESPONSE:
   We have added separate sections to describe the data and methods used in the paper. The level of analysis (state-level), and the regressions are now described in more detail throughout the manuscript.

2. *Proportion and rate data with low values tend to highly skewed and linear regression tends to produce predicted values below the lower limit of zero. Data with this structure can often be thought of as binomial trials with n trials per state and an event rate of p. For the normal distribution top approximate the binomial, n must be large and the event rate is near 0.5. However, when the number of trials is rather large and the proportion of events is small, this can be approximated using Poisson or negative binomial distribution. This combined with the logarithm of the state population as an offset would assure that the model will not predict counts below zero. This, along with a robust variance estimate will also allow the authors to better express the RR and 95% confidence interval for each IV in the model.*

   RESPONSE:
   Thank you for this suggestion. We have included results from exactly this specification in Table 5 on the last page of the replies document. Table 5 presents results from a Poisson model (in marginal effects) where the dependent variable is the mid-point of the number of cases of EVALI in a given state rounded to the nearest whole number. Our results are robust to using either the minimum or maximum case number reported by the CDC. We offset by the natural log of million population in each state so that the coefficients are in comparable units as our regression estimates presented in the original manuscript. The estimated effect is extremely comparable to our regression estimates with no statistically significant association between medical marijuana status and the count of EVALI cases, but a large and negative association between EVALI cases and recreational marijuana.

3. *Were there any covariates or weights included in the modeling to adjust for state level differences?*

   RESPONSE:
   The analysis was unweighted and the only variables we adjusted for were state marijuana laws (recreational and medical) and state level e-cigarette prevalence. The revised manuscript methods section should make this much clearer. Our results are robust to weighting by state population.

4. *Line 53: "multivariate" on line 53 should be "multivariable"*

   RESPONSE:
   We have made this change.

5. *Throughout: model estimated rates and rate differences should include a measure of variability along with the estimate and p-value.*

   RESPONSE:
   In the revised manuscript, we have included confidence intervals and p-values for each statistic. We have also reported these (as well as the standard error) for each statistic in Tables 1-5 attached at the end of this replies document.

6. *Exhibit 1: EVALI estimates: It would be helpful to include the range around each state in combination with the midpoint. Although I understand that this may cause the figure to become unwieldy.*

   RESPONSE:
   Thank you, we have incorporated this suggested change. We note below the figure that this range is depicted using a thin black line.

7. *Exhibit 1: Average cases per by policy estimates could include error/range estimates on the bar charts.*

   RESPONSE:
   Thank you, we have incorporated this suggested change. We note below the figure that each 95% confidence interval is depicted using the bracketed black line.

Reviewer: 2

Thank you for your comments and helpful suggestions. We believe this has improved our manuscript. We describe how we have addressed all of your concerns. Your comments are in italics; our responses are in regular print.

1. *I wonder if the authors push too far in the discussion. While it may be (and I think it even likely) that legal dispensaries safeguard the quality of the "product" (because they can more easily be held accountable than black market dealers or for other reasons), I'm not sure it's a safe bet to say that "further restrictions on the legal market for marijuana could lead to more EVALI." Indeed we have long suspected that raw concentrated product from Colorado is being illegally brought to UT, and adulterated here to "stretch" it. So it may be that the recreational market engendered the epidemic by making available concentrate that can be easily smuggled, diluted, packaged, etc in states where it cannot be mass produced legally.*

   RESPONSE:
   Thank you for this comment. We agree that the statement you mention was not justified by our results. We have removed it and in general tempered the language in the manuscript that suggests anything that is not directly supported by our findings.

2. *In addition, this ending sentence needs rewritten: "Recent proposals to ban e-cigarette products are not supported by the data and seem to raise concerns about the unintended public health consequences of black markets for recreational drugs." How do the data fail to support bans on e-cigs? I can surmise some arguments, but this small analysis is insufficient to weigh on banning things which is a political and public health prerogative. I think the authors go too far here because their simple albeit straightforward analysis is wholly insufficient to support policy decisions. Furthermore, "black markets" do not have unintended consequences - they don't care about any consequences beyond profit. Unintended consequences are when you're trying to achieve some holistic goal and are thwarted by possibilities you didn't think of in your action plan.*

   RESPONSE:
   We have removed this sentence from our discussion. To clarify, with respect to unintended consequences, we simply meant that an unintended consequence of banning a product is the potential creation of a black market for that product and that by operating without safety regulations, a black market may generate more health risks than regulated legal market for the same product. Regardless, we agree with your point that our discussion section should not reach beyond the analysis or make complicated policy suggestions. Accordingly, we have re-written the discussion section of the paper so that it remains closer to the results of the analysis.

3. *A much safer tack to take in the conclusion/discussion, I think, is to return faithfully to the data which show that EVALI is more common in states where THC is not recreationally legal, or conversely, that recreational legality in some states appears to be "protective" against EVALI. Why might that be? Are there differences between THC consumed by vaping between states with and without recreational THC? Because that maybe/probably holds clues to the*

etiology and pathogenesis of the syndrome, and it points to other questions that may hold important clues to the syndrome.

RESPONSE:
We have incorporated this advice in the new discussion section

4. *Given its preliminary nature, I think it is important to show how it points to future lines of inquiry, rather than how it may support policy decisions.*

RESPONSE:
We now highlight that our findings are indicative for important directions of future research rather than focusing on potential how the findings support or do not support particular policy positions.

Reviewer: 3

Thank you for your comments and helpful suggestions. We believe this has improved our manuscript. We describe how we have addressed all of your concerns. Your comments are in italics; our responses are in regular print.

1. *The authors used several databases: CDC reports on lung injury, BRFSS for e-cig, SEER. The authors did not mention which variables they used for the data analyses. They did not acknowledge the difference in the covered observation period (i.e. data in 2019 for the lung injury reports, up to 2017 for the BRFSS and SEER).*

   RESPONSE:
   We have now mentioned the variables used from each dataset and explicitly mention the years for each variable in our data section. Please find links below that can be used to access each respective dataset.

   We obtained data on EVALI cases in 2019 at the state-level from the Centers for Disease Control and Prevention (CDC). Available here: http://dx.doi.org/10.15585/mmwr.mm6839e1

   We obtained data on prevalence of current e-cigarette users from the Behavioral Risk Factor Surveillance System (BRFSS), the most up-to-date data are from 2017. This is available here: https://nccd.cdc.gov/BRFSSPrevalence/rdPage.aspx?rdReport=DPH_BRFSS.ExploreByTopic&irbLocationType=StatesAndMMSA&islClass=CLASS19&islTopic=TOPIC67&islYear=2017&islLocation=

   We obtain data on state population in 2017 from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. Available here: https://seer.cancer.gov/popdata/

2. *It is not clear how the authors could identify the type of product vaped i.e. nicotine and content, different solvent, THC content.*

   RESPONSE:
   Our analysis was at the state level and we did not analyze the type of product vaped by any individual. As far as we know, detailed information on the type of product vaped is not collected in a systematic way that is usable in our analysis. We simply estimated EVALI case rates per million and compared average case rates in states with three types of marijuana policies. The revised manuscript includes a more complete methods section, which clarifies our analysis. We also mention this in our limitations section.

3. *The authors reported number of cases per inhabitant by states without controlling on the prevalence of e-cig and cannabis use, hypothesizing that the prevalence was the same across states. It would be better to report based on the estimation of users.*

RESPONSE:
Thank you for alerting us to the fact that our analysis description was unclear. Our original manuscript did include an analysis in which we controlled for e-cigarette use and marijuana policy status simultaneously. We have reported these results in Table format in column 3 of Table 1 found at the end of this replies document. We have not attempted to adjust for the prevalence of cannabis use. In general, our analysis should be viewed as a simple cross-sectional study. We leave a more complete quasi-experimental study for future work. We have added this as a limitation in the discussion section.

4. *The conclusion is overstated. Because the relationship between the content of e-cig and the lung injury, no conclusion could be drawn on the relationship between legal market and lung injury.*

RESPONSE:
We agree with this point. We have tempered the language and implied conclusions. The revised discussion section is more circumspect.

Table 1: The association of lower EVALI case rates and recreational marijuana is robust to controlling for prevalence of e-cigarette use and there is no clear relationship between EVALI and e-cigarette use

	(1)	(2)	(3)
Intercept	8.057 ***	11.158 *	14.213 *
	(1.858) [0.000] (4.322 to 11.793)	(4.345) [0.013] (2.427 to 19.889)	(5.879) [0.020] (2.387 to 26.040)
E-cigarette use (0-100%)		-0.791	-1.271
		(0.863) [0.364] (-2.525 to 0.944)	(0.982) [0.202] (-3.246 to 0.704)
Medical marijuana only	0.713		0.251
	(2.590) [0.784] (-4.495 to 5.921)		(2.741) [0.928] (-5.263 to 5.764)
Recreational marijuana	-6.359 **		-7.214 **
	(1.936) [0.002] (-10.251 to -2.466)		(2.274) [0.003] (-11.788 to -2.640)
N	51	51	51

Note: Robust standard error reported in parentheses below. P-values reported in brackets. P-values also represented by stars with * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. 95% confidence interval calculated using robust standard errors in parentheses.

Table 2: Mean EVALI case rate per million by marijuana policy

	Prohibition	Medical Only	Recreational
Mean	8.06	8.77	1.70
	(4.14 to 11.97)	(5.09 to 12.45)	(0.30 to 3.10)
N	18	26	7

Note: 95% confidence interval calculated using robust standard errors in parentheses.

Table 3: Difference in mean EVALI case rate per million by marijuana policy

	Medical v Prohibition	Prohibition v Recreational	Medical v Recreational
Difference	0.713	-6.359 **	-7.071 ***
	(2.572) [0.783] (-4.478 to 5.903)	(1.958) [0.004] (-10.410 to -2.308)	(1.887) [0.001] (-10.921 to -3.222)
N	44	25	33

Note: Difference between means of groups reported with the robust standard error of the difference reported in parentheses below. P-values reported in brackets. P-values also represented by stars with * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. 95% confidence interval of difference in means calculated using robust standard errors in parentheses.

Table 3: Mean e-cigarette use prevalence [0-100] by marijuana policy

	Prohibition	Medical Only	Recreational
Mean	4.84	4.48	4.17
	(4.47 to 5.22)	(4.10 to 4.87)	(3.29 to 5.05)
N	18	26	7

Note: 95% confidence interval calculated using robust standard errors in parentheses.

Table 4: Difference in mean e-cigarette use prevalence [0-100] by marijuana policy

	Medical v Prohibition	Prohibition v Recreational	Medical v Recreational
Difference	-0.364	-0.673	-0.309
	(0.257)	(0.391)	(0.392)
	[0.165]	[0.099]	[0.436]
	(-0.883 to 0.156)	(-1.482 to 0.136)	(-1.109 to 0.490)
N	44	25	33

Note: Difference between means of groups reported with the robust standard error of the difference reported in parentheses below. P-values reported in brackets. P-values also represented by stars with * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. 95% confidence interval of difference in means calculated using robust standard errors in parentheses.

Table 5: Using a count model to estimate the association between the EVALI case rate per million and marijuana policy

	(1) Poisson marginal effects
Medical marijuana only	0.18
	(0.27)
	[0.51]
	(-0.37 to 0.73)
Recreational marijuana	-3.17***
	(0.27)
	[0]
	(-3.71 to -2.63)
N	51

Note: Binary policies are discrete changes. Standard error reported in parentheses below. P-values reported in brackets. P-values also represented by stars with * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. 95% confidence interval calculated using standard errors in parentheses.