EDITOR'S SPECIFIC COMMENTS:  
  
We liked this paper despite it is limitations. It is timely and if you are able to modify we would like to fast track.

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.

Reply

Most importantly, you really need to temper your conclusions particularly the last sentence in the face of a rapidly evolving evidence base.

We deleted the last sentence, and rewrote the conclusions section to stick closer to the data presented in the paper.  
  
ADDITIONAL COMMENTS:  
  
Change title to, "Association of states' marijuana legalization policies for medicinal and recreational use and vaping associated lung injury"

We are happy to change the title as you suggest.

However, we also think that an alternative title: “**Cross Sectional Association of Vaping Associated Lung Disease and State Marijuana Policies For Medical and Recreational Marijuana Use”** might satisfy STROBE guidelines a bit better.

Methods: please include study type  
Indicate how this report follows the STROBE reporting guideline for cross-sectional studies. See <http://www.equator-network.org/reporting-guidelines/strobe/>

The proposed title satisfies STROBE 1.

The Introduction satisfies Strobe 2 and 3.

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

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

Label Exhibit 1 and 2 as Figures 1, 2

Done

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.  
  
Done  
  
  
REVIEWER COMMENTS:  
If the reviewers have opted to reveal their identity, please refrain from contacting them directly.  
  
The following individuals involved in review of your submission have agreed to reveal their identity: SCOTT K. ABEREGG (Reviewer #2).  
  
Reviewer #1  
  
Dr. Wing and colleagues report the association of state marijuana laws with CDC reported cases of e-cigarette or vaping associated lung injury (EVALI). The authors report that cases of EVALI are significantly more concentrated in states without recreational marijuana policies. The manuscript is clearly written and the results easy to understand.

Thank you

However, 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).

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.

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.  
  
Minor comments to the authors:  
Were there any covariates or weights included in the modeling to adjust for state level differences?

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

Multivariate regression seems like standard usage to us. But if the journal standard is to use “multivariable regression” to describe a regression of dependent variable on multiple independent variables, we are happy to make the change.  
  
Throughout: model estimated rates and rate differences should include a measure of variability along with the estimate and p-value.

In the revised manuscript, we have included standard errors, confidence intervals, and p-values for each statistic.  
  
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.

We have experimented with an upper and lower range to the graphs and we think it adds clutter without adding much value. However, we are happy to present the results this way at the editor’s discretion.  
  
Exhibit 1: Average cases per by policy estimates could include error/range estimates on the bar charts.  
  
We have experimented with adding CI bars to the graphs and we think it adds clutter without adding much value. However, we are happy to present the results this way at the editor’s discretion.  
  
  
  
Reviewer #2  
  
I think this is important for the ongoing investigations of causality of the VALI epidemic. However, 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.  
  
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.

Some of these points make sense to us and some do not. (With respect to unintended consequences, we simply meant that an unintended consequence of banning a product is the likely creation of a black market in the product. By operating without safety regulations, a black market may generate more health risks than regulated legal market. This is one reason why it might be unwise to unhealthy products like tobacco, alcohol, etc.)

Regardless, we agree with the reviewer that there 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 sticks closer to the results of the analysis.   
  
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.  
  
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.  
  
We have tried to incorporate this advice in the new discussion section  
  
  
Reviewer #3  
  
This short communication reported on the association between cannabis vaping and lung injury using database. Although of interest, there are some room to improve the manuscript.  
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).

Alex: Can you add details about the years for each data set.

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

Our analysis was at the state level and we did not analyze the type of product vaped by any individual. 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 we hope will make things clearer.

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.

In fact, the manuscript did include an analysis in which we controlled for e-cigarette use. (The results were unchanged. 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.)

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.

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)  [0.165]  (-0.883 to 0.156) | (0.391)  [0.099]  (-1.482 to 0.136) | (0.392)  [0.436]  (-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. | | | | | | | |