

After rejection at eLife, the authors elected to submit to PeerJ. I reviewed the eLife Reviewers' comments, the responses to these comments by the authors, and after this review I did not deem it necessary to send out for further peer review. The authors did a fantastic job at responding to the previous Reviewers' comments and criticisms, including some re-analysis of their data.

This paper is an interesting and provocative epidemiological investigation using data recently made available to the public. The authors investigated the putative carcinogenic effect of higher partial pressures of oxygen (lower elevations) on the incidence of lung cancer (as well as other cancers). The authors found a potential link of higher exposure to oxygen being positively correlated to lung cancer incidence. They postulate that people living at higher elevations, due to a lower overall oxygen exposure, may have a lower incidence of lung cancer.

Although any observational study is subject to residual confounding from unmeasured or unknown confounders, the authors have done a very good job with their analysis to assess this potential from multiple angles. The results were all consistent and now they provide a new topic to investigate using individual-level data in the future to strengthen support for what is, at this time, an interesting but uncertain association.

I would like to congratulate the authors on performing this work to such a high standard.

I have made numerous comments in the attached file (to be emailed to you separately). I would appreciate it if the authors would go through this file and respond to each of the concerns raised. I do not think any of the concerns will be difficult to deal with.

This paper will be published in PeerJ assuming a satisfactory response to the issues raised.

**We sincerely thank the editor for his thoughtful and thorough review of our revised manuscript as well as our responses to reviewers. We agreed with all suggestions and have incorporated them in our current revision. Please find our specific responses below:**

- 1. We removed the use of 'concentration' when discussing atmospheric oxygen and replaced with partial pressure where appropriate.**
- 2. We removed 'sensible' from "sensible regression models" in the Abstract.**
- 3. "no evidence of uncontrolled confounding" was changed to "no evidence ... of confounding arising from evaluated factors" in the Abstract.**
- 4. In the Introduction, we replaced "From the concentration at sea level, oxygen decreases to 88.7% at 1000 m" with "From its partial pressure at sea level, oxygen is reduced to 88.7% at 1000 m".**
- 5. We calculated  $I^2$  (a measure of heterogeneity) for state-specific elevation coefficients. The  $I^2$  was imprecise [95% CI: 35–90%], but suggested potential effect heterogeneity. Despite this potential heterogeneity, our choice of a**

**fixed-effects (as opposed to random-effects) meta-analysis was *a-priori* and we believe proper as explained by Viechtbauer in 2010:**

Therefore, contrary to what is often stated in the literature, the fixed-effects model does not assume that the true effects are homogeneous. In other words, fixed-effects models provide perfectly valid inferences under heterogeneity, as long as one is restricting these inferences (i.e., the conclusions about the size of the average effect) to the set of studies included in the meta-analysis. On the other hand, the random-effects model provides an inference about the average effect in the entire population of studies from which the included studies are assumed to be a random selection. [from "Conducting Meta-Analyses in R with the metafor Package" in the *Journal of Statistical Software*]

- 6. We also made a few small grammatical improvements throughout the manuscript, reflected in the track changes file.**

**Thank you for your consideration,  
Kamen Simeonov & Daniel Himmelstein**