Evidence relating cigarette, cigar and pipe smoking to lung cancer and COPD. Meta-analysing recent data from three regions.

Reply to the reviewers on the comments made on the version originally submitted to World Journal of Meta-Analysis (MS 84392)

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The Reviewer Comments

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: The authors have developed an interesting and extensive work on the relationship between smoking and lung cancer and chronic obstructive pulmonary disease (COPD). The issue has been studied for decades, but it continues to be a problem for the health of the world population today. The work is coherent and the methodology is correct. In order to improve the quality of the work I will include two suggestions: - The introduction is very short. It could be expanded by briefly analyzing the state of the art. - Data on the use of electronic cigarettes could be included in the discussion.

Reviewer #2:
Scientific Quality: Grade D (Fair)
Language Quality: Grade C (A great deal of language polishing)
Conclusion: Major revision
Specific Comments to Authors: A very interesting study addressing a timely topic in lung cancer. Some changes are needed. - The introduction should be expanded and the authors should add some recently published papers regarding the evolving systemic treatment scenario for lung cancer (PMID: 35326555; PMID: 36368251; PMID: 36064585; PMID: 33053439). - The limitations of the current manuscript should be better discussed and reported, including the heterogeneity of data. - The discussion should be expanded and a more personal perspective should be included. Major changes needed.

Reply to reviewers

We thank the reviewers for their comments.

1. Language polishing.

We note that both reviewers said language polishing was needed, and Reviewer #2 suggested that a great deal of polishing was needed. However, no examples were given of anything that was unclear. All three authors of the paper are native English speakers and PNL has been the main writer of some hundreds of published papers where no one has previously considered

his English inadequate. Indeed, as a peer reviewer, he commonly suggests English improvements for papers written in English by authors from other countries. Nevertheless, he has been through the complete text once more in an attempt to make the text as clear and well written as possible, and has made a number of changes.

2. Expanding the introduction. Both reviewers say that we should expand the introduction. Reviewer 1 says that we should analyze the state of the art, while Reviewer 2 says that we should "add some recently published papers regarding the evolving systemic treatment scenario for lung cancer", neither reviewer giving any more detail. We regard the point about mentioning changes in treatment for lung cancer as peripheral for reasons mentioned in point 5 below, and only consider it, and then briefly, in the discussion. To cover the point made by Reviewer 1 we have slightly reorganised the introduction by making clear the overall aim of the project we are involved in, and referring to the RR estimates previously obtained in our own two earlier meta-analyses. However, if "analyzing the state of the art" is meant to be to describe results from a number of previous meta-analyses, we prefer to do that later in the paper as one of the objectives of our work is to compare our lung cancer and COPD meta-analysis estimates with estimates obtained by others in recent publications. We are not sure what else we ought to be saying, and note that the length of the introduction is not dissimilar from that in our earlier paper on snus and smokeless tobacco published in World Journal of Meta-Analyses.

3. Mention of electronic cigarettes. Reviewer 1 asks that we refer to electronic cigarettes in the discussion. We now refer to electronic cigarettes in various places in the paper. Firstly, in the Core tip, we note that "While quitting reduces risk most effectively, available evidence suggests switching to nicotine products that are not smoked could potentially reduce these risks". Second, in the introduction, we now note that "More recently introduced products, such as electronic cigarettes and heat-not-burn products, are not considered in our project at this time, as large long-term epidemiological studies relating their use to the main smoking-related diseases have not so far been conducted". Third, in the "General Considerations" section of the discussion, we now note that some studies only classify subjects by baseline status, "when current smokers may have subsequently quit or switched to other products, including e-cigarettes …". Fourth, in the "Limitations of our work" section of the discussion, we now note that we did not "consider the role of e-cigarettes which were introduced towards the end of the follow-up period in some of the cohort studies". Fifth, at the end of the conclusion, we note that the much lower toxicant levels from e-cigarettes than from cigarettes suggests that switching from cigarettes to e-cigarettes may "substantially reduce" the risk of lung cancer and COPD from smoking. This final point is also made in the "Research perspectives" section of the Article Highlights. This should be enough, we believe.

4. Better discussion of heterogeneity of the data. Reviewer 2 asks for this. Clearly there is already extensive detail in the paper about how the current vs never smoking relative risk estimates vary by a range of factors (see Tables 3 and 4 for cigarettes and the related text). However, the section of the discussion headed "General considerations" has now been considerably extended.

5. Changing treatment scenario for lung cancer. Reviewer 2 mentions this. We have now noted in the extended "General considerations" section that "… the precise definition of disease may vary between studies, as may changes over time in how lung cancer and COPD are treated, so affecting survival, possibly differently for current and never smokers." We would rather not get into too much detail on this for a number of reasons: (a) we are only statistically, not medically qualified, and do not have detailed knowledge of how treatments for lung cancer have changed over time, (b) if we mentioned such changes for lung cancer we would also have to investigate whether similar changes apply for COPD, (c) changes in treatment would only be relevant if they affected the probability of lung cancer death quite differently for current smokers and never smokers diagnosed with the disease, and (d) many of the deaths considered in our analyses would probably have occurred long before these treatment changes occurred. It seems to us that this issue is very tangential to the objectives of our work.

6. Better discussion of the limitations of the manuscript. Reviewer 2 asked for a better discussion of limitations, but unfortunately did not give any detail on what was missing from our section headed "Limitations of our work". However, although we thought that the text as submitted in the first version of our paper was reasonably comprehensive, we have been through it carefully and extended it somewhat.

7. More personal perspective should be included. Reviewer 2 asks for this, but surely a meta-analysis should present the results of the planned analysis in an unbiased fashion, and not give a slanted opinion.