Point by point reply to Reviewer 1 comments on the paper "Systematic review with meta-analysis of the epidemiological evidence in Europe, America and Australasia on smoking and COVID-19"

Author: P.N.Lee

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I thank Reviewer #1 for his comments and the time spent on reading our paper. Below I give the Reviewer's comments in bold and my replies in normal font. The replies given below have been agreed with my co-authors Katharine Coombs and Jan Hamling.

Reviewer #1: The authors are requested to resubmit. Quite blunt hypotheses was presented hence requested to sharpen the acquisitions and claims in stronger manner within the manuscript. The original findings should have been presented more accurately thereby suggested to resubmit and present the data to support the hypothesis. Limitations are not mentioned by the authors and impact on clinical practice also has to be mentioned by the authors in discussion section.

These points are covered below, except for mentioning the impact on clinical practice. As none of the authors are clinicians, we would prefer not to make statements about the impact of our results on clinical practice. Clearly if, for some reason, smoking did reduce the chance of infection with COVID-19, one would hardly recommend that people take up smoking to lessen their risk! Our conclusions regarding mortality suggest that any increase in risk in smokers is due to their worse health status pre-pandemic, and does not suggest that clinicians should take any special action for smokers, other than that taken anyway in relation to those with a poorer respiratory and cardiovascular health status. While smokers should clearly be advised to quit, or if unable to do so, switch to a reduced risk form of nicotine intake, the results for smoking and COVID-19 seem not to affect the position.

1. Reduce the size of the background to one or two sentences. Modify the aim of the study as per the hypotheses considered before starting the search in pubmed. Mention the aim in one or two sentences. In introduction section explain the importance of the study in detail but not more than a page. Try to keep the size of this article below 8000 words.

Although the journal specifies a limit to the background section of 100 words, and the current version is exactly 100 words, it has now been reduced to two sentences and 63 words.

The aim section in the abstract is limited to 20 words and will become 20 when Israel is added to the list of countries mentioned. It is now explained at the start of the methods section that "The methods we used were intended to quantify the associations of various indices of smoking with a range of endpoints based on evidence from populations of different types, indicating the extent to which the associations depend on the adjustment factors considered." There is no single specific hypothesis,

but many, though of course each meta-analysis carried out involves a test of the association against a null hypothesis.

The introduction section of the paper was on two pages, but has now been cut down considerably.

Presumably the 8000 words referred to does not include words in the references, figures and tables. The original title and abstract was 1459 words, and the rest of the text up to just before the references was a further 8293 words. For the revised version, the title and abstract are now 1279 words, and the remaining text 6480 words, which now totals 7759, less than 8000. A major part of this saving was derived by giving less details of the methods in the paper itself, and including an extra additional file (now additional file 1) giving more details of the methodology.

2. Please provide a systematic review flow chart explaining the inclusion and exclusion criteria.

The required flow-chart has been added as Figure 1 and is now cited early on in the results section.

3. Reasons for exclusion and inclusion criteria with number of literatures should be mentioned both in flowchart and methodology sections.

The methodology section has now been extended to justify further our inclusion/exclusion criteria. Details about the numbers of publications considered at various stages are given in the flow chart and also in what is now Additional file 2. These are referred to in the results section and not the methodology section as clearly they are results.

4. The articles excluded need not to be provided in reference section, include only 74 articles and other references used in the manuscript.

In fact, in the version submitted originally, the references to the studies excluded were only given in the Additional file on the searches, and not in the main paper. Note that the number of references in the revised version of the paper now submitted has considerably reduced, as the old Table 1 giving details of study characteristics including references has now been moved to Additional file 3.

5. In the discussion section justify your findings with reasons. Add at least one limitation of this study in the discussion section.

Our paper already clearly described what we did and the results we got, and commented on various potential sources of bias. It is not clear what the Reviewer means by wanting us to "justify" our findings. What did the Reviewer want us to say?

The discussion section of the paper already contained considerable text on the limitations of our work: including many studies only providing unadjusted data; the smoking data coming mainly from hospital records with problems of missing and incomplete data; results being variously presented as

odds ratios, relative risks and hazard ratios; some deaths classified as being from COVID-19 likely being due to other causes; and the limited results by age, sex, amount smoked and time quit. Was there some other limitation we missed that the reviewer wanted us to consider?

6. Reduce the size of the manuscript to 60 pages maximum and resubmit.

- The manuscript was 78 pp (32 pp text, 19 pp references, 23 pp tables, and 4 pp figures). We have shortened it in various ways: (i) moving the full details of the methods to the new Additional file 1 and considerably shortening the text in the paper; (ii) moving the old Table 1 giving study characteristics and references to the new Additional file 3 so reducing the references in the main paper from 150 to 55; (iii) moving some of the tables of results to the new Additional file 4 and (iv) trying to make the text more succinct. The manuscript is now considerably shorter, though we cannot tell its exact length until we see a proof. However I note that the Word file of the paper we submitted originally was 82 pages, and that for the current version is 59 pages.

7. E-cig smoker's data is not required in this study.

E-cig users data are not used in the study, but the initial searches we conducted were for another project where the relationship of both smoking and e-cig use was of interest. Publications reporting only e-cig data were not included in the final set of studies used for analysis. The reference to e-cigarettes now, in any case only appears in Additional file 1, where the points made above are explained.

8. The methods section's size in the abstract has to be reduced.

The methods section in the abstract has been reduced from 260 to 209 words. The methods section in the paper has also been reduced considerably by outlining the methods in the main paper, and giving fuller details in the new Additional file 1.

9. Statistical analysis section has to be added in the main body as a heading and with a sentence in the abstract methods section explaining procedure followed to analysis. Mention the highest and lowest significant values considered in this study. Mention the tools used for statistical analysis. Verify if the Journal has specific list of tools used for data analysis.

The statistical methods used are now clearly described in both the abstract and methods section of the paper. It has also been made clear that we have used our own software (RoeLee) to carry out the analyses. While the Journal may well not have a copy of this software, it has been rigorously tested and validated and is sold commercially. It has been used it in a number of previous meta-analyses appearing in the journal.

Given the number of endpoints, populations, smoking groups and degrees of adjustment, is there any merit in picking out the most significant, perhaps most biased, effect estimate? Of what possible interest, when reporting numerous effect estimates, is to point out that which is the least significant? This suggestion has been ignored.

10. Mention the key findings with statistical values in the result section of abstract. Only statistically significant findings has to be presented in abstract.

Some effect estimates and 95% CIs have been added in the abstract. We totally disagree that one should only present statistically significant results in the abstract. We looked at a number of associations and found that some showed significant relationships and some did not. Mentioning only the significant ones is clearly biased reporting of our results.

11. Please refer the Journal's standard procedure of manuscript preparation.

We did, and are experienced with it, having published numerous other meta-analyses in the Journal. The Reviewer did not point out any specific deficiency so we cannot action this comment.

12. Mention only the key words with which maximum search results were obtained in pubmed, no need to mention all the words.

The details of the searches are now only given in Additional file 1, so the words do not now appear in the main text. We did not really understand this point. We have not done work on which specific words in the text most affect the results of the searches. We decided on an appropriate set of search terms, based on our considerable experience, and then ran the search.

13. For tables and graph plot provide only the study characteristics, results obtained among various groups and Forest plot results. Statistical significance should be highlighted in bold.

As regards the first point, we are not sure what the reviewer wants added (or deleted). The tables and Forest plots already clearly show which combined effect estimates relate to which subgroups by smoking definition, population at risk and level of adjustment.

Significant results have been highlighted in bold in our main tables, though this has never been done in previous meta-analyses we have published in the journal. After all, the 95% CI tell one immediately which effect estimates are or are not significant at $p<0.05$.

14. Please be specific if you have included studies from America, Europe, and Australia. Asian articles can be excluded completely. When you speak about America I hope Canadian studies are included, as I can see Brazilian studies are included but not Canadian studies. If the literature not found mention it accordingly in the search result section.

It has been made clearer in the paper in the section on inclusion and exclusion criteria that America includes South America, Central America, USA and Canada. There were no studies in Canada that satisfied our inclusion criteria.

15. At the same time studies conducted in Israel are included which is incorrect procedure of systematic review as it do not matches with the statement provided in the title. Article from Israel can be excluded. If you include it please mention the reason as it is an Asian country.

The title has been amended to say "…evidence in Europe, Israel, America, and Australasia..". The work was all carried out according to a prior specification, and it would be a huge amount of work to rerun all the work excluding the Israel results, completely impossible in the time scale needed for revising the paper. The reason for including studies from Israel is now given in the introduction section of the paper.

16. Please send only one reference list in next manuscript, at present multiple reference list is provided which is confusing.

We initially prepared three documents, the paper itself, one Additional file giving full details of the literature searches with its own reference section, and a second Additional file giving the full details of all the meta-analyses. When the paper was submitted, it appeared that we had to submit only one file, so we joined them together. That is why there were two reference lists in the file that Reviewer 1 looked at. As we have now submitted the paper itself, and each of the Additional files as separate documents, this problem no longer arises.

17. You have to show the statistical significance among groups or studies matching your hypothesis or else mention that your hypothesis and findings are not matching post analysis. For that mention the key findings in the abstract results section.

There was no specific hypothesis, nor prior beliefs about what the analyses might show. For each of a large number of associations we tested whether or not there is a statistically significant relationship. Each effect estimate is, of course, tested for statistical significance against a null hypothesis. We do now give some effect estimates and 95% CIs in the abstract results.

18. Please refer a previously published article in this journal (Systematic review and meta-analysis) before resubmitting.

We do not understand this. We have already published various meta-analyses in World Journal of Meta-Analysis, and are familiar with the style and the instructions for authors.

19. Comorbidities are causing deaths in COVID-19 patients, smoking does not have any relevance with deaths, it is a well known fact and in 2002-03 a SARS-CoV study showed similar results in smokers.

We agree that comorbidities cause deaths in COVID-19 patients. The reviewer's claim that it is a "well-known" fact that smoking does not have any relevance with deaths is presumably meant to apply only to COVID-19 deaths, but even then it is contrary to what various other reviews of the relationship between smoking and COVID-19 deaths have claimed, as noted in the paper. One of the major conclusions of our review is that smoking is associated with an increased risk of COVID-19 deaths in unadjusted analyses, and in analyses adjusted only for age, sex, and other demographic variables, but not in analyses taking comorbidities into account. While we are not familiar with the study in 2002-2003, for which Reviewer 1 has not provided a reference, it presumably refers to an earlier strain of COVID. We are not sure that that evidence is relevant. After all smoking is associated with an increased chance of getting many viruses and infections but the evidence summarized in the paper seems to show it is associated with a reduced chance of getting COVID-19.

20. Please explain if you mean that non smokers without comorbidities are at high risk than smokers without comorbidities. Mention this in abstract with statistical significance. The progression of SARS-CoV-2 pneumonia from hospitalization to ICU admission to death is due to comorbidities and not due to smoking. Hospitalization occurs due to pneumonia and pneumonia exacerbates due to presence of comorbidities.

We did not say that. We show that smokers and non-smokers with a similar pre-pandemic medical history (comorbidities) and with similar demographics have a similar risk of progression of the condition. Again the Reviewer claims to know at the start what the progression is due to, when various publications strongly suggest that smoking is involved, as noted in our paper. Actually smoking is involved, in that it increases the risk of getting a number of the comorbidities, but the analyses adjusted for comorbidities suggest strongly that smoking does not interact with the virus in some way to cause extra risk.

21. In the tables mention the study as Niedzwiedz et al., 2020. Present the tables related to your hypothesis or aim of your study, 17 tables cannot be included.

Niedzwiedz et al., 2020 is one of the many references considered under study BIOBNK in Table 1. We did not understand what the reviewer was suggesting here.

Of the 17 tables submitted originally, the most important are Tables 3, 5, 7, 9, 11, 12 and 14 (detailed meta-analysis results for seven endpoints with substantial data), and Tables 16 and 17 (summary of main results). These are now renumbered Tables 1 to 9. We have moved the old Table 1 (study characteristics) to Additional file 3, and the other seven tables to Additional file 4, referring the reader to these as appropriate.

22. In the study characteristics Figure 1. section add a column for comorbidities. Present the statistical significance properly to further consider this article for publication.

We believe that the Reviewer was referring to Table 1 and not Figure 1. We have amended the column "Adjustment" so that it indicates whether effect estimates were presented that were unadjusted, or were adjusted for demographics, comorbidities and response variables to COVID-19, or to combinations of these three, although this detailed information is already given in the detailed results, now presented in Additional File 5.

As noted before, presentation of effect estimates and 95% CIs is a standard and appropriate way of presenting statistical significance, and significant effect estimates are now highlighted in the tables in the paper. Giving p-values for every analysis seems unnecessary and inappropriate.

23. The language should be short and precise.

Although our original paper was phrased in language believed to be quite precise and succinct, the whole text has been edited to try to improve it in this regard.

The reviewer said could not find the systematic review flow chart, but this was provided as Figure 1 in the revised paper.