"Evidence relating cigarettes, cigars and pipes to cardiovascular disease and stroke: Meta-analysis of recent data from three regions" (World Journal of Meta-Analysis Manuscript No: 86522)"

Reply to reviewer comments

Authors: Peter N Lee, Katharine J Coombs, Jan S Hamling

Date: 14th August 2023

We thank the reviewers for the time they spent and for their helpful comments. Below we give a point-by-point answer to the points the reviewers made. Our replies are in upper case to distinguish them clearly from the reviewer comments.

Reviewer #1:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade B (Minor language polishing)

ALTHOUGH ALL THREE AUTHORS ARE NATIVE ENGLISH SPEAKERS, WE HAVE REREAD THE PAPER CAREFULLY TO TRY TO IMPROVE THE ENGLISH AND THE CHANGES MADE ARE EVIDENT IN THE REVISED VERSION OF THE PAPER.

Conclusion: Accept (General priority)
Specific Comments to Authors: The paper of Lee et al., "Evidence relating cigarette, cigar and pipe smoking to AMI, IHD and stroke: Meta-analysis of recent data from three regions" analyses the evidence between AMI, IHD and stroke and current smoking. The authors have considered the influence of current smoking and the relative risk of the three products (cigarette smoking, cigar, and pipe smoking) on AMI, IHD, or stroke in the three regions. It is a comprehensive and up-to-date systematic review and a meta-analysis of the available data on these topics that significantly contribute to this field of research; it is also well-organized, scientifically valid, and well-written. Minor suggestions: Did the authors register the protocol in the PROSPERO database?

THIS PAPER HAS NOT BEEN REGISTERED IN PROSPERO AND NOR WERE ITS TWO PREDECESSOR PAPERS IN THE JOURNAL[1, 2] WHICH FORMED PART OF THE TOTAL PROJECT AND ARE CITED IN THE INTRODUCTION SECTION. OUR UNDERSTANDING IS THAT WHERE PROSPERO IS USED, THE PROJECT SHOULD BE REGISTERED FIRST AND THEN APPROVED <u>BEFORE</u> THE WORK IS CARRIED OUT AND THE PAPER(S) SUBMITTED. AS THIS HAS NOT HAPPENED, AND IT WOULD DELAY PUBLICATION TIME CONSIDERABLY TO TRY TO GO DOWN THIS PATH AT THIS LATE STAGE, I SUGGEST THAT WE DO NOT REGISTER THIS PROJECT, BUT BEAR IN MIND POSSIBLY USING PROSPERO IN OTHER PROJECTS.

If not, I recommend doing so. In the first sentence of the Introduction section, cited references (1,2) should be placed at the end of the sentence because the current position has no sense.

WE HAVE DONE THIS

REVIEWER 1 ALSO MADE THE POINT ABOUT MINOR LANGUAGE POLISHING. AS WE NOTE EARLIER ALL THREE AUTHORS ARE NATIVE ENGLISH SPEAKERS, BUT NEVERTHELESS WE HAVE REREAD THE PAPER CAREFULLY TO TRY TO IMPROVE THE ENGLISH, ANY CHANGES MADE BEING EVIDENT IN THE REVISED VERSION OF THE PAPER.

Conclusion: Major revision
Specific Comments to Authors: In this study the authors performed meta-analyses of recent results for acute myocardial infarction (AMI), ischaemic heart disease (IHD) and stroke for North America, Europe and Japan. Some concerns and suggestions are listed as below: Full names of acute myocardial infarction (AMI) and ischaemic heart disease (IHD) should be provided in the title.

WE HAVE AMENDED THE TITLE SO THAT "AMI, CHD" IS REPLACED BY "CARDIOVASCULAR DISEASE", THUS AVOIDING USE OF ACRONYMS . TO KEEP TO THE WORD LIMIT OF 18 FOR THE TITLE, WE HAVE ALSO CHANGED "CIGARETTE, CIGAR, AND PIPE SMOKING" TO "CIGARETTES, CIGARS AND PIPES."

The potential relationship has already been established in the literature. In the part of introduction, the author should mention why this meta-analyses should be performed.

WHILE IT IS CLEAR FROM THE EXISTING LITERATURE THAT SMOKING IS ASSOCIATED WITH AN INCREASED RISK OF THE DISEASES STUDIED, THE INTRODUCTION ALREADY MAKES IT CLEAR THAT THIS IS AN UPDATE OF THE EVIDENCE. TOBACCO PRODUCTS CHANGE OVER TIME, AS DO OTHER FACTORS RELATED TO THE INCIDENCE OF THESE DISEASES.

Why only three regions were included? I wonder if it may cause selection bias.

THE PROJECT WAS RESTRICTED TO NORTH AMERICA, EUROPE AND JAPAN PARTLY TO TRY TO AVOID AREAS WHERE A VARIETY OF OTHER LESS STUDIED TOBACCO PRODUCTS ARE COMMONLY USED, AND PARTLY BECAUSE WE HAVE BEEN CARRYING OUT MODELLING WORK FOR THESE DISEASES IN THESE THREE REGIONS[3-7] AND WISHED TO KEEP OUR RELATIVE RISK ESTIMATES UP TO DATE. WHY THE RESTRICTIONS WERE MADE WAS NOT EXPLAINED IN DETAIL IN THE

TWO EARLIER PAPERS FROM THIS PROJECT WHICH HAVE ALREADY BEEN PUBLISHED[1, 2] AND WE SEE NO STRONG REASON TO GO INTO CONSIDERABLE DETAIL AT THIS LATE STAGE OF THE PROJECT. HOWEVER WE HAVE ADDED EXTRA TEXT IN THE INTRODUCTION. SOME OF IT IS PROBABLY UNNECESSARY AS IF, FOR EXAMPLE, A PAPER REPORTS ON THE RELATIONSHIP OF SMOKING IN THE USA TO HEART DISEASE, ONE DOES NOT USUALLY EXPECT THE AUTHORS IN THAT PAPER TO EXPLAIN WHY THE RELATIONSHIP OF SMOKING IN ANOTHER REGION TO ANOTHER SMOKING-RELATED DISEASE WAS NOT STUDIED.

AS REGARDS SELECTION BIAS, WE ARE NOT CLAIMING THAT OUR RESULTS RELATE TO REGIONS OR DISEASES OTHER THAN THOSE STUDIED, SO WE DO NOT SEE HOW SELECTION BIAS COMES INTO IT.

Any potential differences between developing and developed countries?

SINCE WE ONLY CONSIDERED REGIONS WHICH DID NOT CONTAIN DEVELOPING COUNTRIES WE CANNOT GIVE ANY RESULTS COMPARING DEVELOPED AND DEVELOPING COUNTRIES. HOWEVER WE NOW NOTE IN THE DISCUSSION THAT THERE ARE POTENTIAL DIFFERENCES.

Subgroup analysis should be performed.

TABLES 4, 5 AND 6 ALREADY INCLUDE QUITE EXTENSIVE SUBGROUP ANALYSES. UNLESS THE REVIEWER CAN SUGGEST MAJOR SUBGROUPS WE HAVE MISSED, WE HAVE NOT AMENDED THE PAPER HERE.

Dose-dependent effect of smoking should be performed.

AT THE END OF PARAGRAPH 1 OF THE INTRODUCTION THERE IS A SENTENCE (SIMILAR TO THAT IN THE EARLIER PAPER ON LUNG CANCER AND COPD[2]) SAYING THAT IT WAS NOT THE OBJECTIVE TO INVESTIGATE VARIATION BY FACTORS SUCH AS AMOUNT SMOKED, DURATION OF SMOKING AND TIME QUIT. HOWEVER, THOUGH DETAILED META-ANALYSES RELATING TO THESE FACTORS WILL HAVE TO WAIT UNTIL A POSSIBLE FUTURE PROJECT, WE HAVE EXTENDED THE METHODS AND RESULTS SECTIONS TO REFER TO A BRIEF SUMMARY OF RESULTS RELATING RISK TO AMOUNT SMOKED, THE DATA BEING GIVEN IN A NEW SUPPLEMENTARY FILE 3.

Has this meta-analyses been registered?

NO. SEE OUR ANSWER TO REVIEWER 1 ABOUT REGISTRATION WITH PROSPERO.

Reviewer #3:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: The authors present the results of a systematic review with

meta-analysis of the evidence relating current cigarette, pipe and cigar smoking to the risk of acute myocardial infarction (AMI), ischaemic heart disease (IHD) and stroke, based on 10 studies of AMI, 23 of IHD and 31 of stroke published in 2015-2020 (for North America, Europe, and Japan). The authors found that cigarette smoking increases the risk of AMI, IHD and stroke. Very limited evidence for current cigar and current pipe smoking shows no increase in risk for IHD and stroke, no data being available for AMI. The study is potentially interesting, but can be improved if the following considerations are addressed: 1. Please avoid acronyms in the title of the publication.

AS WE NOTE IN OUR REPLY TO REVIEWER 2 WE HAVE AMENDED THE TITLE SO THAT "AMI, CHD" IS REPLACED BY "CARDIOVASCULAR DISEASE", SO AVOIDING USE OF ACRONYMS AND HAVE MADE OTHER MINOR CHANGES TO KEEP TO THE WORD LIMIT FOR THE TITLE.

2. The authors should indicate that an essential line of research in the future would be precisely the assessment of the evidence relating cigarette, cigar and pipe smoking to stroke in lacunar versus non-lacunar ischemic stroke. This recommendation is because the pathophysiology, prognosis, and clinical features of lacunar strokes are different from other acute cerebrovascular diseases (Int J Mol Sci 2022; 23, 1497). We recommend including and commenting on this reference.

WE HAVE ADDED A PARAGRAPH IN THE DISCUSSION SECTION OF THE PAPER ABOUT VARIATION IN RISK BY TYPE OF STROKE, CITING SOME PUBLICATIONS COMPARING FREQUENCY OF SMOKING IN THOSE WITH LACUNAR AND NON-LACUNAR STROKE. HOWEVER WE HAVE NOT COMMENTED ON THE SPECIFIC REFERENCE CITED BY THE REVIEWER[8] AS IT DOES NOT REVIEW DATA ON SMOKING BY STROKE TYPE.

REFERENCES

1   Lee PN, Coombs KJ and Hamling JS. Review with meta-analysis relating North American, European and Japanese snus or smokeless tobacco use to major smoking-related diseases. *World J Metaanal* 2022; **10**: 130-142. [DOI: 10.13105/wjma.v10.i3.130]

2   Lee PN, Coombs KJ and Hamling JS. Evidence relating cigarette, cigar and pipe smoking to lung cancer and COPD. Meta-analysing recent data from three regions. *World J Metaanal* 2023; **11**: 228-252. [DOI: 10.13105/wjma.v11.i5.228]

3   Djurdjevic S, Lee PN, Weitkunat R, Sponsiello-Wang Z, Ludicke F and Baker G. Modeling the population health impact of introducing a modified risk tobacco product into the U.S. market. *Healthcare (Basel)* 2018; **6**: 47; doi: 10.3390/healthcare6020047. [PMID: 29772688 DOI: 10.3390/healthcare6020047]

4   Djurdjevic S, Pecze L, Weitkunat R, Luedicke F, Fry J and Lee P. Using data on snus use in Sweden to compare different modelling approaches to estimate the population health impact of introducing a smoke-free tobacco product. *BMC Public Health* 2019; **19**: 1411. [PMID: 31664971 DOI: 10.1186/s12889-019-7714-0]

5   Lee PN, Fry JS, Hamling JF, Sponsiello-Wang Z, Baker G and Weitkunat R. Estimating the effect of differing assumptions on the population health impact of introducing a Reduced Risk Tobacco Product in the USA. *Regul Toxicol Pharmacol* 2017; **88**: 192-213. [PMID: 28651854 DOI: 10.1016/j.yrtph.2017.06.009]

6   Lee PN, Djurdjevic S, Weitkunat R and Baker G. Estimating the population health impact of introducing a reduced-risk tobacco product into Japan. The effect of differing assumptions, and some comparisons with the U.S. *Regul Toxicol Pharmacol* 2018; **100**: 92-104. [PMID: 30367904 DOI: 10.1016/j.yrtph.2018.10.010]

7   Rytsar R, Djurdjevic S, Nussbaum AK, Kaul A, Bennewitz E, Lee PN and Fry JS. Estimated public health gains from German smokers switching to risk-reduced alternatives: Results from population health impact modelling. *Contributions to Tobacco & Nicotine Research* 2022; **31**: 35-51. [DOI: 10.2478/cttr-2022-0004]

8   Rudilosso S, Rodríguez-Vázquez A, Urra X and Arboix A. The potential impact of neuroimaging and translational research on the clinical management of lacunar stroke. *Int J Mol Sci* 2022; **23**: 1497. [PMID: 35163423 DOI: 10.3390/ijms23031497]