Author’s response to reviews

Title: Smoking, dementia and cognitive decline in the elderly, a systematic review

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Version: 2 Date: 17 July 2008

Author’s response to reviews: see over
Dear Melissa,

Please find enclosed the revised manuscript entitled ‘SMOKING, DEMENTIA AND COGNITIVE DECLINE IN THE ELDERLY, A SYSTEMATIC REVIEW’.

This topic is important as it provides further information on the prevention of dementia and cognitive decline. With dementia being particularly high profile at the moment, we feel that this article would be of particular interest to the readers. This is a key update to the recently published meta analysis, with our most significant finding being the relationship between smoking and Alzheimer’s disease.

We appreciate the extra time given to us to revise the manuscript. We have addressed the reviewer’s comments and made some changes to the manuscript; details of these follow. Our responses and changes to the manuscript are written in red.

We look forward to hearing your comments.

Yours sincerely,

Ms Ruth Peters
on behalf of the authors
Reviewer’s report
Title: Smoking, dementia and cognitive decline in the elderly, a systematic review
Version: 1 Date: 18 March 2008
Reviewer: Danielle Laurin

Reviewer’s report:
Major Compulsory Revisions:
1) Given the fact that a meta-analysis covering the association between smoking and dementia or cognitive decline was recently published in the American Journal of Epidemiology by Anstey et al (2007), the authors should provide a better justification to why they propose to replicate a similar exercise except for more recent data.

We feel that more recent data is a good reason, plus, the use of different databases and search terms. It reinforces the previous message but the constituent studies are not all the same due to the different databases and search terms used. In fact we did not replicate their exercise but were working in parallel finishing a little later than they did.

2) According to the method, all searches were limited to subjects aged 65 and over, but when you look at table 1, subjects aged <65y at baseline were included in several studies (references 22-23, 25, 29-30, 36, 38, 44-45). Please explain.

Some of the longitudinal studies had run for tens of years and did not start in those >=65, however, we aimed to examine the impact of former and current smoking in those aged >=65 at the time of dementia/follow up assessment– we calculated as best we could that the assessments of dementia and cognitive decline all occurred in those aged >65. We refer to this on page 7.

‘Not all studies gave a clear indication of participant age at baseline with some reporting mean age, some minimum age and some age range. Despite this, when taking the available data regarding baseline age and follow up time into account mean age at follow up seems likely to be 65 or over.’

We previously stated in the method that ‘All searches were limited to subjects aged 65 and over in accordance with the limits allowed by each search engine’ …we have changed this to read ‘All searches were limited to the search engine pre-defined limits of subjects aged 65 and over’

We hope that this helps to explain and clarify this issue.

3) Smoking status: The authors provide results for the association between current smoking and dementia or cognitive decline. For having done CSHA statistical analyses (reference 47: Lindsay et al, 2002), our results corresponded to ever (current and past) smoking (including pipe and cigar). These results are included in the present meta-analysis as current smoking, which is false. In addition, as mentioned in reference 47, data for smoking were available for 3973 subjects of the 4615 (as specified in table 1) included in the core analysis. The authors of the meta-analysis should have contacted directly the authors of all papers included in the meta-regression in order to clarify correctly the information pertaining to smoking exposure or study sample.

Thank you for spotting this, we have changed the number of participants in table 1. As the paper is relevant we have kept the study in our review but have excluded it from the meta analysis. Unfortunately it was not possible to contact each author due to lack of resources – we sought to review the published literature.

4) Results should be discussed in extensive details.

We are unsure what is required here – we have tried to present the results in full, the basic findings, meta-analyses, methodological issues including constituent study design and outcome and provided a table with the key points relating to these studies.

5) In page 6, the authors mentioned that “Measurements of heterogeneity were not significant with the exception of that for AD with current smoking”, but they don't mention what they did for this particular case.
The summary ratios for measurements of heterogeneity for all four outcomes are listed above for both current smokers vs never/non-smokers and ex smokers vs never/non-smokers. We have added the following to the discussion. "Although only one of our meta-analyses was significant in measures of heterogeneity there remain methodological issues inevitably associated with combining several different studies and the flaws inherent in those studies themselves, however, it seems clear that current smoking may be a risk factor for the most common dementia, Alzheimer’s disease.”

6) Reference 45 includes prevalent cases of dementia. This study should not be considered for the meta-analysis including only incident cases.

This reference looks at mid life smoking and late life dementia. Although they use the term prevalent cases at exam 4, they were not prevalent cases at the time of collecting smoking information. Therefore we would see these subjects with dementia as being incident cases.

Minor Compulsory Revisions:
1) Page 2, line 8: “Although the smokers did die earlier”. Is this sentence supposed to be part of the sentence before?
   Yes, we have re-phrased this to make it clearer:
   “The smokers however, did die earlier.”

2) Page 3, 2nd paragraph, 2nd line: the review was published in 2007
   Changed to 2007.

3) In table 1: please provide the proportion of men and women. For reference 42, we don't have the information on age at baseline (or follow-up). Diagnostic criteria should be reported in the table.
   As proportion of men and women is not available for all studies we have not included it. For reference 42 this information is not quoted in the paper.
   Diagnostic criteria now added to table 1.

4) In figure 4, how come the square of reference 30 overlaps the value of 1, since the lower CI is 1.03.
   This is how it is plotted by the statistical software – we have adapted the figure.

5) What is the quality assessment used by researchers? This result should be added in table 1. We used the standard guidelines (those recommended by the BMJ http://www.equator-network.org/index.aspx?o=1052) and referenced them – they do not result in a scoring system but rather are guidelines – in the text this is mentioned on page 4
   "Studies were quality assessed by both researchers in accordance with the guidelines presented by Stroup et al for the reporting of meta-analyses of epidemiological studies [21].”

We feel that to detail each point mentioned in the guidelines would make the table too long.

6) Please define the summary ratios in page 5: OR or RR? These are summary ratios generated from the constituent studies where different ratios were reported. They are not defined as either OR or RR.

7) Page 11, last sentence: please rephrase: "Further studies are clearly although smoking is clearly not an advantageous way to test this”.
   The word ‘required’ has been added.

Discretionary Revisions:
1) Please write:
   -Alzheimer's disease with a small D throughout the text.
   -Idem for vascular dementia (with a small V)

Done – only exception is where Alzheimer’s Disease refers to an abbreviation (/Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA])

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of limited interest
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: I declare that I have no competing interests.
Reviewer's report
Title: Smoking, dementia and cognitive decline in the elderly, a systematic review
Version: 1 Date: 19 February 2008
Reviewer: Chengxuan Qiu

Reviewer's report:
Evidence from prospective longitudinal studies has been increasing over the last decade that smoking may be a risk factor for dementia and Alzheimer disease. This systematic review is another effort trying to make conclusions on the relationship between smoking and dementia and cognitive decline by summarizing the evidence from the longitudinal studies. The topic is relevant for public health and for dementia prevention in particular.

-- Major Compulsory Revisions

Background
1. The Authors are encouraged to shift their focus in the "Background" section from biological mechanisms (nicotine receptors) and retrospective (case-control and cross-sectional) studies to the specific issues (smoking as a risk factor for dementia, subtype dementias, and cognitive decline from longitudinal and prospective studies), which they are going to address in this review.

Additional comment relating mechanisms to dementia and smoking in a wider population sense has been added to the discussion to balance the paper.
2. The purposes of this review should be clearly specified.

The following sentence has been added:
"Our review was aimed to examine the relationship between smoking, dementia and cognitive decline in an elderly population."

Methods
1. What are the inclusion criteria of literature used for this review? This is described in the method in chronological order. We searched on the terms ‘smoking’ and ‘dementia’ or ‘vascular dementia’ or ‘multi infarct dementia’ or ‘Alzheimer’s disease’ or ‘cognitive impairment’ or ‘cognitive decline’ and included subjects aged 65 or older, we only used longitudinal studies that occurred between 1996 and November 2007.

2. In the section of "Methodological issues", the Authors are very much critical of many individual studies they reviewed in terms of the "Study design" and definition of "Outcome". This may raise the question about the quality of the studies included in this review, and thus, about the validity of conclusions drawn by this review.

We wanted to state the differences between the studies and how we had dealt with them. We feel the way we dealt with them does not compromise the validity of the conclusions.

Conclusions/Discussion
1. The Authors may want to explain what the differences between this review and the previous meta-analysis are. It is also important to explicitly specify what additional information this review could provide, compared with the latest meta-analysis of the same topic (reference no. 20), and why this review is still imperative and relevant.

As stated in paragraph 2 “The meta-analysis reported here focused on the last 10 years of published literature up until November 2007 and included the database Embase whereas the most recently published analysis [20] omitted Embase but included ‘Cochrane CENTRAL’ and reported on older literature until June 2005. Although we chose to include more recent literature, less and different search terms and arguably wider inclusion criteria it is interesting to note that our findings are broadly in support of theirs and
strengthening the conclusion that current smoking is likely to increase risk of incident dementia particularly Alzheimer’s disease.”

-- Minor Essential Revisions
1. Carefully editorial revisions throughout the manuscript are recommended.
Here are a few examples, on page 2, One of the difficulties with are
(is). Former smokers had lower risk that (than)
current Seven studies (??) a significant; on page 8, but those who (that??) did found (find)
Corrections made, see text highlighted in red.
2. The sentence starting No studies found on page 5 can be deleted.
We felt it was important to state all our findings.
3. The sentence in the bottom lines of page 6 is unclear.
Sentence revised.
-- Discretionary Revisions
No comments.

What next?: Unable to decide on acceptance or rejection until the authors have
responded to the major compulsory revisions
Level of interest: An article whose findings are important to those with closely
related research interests
Quality of written English: Needs some language corrections before being
published
Statistical review: Yes, but I do not feel adequately qualified to assess the
statistics.
Declaration of competing interests:
I declare that I have no competing interests.

Reviewer’s report
Title: Smoking, dementia and cognitive decline in the elderly, a systematic
review
Version: 1 Date: 8 April 2008
Reviewer: Jose A Luchsinger
Reviewer’s report:
This is an interesting metaanalysis of studies relating smoking to dementia.
Major comments:
the discussion does not have comments on potential mechanisms explaining the
associations. Is smoking causative of Alzheimer’s disease, is it a precipitant, is
this association mediated through cerebrovascular disease? Although this
cannot be addressed directly with the data, some discussion can be done
based on existing literature.
We have added further information to the discussion:
“These findings fit with other evidence of smoking as a risk factor for cardiovascular and cerebrovascular
disease, stroke, silent infarction, increased oxidative stress, atherosclerosis and inflammation all of which
may impact negatively on cognitive functioning and dementia incidence [50].”
Minor comments
In page 7 there is the following statement “For the publications from the
Washington Heights data set, the cohort analysis reporting possible or probable
Alzheimer’s disease was used in preference to the case control analysis
incorporating Alzheimer’s disease”...this statement is confusing. Are you saying that this study reported both a cohort and a case-control analysis (not the case, it reported only cohort analyses).

We found two publications on this and used only one. Sentence changed to “Of the two publications…”

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
'I declare that I have no competing interests'