Author’s response to reviews

Title: Epidemiologic studies of modifiable factors associated with cognition and dementia: Systematic review and meta-analysis

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Author’s response to reviews: see over
**Response to Reviewers:**

**Reviewer 1 report:**
This is a well-designed and conducted review of the current evidence of the association of modifiable factors with cognitive function and dementia. Its strength is in its comprehensive examination of the literature and explanation of hypothesized mechanisms of the association.

**Response:** Thank you! We greatly appreciate this positive feedback!

Major revisions
There are, however, some potential weaknesses in the paper that I would like the authors to discuss.

1. The search database only included Medline. Although PubMed encompasses a very wide range of literature. It is not all-inclusive.

**Response:** We appreciate this comment. We have added this among our limitations and explained further limiting the choice of the database as follows:

"First, the literature search was limited to published articles in English available in the Medline database, thus excluding other databases and non-English language literature."

2. Did the authors use only articles in English? If so, this could have contributed to some bias in the reported findings.

**Response:** Yes, that is correct. We also have added this as a potential limitation in the discussion section in the above statement.

3. The study selection criteria, mainly consisting of a sample size of over 300, may have been a bit too lenient. Studies vary greatly in quality and use of some standardized quality guidelines may have helped to delineate studies of high quality and reliability.

**Response:** We appreciate this comment. We have thought about including measures of study quality. However, since we have many different exposures that we are studying sample size and other measures of quality may differ given the samples size of studies within each exposure may have differing standards compared to other exposures (e.g. studies with blood sample exposures are usually smaller than studies using questionnaire measurements). However, we thought that a sample size of 300 would be a reasonable cutoff to choose and have relatively precise estimates effects in well-powered studies. We added a related statement in the discussion as follows:

"Finally, our study was limited by the inability to create a common quality measure for all studies given the diversity of the exposure variables and the relative importance of having a large sample size given the type of exposure (e.g. a larger sample size is needed for a questionnaire-based exposure vs. a blood level based exposure)."

4. For conducting meta-analysis, dichotomization of physical activity was performed. However, how did the authors decide on the “comparability” of the different definitions used by various studies?

**Response:** We added a statement in the discussion regarding this choice which is detailed in the footnote of each of the forest plots. The statement is as follows:
“However, the datapoints that were included in the meta-analysis were relatively comparable and the definition for each cutoff used or type of measurement are delineated in footnotes of Figures 3A-3E. ”

Level of interest:
An article of outstanding merit and interest in its field

Quality of written English:
Acceptable

Statistical review:
No, the manuscript does not need to be seen by a statistician.

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

Reviewer 2 report:

Authors systematically reviewed 247 studies on modifiable socio-economic status (education), behavioural (smoking, alcohol, physical activity), and nutritional (caffeine, antioxidants, homocysteine (Hcy), n-3 fatty acids) risk/protective factors of various cognitive health outcomes, including incident Alzheimer’s Disease (AD). They found that each risk factor suggested positive findings ranging from about 39% for caffeine to 90% for physical activity. Education also had a significantly higher propensity for “a positive finding” compared to caffeine, smoking and antioxidant-related studies. Meta-analysis of 31 studies with incident AD yielded pooled RR for low education, high Hcy, and current/ever smoking status while indicating protective effects of higher physical activity and n-3 fatty acids. Estimated PAR% were particularly high for physical activity and smoking. Overall, no significant publication bias was found. Higher Hcy levels, lower educational attainment, and decreased physical activity were particularly strong predictors of incident AD. Further studies are needed to support other potential protective modifiable factors, such as caffeine. This is an interesting report with systematic and meta-analysis on modifiable risks. This is an important question to address at this time point as there are numerous studies being published and consensus report/analysis helps to formulate current opinions. The study appears well performed with use of sound methods and appropriate analysis. It is not surprising that low level of education is a risk for cognitive impairment. This the case even in LMIC.

Response: Thank you! We greatly appreciate this positive feedback!

Attention to some format and stylistic comments would improve this excellent report.

Response: Done.

Authors can improve the report by separating the results and discussion sections. There is no reason for these to be together as they too the trouble to go through all the analyses and then weave their findings with discussion? Clear statements on their findings would be helpful to the interested reader.

Response: Done.
The Discussion would be curtailed and made more succinct. Without necessarily expanding the Discussion section authors could also briefly highlight the common shortfalls of some of the previous studies.

**Response**: We appreciate this comment. However, because of the diversity of the studies and exposure variables, it would be very difficult to list those limitation in a succinct way. However, we have added further limitations of the review and meta-analysis itself based on reviewer 1’s comments. We have revised the discussion to reduce its word count and make it more succinct.

Abstract: some clarifications and brevity could improve it. For example, why equate education with socio-economic status why not say education?

“We systematically reviewed selected modifiable factors such as education, smoking, alcohol, physical activity, caffeine, antioxidants, homocysteine (Hcy), n-3 fatty acids that were studied in relation to various cognitive health outcomes, including incident Alzheimer’s Disease (AD).”

The concluding paragraph (page 27) should be re-written with clear direct statements. There are several convoluted and confusing sentences e.g.

“...consistency analysis and meta-analysis indicate....a wide range of consistency in findings...”. Avoid phrases in parentheses for better flow.

“In conclusion, our systematic review, analysis of consistency between studies and meta-analysis to obtain pooled measures of association yielded the following key results: First, consistency between studies of findings varied for each selected risk or protective modifiable factors (highest for physical activity). Second, a moderate to strong association between some selected factors and incident AD was found (strongest for low education and elevated Hcy).”

There are a few typos e.g. abstract “various”. Authors should proof read the manuscript.

**Response**: Done.

Level of interest:
An article of importance in its field
Quality of written English:
Acceptable

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

Declaration of competing interests:
No conflicts of interest

Additional Editorial Request:
1.) The Background section of Abstract needs context information.
Response: We expanded the background part of the abstract to:

“Cognitive impairment, including dementia, is a major health concern with the increasing aging population. Preventive measures to delay cognitive decline are of utmost importance. Alzheimer’s disease (AD) is the most frequent cause of dementia, increasing in prevalence from less than 1% below the age of 60 years to more than 40% above 85 years of age.”

2.) PRISMA guidelines

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