Peer-Review comments and authors responses

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Authors:

"**Dear Professor Fregni,** the authors acknowledge the contribution of the reviewers and faculties comments to the process of clarifying and enhancing specific topics in the manuscript. The authors have considered the reviewer's comments and incorporated these observations as changes to a revised manuscript. Modifications and additions are highlighted in red in the revised manuscript. Below you can find the answers to the reviewers' comments as well as exact changes made in the manuscript.

Regards,

The authors"

COMMENTS:

Reviewer #1: "In the manuscript the relationship between physical activity (PA) levels and memory problems in adults aged 50 to 85, leveraging data from NHANES 2005–2006 is explored. The authors provide a comprehensive assessment of the impact of physical activity across various age groups and highlight the role of modifiable lifestyle factors in mitigating memory decline. Proposed paper shows a good quality of writing, clear, logical structure and well-organized content. The methodology and results are detailed and presented effectively. Authors supported the discussion by existing literature. There are minor areas where greater conciseness or precision could enhance readability."

Response: Dear Reviewer, we appreciate your feedback. We checked the manuscript writing to improve the clarity.

Comment 1: "The manuscript is on an important and relevant topic. The findings contribute valuable insights regarding preventive strategies for cognitive decline in middle-aged and older populations. However, the cross-sectional nature of the study limits its ability to establish causality, which slightly diminishes its broader impact. In terms of limitations authors based the manuscript on self-reported data, which, as is well known, depends on subjective measures (e.g., self-reported memory problems or levels of physical activity). This approach may introduce biases and inaccuracies. However, at this stage, using these datasets limitations has to be accepted, perhaps this could be recommended as a direction for future development or continuation of the research in this area?"

Response: Thank you very much for your comment. We agree with the raised point. We have acknowledged this limitation under its respective subsection and added this as direction for future research in this specific field.

Comment 3: "Also, different factors, such as dietary habits, metabolic health, and genetic predispositions, are not considered but could potentially influence memory problems. Moreover focus on USA population restricts generalizability of other cultural/geographical regions."

Response: Thank you for your observation. We agree with you that there are other important factors that could account for memory issues. However, the database does not provide genetic information and the dietary variables do not account accurately for the dietary habits and also possess a lot of missing data.

Comment 4: "What could also be interesting is identifying the association between mechanisms of how physical activity affects memory problems (taking into account different age groups)."

Response: Thank you so much for your comment. We added some of the mechanisms behind that may explain the physical activity and memory.

Comment 5: "It could be interesting to address wider obtained results e.g. to answer the question like why the age group 65+ showed weaker association in comparison to middle-aged."

Response: We appreciate the comment to improve the clarity of the association. In the unadjusted model, being less active showed twice higher odds in the middle age population and in elderly population being less active represented 67% higher odds of presenting memory issues (p<0.005). However, after adjusting the model with the confounders, in both cases being less active have no significant relationship with memory issues. Interestingly, when assessing the age as an effect modifier, the interaction effect was only significant in the middle age group.

Comment 6: "Regarding novelty, the manuscript reinforces existing knowledge on physical activity and cognitive function."

Response: The authors appreciate your acknowledgment of the novelty of the present study.

Comment 7: "Exploration of age-related trends and inclusion of a comprehensive age range in the study population adds some originality, even though it needs to be said that the topic itself is widely studied."

Response: Thank you so much for the suggestion. We agree to clarify this.

Comment 8: "Some suggestions for improvements/ further research would be to use validated tools for assessing memory (e.g., neuropsychological tests) and physical activity (e.g., accelerometers) which would improve validity of the study. Try to expand the field and search for other variables, such as dietary patterns, metabolic conditions, and genetic factors that could provide a more comprehensive understanding of memory problems."

Response: Thank you for this comment. We agree to add the inclusion of these fundamental factors.

Comment 9: "Also it would be worth conducting a similar analysis but on diverse populations which would improve the external validity of the study."

Response: Thank you for your valuable suggestion, we agree to include the suggested analysis to improve the external validity.

Comment 10: "In conclusion, it's a well written logically structured manuscript that has the contribution to understanding the role of physical activity on memory problems in different age groups. While the study has limitations, findings serve as a solid foundation for future research exploring the relationship between physical activity and cognitive health of different age groups."

Response: Dear Reviewer, thank you for your comments. We changed the conclusion, as a suggestion from Reviewer 2.

Reviewer #2:

Reviewer: The manuscript is generally well-written, with clear descriptions of methods, results, and implications. However, some sentences would benefit from further editing. The study addresses a significant public health issue—memory decline in older adults—and explores the relationship with physical activity, an accessible intervention. Attached you can find the word doc. with the specific comments, suggestions and also some minor grammar corrections. Below is a summary of the revision:

Response: Thank you very much for your insightful comments. We accepted all the suggestions you added in the word doc, they are highlighted in red in the respective document.

1. "Introduction: Please add references where they are missing."

Response: We added the reference "(Zlotnik & Vansintjan, 2019)", "(Mammen & Faulkner, 2013)" to the revised manuscript.

2. "The gap in research is well-stated, but the aim should clearly highlight the novelty of examining age as an effect modifier.

Response: Thank you very much for your comment. We addressed your valuable input in different parts of the manuscript including the introduction and discussion, which are highlighted in red in the revised manuscript.

3. Methods: "The justification for categorizing age into three groups should be stronger, perhaps by citing similar studies or demographic reasons."

Response: Thank you so much for your comment. We have added the rationale behind the age group categorization in the methods section, highlighted in red.

4. Discussion:

"This section should be more focused. The first two paragraphs reiterate known literature without sufficiently connecting to the findings. You could introduce your findings immediately and then integrate with literature. That would help the reader to better contextualize the results. For example: "This study demonstrated that lower physical activity levels are significantly associated with higher odds of memory problems among adults aged 50 to 85, with the most pronounced association observed in the middle-aged group (50–64 years). These findings align with previous studies showing that physical activity can slow cognitive decline and improve memory (Mammen & Faulkner, 2013). Notably, the strong association in the middle-aged group suggests that this period might represent a critical window for the protective effects of physical activity, requiring additional investigation.""

Response: We appreciate your help to improve the discussion structure. Your suggestions were considered and included in the text.

"Finally, please underscore that interestingly, while the association was strongest in the middle-aged cohort, it weakened in the elderly group (65+) and please provide a possible explanation of that. To strengthen this section, consider addressing the following questions, which may help clarify why the association was stronger in the middle-aged group:
Is the cumulative lifetime impact of physical activity a reason for the weaker association observed in the elderly group? Which specific age-related factors could diminish the benefits of physical activity in the elderly? Could differences in physical activity intensity or type across age groups account for the observed variation? Are there other lifestyle factors in later life, such as diet or comorbidities, that might mediate or weaken the association? How might the timing of physical activity (e.g., early-life vs. midlife engagement) influence its protective effects in older age?"

Response: Thank you so much for your comments on highlighting evidence from previous studies and explaining age-group differences. We have expanded our discussion to incorporate these elements and address the suggested questions about age-group differences.

5. References: "Please highlight your build on evidence from Mammen and Faulkner (2013) and Ruscheweyh et al. (2011), which highlighted the protective role of physical activity in preserving memory. Then highlight that however, your study underscores the importance of assessing physical activity's effects across age groups."

Response: Thank you very much for your comment. We added the pertinent discussion on the evidence from Mammen and Faulkner (2013) and Ruscheweyh et al. (2011) and contextualized the present study as suggested in the first paragraph of the discussion.

6. Limitations: "Address limitations more explicitly. For example, discuss how reliance on self-reported physical activity and memory issues might introduce

bias. Consider including a brief discussion on how future studies could use objective measures (eg. Wearables for activity and validated memory tests)."

Response: Thank you for your comment. We agree with the point made by Reviewer 2. We have expanded the limitations subsection of the discussion to address them more explicitly, as suggested.

9 - Conclusion (also valid for the abstract): "should avoid overgeneralizing the findings. Specify that results are based on self-reported data."

Response: Thank you very much for your comment. We have expanded our limitations section and revised both the abstract and conclusion to be more specific about the nature of our data and findings.

Coaching Meeting - Ben M.W. Illigens - November 21st:

1 – "Address the immortal time and recall bias."

Response: Thank you for your comment. Immortal bias is a concern in observational studies where the timing of events or exposures matters, like a longitudinal or cohort studies. However, in a cross-sectional study, it is not typically relevant because these studies capture data at a single point in time. On the other hand, recall bias is particularly important in cross-sectional studies, this can be a potential source of bias.

2 – "Older people take more medications so it can have an effect on sleep disorders. Why don't we go with sleep disorder as a variable?"

Response: Thank you for your comment. We are agree with you, so we added this variable.

3 – "Stroke history in the study showed no significance, but this is wrong. Previous literature found the relationship between memory loss and stroke. Should you keep it in the analysis."

Response: Thank you for your comment. We agree with you, so we included this variable.

4 – "How representative NHANES is? It is only for the US population, does not include Hispanics or other. Describe the ethnicity and the bias introduced because of this."

Response: Thanks for your comment. Now we add a section in the discussion topic that specify the limitation of the external validity due to the use of NHANES database

5 – "Add units (ex - age in years) in table 2."

Response: Thank you for your comment. Now the table has the appropriate units.

6 – "Variable age: in Table 1 there are 4 categories and in tables 2 there are 3 categories, please explain why."

Response: Thank you for your comment. Now we merged both tables, and we keep with 3 categories: young, middle age and elderly.

7 – "Add a Mantel-Haenszel graphic, if possible."

Response: Thank you very much for your comment. We have considered your intelligent suggestions. We have presented the findings in a more appropriate way that approximates to the clarity transmitted by a Mantel-Haenszel plot.

8 – "Explain why PHQ was used for depression."

Response: Thanks for your comment. PHQ9 is a very useful and valid tool for assessing depression. We use this test because of its simplicity, reliability and focus on core depression symptoms.

9 – "Table 1: bring more clarity, make it more clean."

Response: Thank you for your comment. Now table 1 is modified to be cleaner and understandable.

10 – **"**Why do you describe the population as elderly, but analyze 20-85 years?"

Response: Thanks for your comment. We think it is very important to have a baseline population from which we are going to compare other populations. So first we converted age as a category variable. And the young population (20-}49 years) was used as a baseline

Coaching Meeting - David Wypij - November 21st:

1 – "In table 1 there is a lot of text, not full sentences, you need to put the ideas in bullet points and reduce the words."

Response: Thank you for your comment. We now have modified and summarized the content in table 1.

2 – "Too many decimal places, change one space after the decimal in the percentages. Number and then the percentage."

Response: Thank you for observation, the decimals were changed in all the presented values in table 1.

3 – "Why do you have age in continuous and categorical? In table 1 it has to be categorical, because you have it in the regression."

Response: In the adjusted model, the age was included as a continuous variable, but to assess the effect modification it was used as a categorical variable, for a better appropriate interpretation with the categorical exposure.

4 – "Education level, you need to put the ends (order the format, is confusing)."

Response: It was corrected in table 1.

5 – "History of stroke and alcohol consumption does not align with sleep disorders (change the format - change the style)."

Response: It was corrected in table 1.

6 – "Put the zero in the table, not a space."

Response: It was removed, thank you.

7 – "Address missing data for the results in table I (in less active and more active)."

Response: Thank you so much for your comment. We have carefully considered your astute suggestions. We have revised table 1 to present our findings in a more clear manner.

8 – "In Table 2, it has too many decimals in OR and P value (not put zero instead put < 0.001)."

Response: We have discuss in the group and decided to remove the table 2 and mentions the main findings in the text

9 – "Change the objectives and put those variables first like activity and then the others (put the primary covariates first)."

Response: Thank you for your suggestion, we have included the changes

10 – "The confounders are not confounders, they are significant predictors or independent predictors."

Response: In this specific case, we are in an explanatory study, not a predictive study, in thus those factors may behave as confounding variables. Additionally, there is literature that supports the association between those factors and the outcome. We discussed in the manuscript.

11 – "Methods and objectives were good."

Response: Thank you for your comments. We really appreciate your insightful review

12 – "You need to put the categorical age in the table because there is no relationship with the image."

Response: Thanks for your comment. The variable age is categorical now

13 –" Put the 20 to 49 patients (youngest group) to compare it with the older patients."

Response: It was added in the table 1.

Poster Presentation Suggestions:

1 – "Age as confounder is not clear."

Response: We have revised the poster, and it was removed and leaved as a possible effect modifier.

2 – "What happened with the high level of physical activity on table 1?"

Response: We combine the same activity level and higher activity level in the same category while less activity level remains separate, because as this a subjective self reported data, it could be difficult to differentiate the level between equal or more active level.

3 – "Table is very small, and there is no clear information. We suggest making it more clear or change to graphics is possible?"

Response: Thank you so much for your comment. Table 1 is much more clear and improved now, with its size adjusted as well, as suggested.

4 – "Poster: change introduction to bullets; address missing data; OR only one decimal; add in the graphic 20-49 years in the baseline."

Response: The suggested changes were addressed in the corresponding poster section