**Review history of manuscript 457 “Relationship between Persistent Dizziness and Markers of Alzheimer's Disease”**

**Reviewer 1.**

This research manuscript, entitled " Relationship between Persistent Dizziness and Markers of Alzheimer's Disease – Mayo Clinic Study of Aging", is timely, well researched, thoroughly documented and cited, and well written. This article aims to discuss the relationship between persistent dizziness and Alzheimer's disease (AD) markers among an important number of 924 individuals. There is nothing that I could add in terms of edits that would significantly improve the manuscript.

**Reviewer 2.**

1. Is it scientific to select and use anxiety and depression scales? Why not HAMA, HAMD, SDS, PHQ9 and GAD7?

2. Although MRI and PET are widely used in clinical settings, there is some controversy over slight changes.

3. Kaplan-Meier method is the most basic single factor, and I cannot see the original diagram.

**Reviewer 3**

Dear editor, I have found two preprints of this manuscript on the research square website. Both of them had a little difference from the present manuscript. The present manuscript needs a major modification. Following are the comments to the author.

Razan Al Fakir had studied the relationship between persistent dizziness and the Alzheimer’s disease markers using 924 individuals aged ≥50 years selected from 5707 individuals who participated in the population-based Mayo Clinic Study of Aging. The results indicated that there was a significant association between persistent dizziness/lightheadedness and depression/anxiety, and Amyloid-β deposition. However, the methods and discussion sections are poor and sometimes confused. Detailed comments are listed below:

Major points

1. The “Markers of Alzheimer's Disease” in the title and abstract should be given a detailed description.

2. The introduction section was kind of disconnected.

3. The “AD markers” should be stressed in the introduction or methods section. The author needs to explain which AD markers were used in the beginning of the manuscript.

4. In Table3, some confused points:

(1) The mean (SD) of Beck depression inventory in the 3rd years was 4.6 (4.7) and was not significant when compared to the baseline which was 5.0 (5.1).

(2) The mean (SD) of Beck depression inventory in the 7th years was 5.0 (4.9) and was significant when compared to the baseline which was 5.0 (5.1).

(3) The mean of Attention/executive z-score in the 10th years was 0.9, while others were all below zero.

(4) The mean (SD) of Visuospatial skills z-score in the 10th years was -0.3 (1.0) and was significant when compared to the baseline which was -0.3 (1.1).

5. There was an “a” after the SD of Amyloid-β deposition in the 10th years without any explanation.

6. In the discussion part,

(1) The first paragraph, the author stated that “This implies that the underlying AD biology may drive both the neuropsychiatric symptoms (depression and anxiety) and persistent dizziness or lightheadedness...”. However, as indicated in the results section, there was a significant association between persistent dizziness and depression/anxiety, and between persistent dizziness and amyloid-deposition, respectively. There is no result supporting the association between amyloid-deposition and persistent dizziness in the manuscript. So the description that “the underlying AD biology may drive both the neuropsychiatric symptoms (depression and anxiety) and persistent dizziness or lightheadedness” was inappropriate.

(2) The second paragraph, the author discussed the association between depression and AD pathology. But the focus of the manuscript is the relationship between persistent dizziness and the Alzheimer’s disease markers. That was confused and please explain the reason.

(3) In addition, the author also discussed the central and peripheral dizziness in the last sentence of the paragraph and the third paragraph. The author explained that persistent dizziness might be central dizziness, which may be the difference from the study conducted by Kamil et al. I think it need more lines to discuss dizziness and AD pathology or cognitive deficits.

Minor points

1. The statistical analysis section should be improved and given more detail. For example, the statistical methods described in the second paragraph of the results section could be moved to the methods section.

2. In conclusion section, the sentence should be corrected, it is “After adjusting for age, sex, education, medical comorbidities, and other variables, a statistically significant association between persistent dizziness/lightheadedness and neuropsychiatric symptoms, and Amyloid-β deposition.”

**Response from the author.**

**Thanks for the reviewers’ comments. They are very constructive.**

**Reviewer 1:**

Major points

1. The “Markers of Alzheimer's Disease” in the title and abstract should be given a detailed description.

I agree. The title is changes to: Association of Persistent Dizziness or lightheadedness with Neuropsychiatric Symptoms and Amyloid-β plaque Deposition Among Aging Population

1. The introduction section was kind of disconnected.

I agree, I modified the introduction to be more fluent

1. The “AD markers” should be stressed in the introduction or methods section. The author needs to explain which AD markers were used in the beginning of the manuscript.

Done and considered in the introduction

4. In Table3, some confused points:

(1) The mean (SD) of Beck depression inventory in the 3rd years was 4.6 (4.7) and was not significant when compared to the baseline which was 5.0 (5.1).

(2) The mean (SD) of Beck depression inventory in the 7th years was 5.0 (4.9) and was significant when compared to the baseline which was 5.0 (5.1).

(3) The mean of Attention/executive z-score in the 10th years was 0.9, while others were all below zero.

(4) The mean (SD) of Visuospatial skills z-score in the 10th years was -0.3 (1.0) and was significant when compared to the baseline which was -0.3 (1.1).

All values in Table 3 were re-reviewed.

1. There was an “a” after the SD of Amyloid-β deposition in the 10th years without any explanation.

“a” was removed.

6. In the discussion part,

(1) The first paragraph, the author stated that “This implies that the underlying AD biology may drive both the neuropsychiatric symptoms (depression and anxiety) and persistent dizziness or lightheadedness...”. However, as indicated in the results section, there was a significant association between persistent dizziness and depression/anxiety, and between persistent dizziness and amyloid-deposition, respectively. There is no result supporting the association between amyloid-deposition and persistent dizziness in the manuscript. So the description that “the underlying AD biology may drive both the neuropsychiatric symptoms (depression and anxiety) and persistent dizziness or lightheadedness” was inappropriate.

Modified

(2) The second paragraph, the author discussed the association between depression and AD pathology. But the focus of the manuscript is the relationship between persistent dizziness and the Alzheimer’s disease markers. That was confused and please explain the reason.

Modified

(3) In addition, the author also discussed the central and peripheral dizziness in the last sentence of the paragraph and the third paragraph. The author explained that persistent dizziness might be central dizziness, which may be the difference from the study conducted by Kamil et al. I think it need more lines to discuss dizziness and AD pathology or cognitive deficits.

Modified

Minor points:

1. The statistical analysis section should be improved and given more detail. For example, the statistical methods described in the second paragraph of the results section could be moved to the methods section.

Done

1. In conclusion section, the sentence should be corrected, it is “After adjusting for age, sex, education, medical comorbidities, and other variables, a statistically significant association between persistent dizziness/lightheadedness and neuropsychiatric symptoms, and Amyloid-β deposition.”
2. Modified

**Reviewer 2:**

1. Is it scientific to select and use anxiety and depression scales? Why not HAMA, HAMD, SDS, PHQ9 and GAD7?

The data collected based on the MCSA protocol. The Beck Depression index and Beck Anxiety index are well accepted scales in clinal practice and research

1. Although MRI and PET are widely used in clinical settings, there is some controversy over slight changes.

I agree, but the study will open a new window for research in this area.

1. Kaplan-Meier method is the most basic single factor, and I cannot see the original diagram.

Added

**Additional concerns from the editor for Manuscript 457**

We thank the author for the revised manuscript, but the concerns and suggestions have only partially been addressed. Please consider the following points.

1. It appears data from both males and females were pooled. Does the author have data providing the rationale to pool the data? In other words, was an analysis actually done to see if there were any gender differences related to any of the factors? If this was not done, we will not be able to publish the manuscript as currently presented.

2. There is still confusion about how participants were classifed with dizziness. First of all, demographics (including table 1) are not results and should be in the Methods section. Secondly, it is stated that participants were categorized into three themes: normal, vestibular dysfunction, and unexplained dizziness. What group was used to make the correlation analyses?

3. There is now confusion about the follow up time. Was it 10 years or 14.5 years?

4. The data is still not presented in the text in any meaningful way with logical explanations.

5. Figure 1 has low resolution and cannot be published as is. We suggest Figure 1 be deleted and results simply stated in the text.

6. Questions regarding Table 3 have not been addressed. On further consideration, is Table 3 really necessary? Were these factors really used to determine correlation with AD markers? Revised Table 2 is okay.

7. The following statement was in the first paragraph of the Discussion section: “After adjustment for demographic and other factors listed in table 2, a statistically significant association between persistent dizziness or lightheadedness, neuropsychiatric symptoms, and Amyloid-β plaque deposition was found.” There was no mention in the Methods section or the Results section of how these adjustments were made and what specific factors were actually used to make the adjustments.

8. The Discussion section still needs additional attention. The first paragraph is quite good in summarizing the paper. However, the remaining text does not address the important observations described in the Results section, nor is there adequate discussion on how to interpret the data and potential impact. Each paragraph should be driven by some aspect of the data, with a logical and related flow. As an example, the conclusion paragraph the author presented in the text as the last paragraph can be used to identify specific points that could be developed into a stand alone paragraph leading to the next point and paragraph, etc., as shown below.

Paragraph 1. Keep the first paragraph in tact.

Paragraph 2. “Older adults with persistent dizziness or lightheadedness with shared risk factors may have neuropathological features of AD compared to older adults without persistent dizziness or lightheadedness.”

Paragraph 3. “Even after adjusting for covariates, there was a significant association between persistent dizziness or lightheadedness and some of the major positive hallmarks of AD.”

Paragraph 4. “Screening for persistent dizziness or lightheadedness as a risk factor for AD may be warranted.”

Paragraph 5. New conclusion paragraph.

This is just presented as an example of organization. The author can decide on specific points to cover.

9. The following statement may be true: “To best of our knowledge, this is the first study to report on the association between persistent dizziness or lightheadedness and Amyloid-β plaque deposition.” However, unless the author knows categorically this to be the case we suggest it be deleted. It could be replaced with a statement such as: “This study was novel in an attempt to associate long term dizziness in older people with an increased risk for developing neuropathogical aspects of Alzheimer’s disease.”

10. One last point. The new first paragraph of the Introduction section is confusing and should be replaced with the original first paragraph. The relationship of vestibular dysfunction with dizziness should be integrated into this paragraph or a second stand alone paragraph.

**Author’s response to editor concerns:**

1. The manuscript appears to involve only males. If this is correct, please provide the rationale for not including females.

**reply:** **No, it involves males and females. Male we used as a reference. Anyhow, sex, female data were added to the table.**

2. The connection between vestibular dysfunction and dizziness was not clearly defined so that there was confusion when discussing vestibular dysfunction and Alzheimer's disease.

**reply:** **Sentences about the connections were added (In green)**

3. In the Results section, there is no description of the data in the text. There is only reference to saying "Results are presented in the tables". The data should be described in the text (citing the appropriate table or figure) along with logical conclusions.

**reply:** **Done**

 4. The tables are awkward and difficult to read, especially table 3. At the very least they need to be reformatted. Table 3 could easily be subdivided and presented as groups of figures, for example bar graphs.

**reply:** **I am not sure why it is difficult to read. The alternative is to include a comparison between baseline and 10 years of follow-up. (table provided in green)**

 5. Figure 1 needs to be redone with a higher resolution.

**reply: I am not able to provide a higher resolution**

 6. The Discussion section in general needs to focus more on the authors interpretations of the results involving dizziness as a risk factor. The second paragraph needs to be broken down into several paragraphs, each focusing on a specific but related point with descriptions of what the authors' results mean in relation to what has been published.

**reply:** **Done**

**Author response to editor request for clarification**

I don't understand what is the problem with gender? We used male as a reference, in which male was coded as 1 and female as 0.

In the first table, we estimated the prevalence rates between gender and this rate was not significant. In the other table, we estimated gender effect on dizziness and that difference showed to be significantly similar. Although other studies showed that women could be higher but this is because they tend to have more depression and anxiety. We have not looked at gender differences among other factors, as it was not one of the aims.

Further, our results are supported by others finding that there is a gender difference between male and female who experiences dizziness at age 65 but there is no gender difference at age 85 and above.

If adding this information to the draft can solve the problem, please let me know.