**Title**

Relationship between Persistent Dizziness and Markers of Alzheimer's Disease – Mayo Clinic Study of Aging

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**ABSTRACT**

**Background:** Persistent dizziness or lightheadedness, which lasts for three months or more, ranks among the most frequent complaints in healthcare services. Persistent dizziness/lightheadedness is potentially disabling and has a distinct impact on participation, psychosocial interaction, and quality of life.

**Methods:** We examined the relationship between persistent dizziness/lightheadedness and Alzheimer's disease (AD) markers among 924 individuals aged ≥50 years (52.3% male, mean age 74 years) selected from 5707 individuals who participated in the population-based Mayo Clinic Study of Aging in Olmsted County, Minnesota. Neuropsychiatric symptoms (depression and anxiety), cognitive evaluation, magnetic resonance imaging for AD-signature "regional thickness," and 11Carbon-Pittsburgh compound B positron emission tomography for Amyloid-β deposition are all investigated.

**Results:** Age, sex (male), lower education, comorbidity, lipidemia, balance problems, neuropsychiatric symptoms, cognitive impairments (total cognitive scores and across the domain), Amyloid-deposition, and AD-cortical signature thickness were found to be significant contributing factors to persistent dizziness in older adults. After adjusting for these factors, a statistically significant association between persistent dizziness/lightheadedness and neuropsychiatric symptoms, and Amyloid-β deposition.

**Conclusion:** The finding implies that the underlying AD biology may drive both the neuropsychiatric symptoms and persistent dizziness or lightheadedness, even before the onset of cognitive impairments and dementia. Further studies are needed to support the findings.

**KEYWORDS:** Aging, Persistent Dizziness, Alzheimer’s disease, Cognitive Impairment, Depression, Anxiety

**INTRODUCTION**

Dizziness is a subjective perception of disorientation or involuntary motion that occurs during head or body movement or when the head or body. Dizziness can be further characterized as lightheadedness, which is the sensation of impending loss of consciousness associated with transient diffuse cerebral hypoperfusion. Dizziness and/or lightheadedness is frequently described as a consequence or side effect of defined entities such as cardiovascular, neurological, psychiatric, and neuro-otologic disease. Persistent dizziness and/or lightheadedness, which lasts for three months or more, ranks among the most frequent complaints in healthcare services as it can be easily provoked by physical activities (i.e., postural change and head and neck movement, active or passive motion of self ), environmental or social stimuli (i.e., light, crowds), behavioral factors (i.e., high level of anxiety, introverted temperaments, or pre-existing anxiety or depressive disorder), and many others [1, 2]. In clinical practice, persistent dizziness/lightheadedness lacks uniform criteria for its classification and definition, especially when not better accounted for by vestibular diagnosis [3, 4]. If left ignored or untreated, persistent dizziness/lightheadedness becomes a potentially disabling disorder that has a distinct impact on participation, psychosocial interaction, and quality of life.

Previous studies have reported that dizziness may be associated with various cognitive impairments, including visuospatial ability, attention, memory, and executive function [4-8]. Alzheimer’s disease (AD) is a neurodegenerative pathology that leads to behavioral and changes in memory loss and is ultimately fatal [9]. One hypothesis for the pathogenesis of AD is the excessive extracellular Amyloid-β plaque deposition, which occurs years before the onset of symptoms and is associated with brain cell death [10, 11]. Amyloid-β accumulation, which can be detected by Carbon-Pittsburgh compound B positron emission tomography (11C-PiB PET) imaging, causes synaptic dysfunction due to either a breakdown of Amyloid-β clearance or Amyloid-β overproduction [12]. The increased use of 11C-PiB PET imaging has led to the discovery that Amyloid- is present in nondemented but preclinical Alzheimer's disease patients [13, 14]. A high level of Amyloid-β deposition has been linked to spatial cognition deficits, depression, and anxiety, as well as an increased risk of progression to AD [13-15]. In addition, the application of structural magnetic resonance imaging (MRI) has revealed a specific pattern of cortical thinning among older adults that appears to be associated with AD risk and progression. This pattern, known as the AD cortical signature, has consistently been found in medial and lateral temporoparietal regions [10, 11, 16, 17].

Noteworthy, a major projection to this brain area emanates from the semicircular canals of the vestibular labyrinth, with vestibular damage leading to severe degeneration of the medial-temporal region.

Vestibular loss as a contributor to the burden of the AD process has been reported in the literature [18-21]. Given that patients with or who are at risk of AD may experience increased rates of vestibular dysfunction, the relationship between AD markers and persistent dizziness remains to be investigated. This study aimed to examine the relationship between persistent dizziness and AD markers.

**MATERIALS AND METHODS**

**Design and sample**

This cross-sectional study was derived from the ongoing, population-based Mayo ClinicStudy of Aging (MCSA) in Olmsted County, MN [22]. MCSA study protocols have been approved by the IRB of the Mayo Clinic and Olmsted Medical Center in Rochester, Minnesota. All participants provided written informed consent. We included people who reported a degree of dizziness or lightheadedness ranged from mild to severe and remain persistent over time. Outcomes were compared with people who have not reported any degree of dizziness or lightheadedness over time.

**Neurocognitive evaluation**

 Briefly, all participants of MCSA underwent a face-to-face evaluation including a neurological examination performed by a physician, a risk factor ascertainment conducted by a study coordinator, and standardized neuropsychological testing administered by a psychometrist to assess four cognitive domains (i.e., memory, language, visuospatial skills, executive functions). An expert consensus panel consisting of physicians, study coordinators, and neuropsychologists evaluated the results and classified each participant as being cognitively normal (based on normative data developed on a separate sample in this community) or having mild cognitive impairment based on published criteria.

**Measurement of neuropsychiatric symptoms**

Neuropsychiatric symptoms were assessed using the Beck Depression Inventory (BDI-II) and Beck Anxiety Inventory (BAI). The BDI-II and BAI are validated, self-administered inventories consisting of items that measure symptoms of depression (such as loss of interest) 16 over the last 2 weeks, or symptoms of anxiety (such as fear of losing control) over the last 7 days, respectively. The severity of each symptom is rated on an ordinal scale ranging from 0 (low) to 3 (high). The total score for both BDI-II and BAI ranges from 0 to 63, with a higher score indicating a higher severity of symptoms.

**Imaging**

 Participants completed MRI and PET scans at a single visit. All MRI scans were completed on one of three General Electric 3T scanners using a sagittal 3D magnetization prepared rapid acquisition gradient recalled echo (MP-RAGE) sequence. Repetition time (TR) was ≈2,300ms, echo time (TE) ≈3ms and inversion time (TI) = 900ms. Voxel dimensions were ≈1.2 × 1.015 × 1.015 mm. Gradient distortion in the sagittal plane was performed on-scanner, and a through-plane correction was performed as part of image processing. Intensity inhomogeneity was corrected using first the N3 algorithm, followed by the SPM5-based bias correction. From these preprocessed images, the cortical surface was segmented, and cortical thickness values were estimated using FreeSurfer version 5.3.0. Cortical thickness estimations were then resampled from FreeSurfer outputs to the input images’ native space using FreeSurfer tools. Amyloid PET imaging was performed using the Pittsburgh Compound B tracer. Briefly, PiB scans, consisting of four 5-min dynamic frames, were acquired from 40 to 60 min after intravenous injection with 292–728 MBq of 11C-PiB. Images were analyzed using an in-house, fully automated image processing pipeline in which image voxel values were extracted from automatically labeled regions of interest propagated from regions defined on each participant’s own MRI. A global amyloid PET standardized uptake value ratio (SUVR) was formed from the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions of interest and normalized to the cerebellar gray matter. Participants with an SUVR > 1.42 15 were classified as having an abnormal PiB-PET retention (elevated β-amyloid burden; A+) as we have previously validated by autopsy [23]. The reader is referred elsewhere for details on PiB-PET imaging in the MCSA [24].

**Statistical analysis**

Statistical analyses were conducted using SAS software v.9.4 (SAS Institute, Inc, Cary, 224 NC). For the analytical assessment of neurocognitive testing and 11C-PiB PET imaging, the raw scores or tests in each cognitive domain were z-scored, averaged, and scaled to create domain specific cognitive z-scores. Besides, a global z-score for overall cognitive performance was also created by averaging and scaling the four-domain z-scores. Hazard ratios (HR) for potential risk factors for each of the follow-up endpoints were obtained using Cox proportional hazards models. Univariate as well as multivariate models were assessed. Multivariate relationships were evaluated adjusting for age, sex, years of education, and other comorbidities. All analyses were considered statistically significant at a P-value <0.05 and were performed using the SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina).

**RESULTS**

**Demographics and presence of persistent dizziness or lightheadedness**

The MCSA sample consisted of 5707 participants, of whom 924 who aged ≥ 50 years (52.3% male, mean age 74 years) had reported persistent dizziness/lightheadedness during the follow-up time, which was 14.5 years. The risk of persistent dizziness/lightheadedness during the follow-up period after the initial visit to the study was estimated using the Kaplan-Meier method. The estimated risk of developing symptoms of dizziness/lightheadedness at 10 years was 49%. Figure 1 represents the survival curve.

Participants’ characteristics by significant dizziness/lightheadedness at baseline using Wilcoxon signed-rank test or χ2 test as appropriate are presented in **Table 1**. Age, sex (male), lower education, comorbidity, lipidemia, balance problems, neuropsychiatric symptoms, cognitive impairments (total cognitive scores and across the domain), Amyloid-deposition, and AD-cortical signature thickness were found to be significant contributing factors to persistent dizziness in older adults. Details are presented in **Table 2.**

**---------------- Insert Figure 1 and Table 1 &2 --------------------**

**Association between persistent dizziness and AD markers**

Neuropsychiatric symptoms, Cognitive evaluation, and AD markers by follow-up events as compared to baseline are presented in Table 3. After adjusting for age, sex, education, and other variables (e.g., hearing loss, Charlson comorbidity index, balance difficulties), the analysis revealed a significant association between persistent dizziness and Neuropsychiatric symptoms [HR=1.0 for depression and anxiety, P=0.001] and AD markers as measured by PET Aβ imaging [HR=1.8, P=0.009]. Results are presented in **Table 4**.

**---------------- Insert Tables 3 & 4 ----------------------**

**DISCUSSION**

This study aimed to examine the relationship between persistent dizziness/lightheadedness and AD markers. A study highlighted that age, sex (male), lower education, comorbidity, lipidemia, balance problems, neuropsychiatric symptoms, cognitive impairments (total cognitive scores and across the domain), Amyloid-deposition, and AD-cortical signature thickness were found to be significant contributing factors to persistent dizziness in older adults. After adjusting for potential confounders, we found an association between persistent dizziness/lightheadedness and depression, anxiety, and Amyloid-β deposition in a population of older adults. The probability of positive association between persistent dizziness/lightheadedness and elevated brain Amyloid-β deposition was 1.8 times. This implies that the underlying AD biology may drive both the neuropsychiatric symptoms (depression and anxiety) and persistent dizziness or lightheadedness, even before the onset of cognitive impairments and dementia.

Our findings should be interpreted within the context of published literature. First, depression might be a risk for dementia and AD in midlife, but dementia in later life and AD might cause depression [25, 26]. Second, the underlying AD biology as measured by PET imaging can contribute to an increased frequency of neuropsychiatric symptoms in cognitively normal or cognitively impaired people [27-31]. Third, a cross-sectional study based on the MCSA cohort discovered a significant but weak link between increased neuropsychiatric symptom scores [(OR = 1.04; 1.01–1.08 for anxiety and (OR = 1.03; 1.00–1.06) for depression] and elevated brain Amyloid deposition in cognitively normal elderly people [29, 30]. However, when compared to mild cognitive impairment without brain Amyloid-deposition, the elderly with mild cognitive impairment and brain Amyloid-deposition were found to have an increased risk of having neuropsychiatric symptoms. This implies that the underlying AD biology (i.e., brain Amyloid-β deposition) may drive both cognitive and psychiatric symptoms [29-30]. Similarly, a study investigated whether current depressive symptoms are related to brain Amyloid-β deposition [32]. After controlling for potential confounds, including the history of major depression, they found that current depressive symptoms were not related to brain Amyloid-β deposition. Fourth, a previous study using the Baltimore Longitudinal Study of Aging examined a relationship between measures of vestibular function and brain Amyloid-β deposition in cognitively intact older adults who have peripheral dizziness/vertigo [33]. While that study did not observe a significant relationship between the two, a study found that the proportion of central dizziness/vertigo tends to increase with dementia [34].

 In our study, the tendency of the peripheral cause of dizziness was not observed in their medical records. Noteworthy, persistent dizziness/lightheadedness has an important cortical representation in the frontal and parietal regions [35]. Research has found that brain Amyloid-β deposition and psychiatric outcomes can appear as early as 20 years before the first sign of the AD pathology, such as cognitive decline and memory loss [36, 37]. Along with our study findings, this can imply that persistent dizziness/lightheadedness among the elderly can be an early sign of AD. Given that persistent dizziness/lightheadedness can be associated with poor physical and mental health, the overall result of our study can be a valuable addition to current knowledge and may have clinically relevant results to potentially screen for and manage persistent dizziness/lightheadedness among older adults.

Limitations of this study include its retrospective nature. Although dizziness is a broad and non-specific term with varying etiologies and is often cited as a vestibular symptom and attributed to disorders of the vestibular system, a major challenge is that nomenclature in research studies lacks uniform criteria for classification and definition. The generalization of our results is limited due to lack of standard outcome measures that quantify and classify dizziness, which must be thoroughly considered in future studies.

**CONCLUSION**

Age, sex (male), lower education, comorbidity, lipidemia, balance problems, neuropsychiatric symptoms, cognitive impairments (total cognitive scores and across the domain), Amyloid-deposition, and AD-cortical signature thickness were found to be significant contributing factors to persistent dizziness in older adults. 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. This finding implies that the underlying AD biology may drive both the neuropsychiatric symptoms and persistent dizziness or lightheadedness, even before the onset of cognitive impairments and dementia. Further studies are needed to support the findings.

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**Figure’s Legend**

**Figure 1.** Kaplan-Meier method: The 10-year risk of developing symptom of dizziness or lightheadedness in the group